Gastric emptying, mouth-to-cecum transit, and glycemic, insulin, incretin, and energy intake responses to a mixed-nutrient liquid in lean, overweight, and obese males

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Am J Physiol Endocrinol Metab 304: E294–E300, 2013. First published December 4, 2012; doi:10.1152/ajpendo.00533.2012.—Observations relating to the impact of obesity on gastric emptying (GE) and the secretion of gut hormones are inconsistent, probably because of a lack of studies in which GE, gastrointestinal hormone release, and energy intake (EI) have been evaluated concurrently with previous patterns of nutrient intake. GE is known to be a major determinant of postprandial glycemia and incretin secretion in health and type 2 diabetes. The aims of this study were to determine the effects of a mixed-nutrient drink on GE, oro-cecal transit, blood glucose, insulin and incretin concentrations and EI, and the relationship between the glycemic response to the drink with GE in lean, overweight, and obese subjects. Twenty lean, 20 overweight, and 20 obese males had measurements of GE, oro-cecal transit, and blood glucose, insulin, GLP-1, and GIP concentrations for 5 h after ingestion of a mixed-nutrient drink (500 ml, 532 kcal); EI at a subsequent buffet lunch was determined. Habitual EI was also quantified. Glycemic and insulimic responses to the drink were greater in the obese (both \( P < 0.05 \)) when compared with both lean and overweight, with no significant differences in GE, intragastric distribution, oro-cecal transit, incretins, or EI (buffet lunch or habitual) between groups. The magnitude of the rise in blood glucose after the drink was greater when GE was relatively more rapid (\( r = 0.55, P < 0.05 \)). In conclusion, the absence of differences in habitual EI, both GE and incretin hormones are unaffected in the obese despite greater glucose and insulin responses, and GE is a determinant of postprandial glycemia.

glucagon-like-peptide-1; glucose-dependent insulinotropic peptide; habitual food intake; blood glucose control

GASTROINTESTINAL (GI) function, including pyloric activity, gastric emptying (GE), and intragastric meal distribution, is pivotal to the regulation of appetite (36) and blood glucose homeostasis (20) and accordingly is of relevance to an understanding of the pathogenesis, and for rational management, of obesity. Moreover, macronutrient intake per se modulates GI function and thus potentially appetite regulation in both animals and humans. For example, in rats, exposure to a high-fat diet attenuates the suppressive effects of small intestinal fat on GE (11) and energy intake (12), and there is evidence that the sensitivity to the effects of fat on GI function and energy intake is reduced by a high-fat diet (4, 14). Although specific aspects of GI function in the obese have been investigated in a number of studies, there is a lack of studies that have evaluated changes in GI function in lean, overweight, and obese individuals, as well as previous nutrient intake, concurrently. Human obesity is associated with an increased preference for fatty foods, suggesting that fat intake is poorly regulated in this group (39). Postprandial plasma peptide YY, which is stimulated by dietary fat, has been reported to be reduced (23) or comparable (5) in obese vs. lean individuals, and there is evidence that obese individuals have a compromised ability to detect fatty acids both in the oral cavity and small intestinal lumen (39). Obesity is well recognized as a risk factor for a number of disorders, perhaps most importantly type 2 diabetes (33), and glycemic variability, which appears to be a determinant of macrovascular disease, may also be increased in the obese (25). There is a substantial interindividual variation in GE in health (8), and GE is modulated by acute changes in macronutrient intake (4, 14, 15). Although there is a relationship between subsequent energy intake and gastric emptying (37), this may relate particularly to the intragastric distribution of a meal, particularly the content of the distal stomach (41). GE is also a major determinant of postprandial glycemia in health and type 2 diabetes (20, 22, 26) so that relatively more rapid emptying may potentially predispose to the development of diabetes (31). GE has been reported to be comparable, faster, and slower in the obese (38). Surprisingly, the impact of GE on glycemia in the obese has hitherto not been evaluated.

The “incretin” hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) account for the substantially greater insulin response to enteral, as opposed to an isoglycemic, intravenous glucose load (13) and accordingly play a major role in blood glucose homeostasis. In both health (32) and type 2 diabetes (26), GLP-1 and GIP secretion are modulated by the rate of small intestinal carbohydrate delivery. The “incretin effect” is diminished in type 2 diabetes (1), at least in part because the insulinotropic capacity of GIP is reduced (29). There is limited and inconsistent information about GLP-1 and GIP secretion in obesity (6, 16, 24, 44, 45). Dipeptidyl peptidase-IV (DPP-IV) activity, which accounts for the rapid degradation of GLP-1 and GIP, has been reported to be increased modestly in obesity (6).

The primary aims of this study were to determine the effects of a mixed-nutrient drink on GE, oro-cecal transit, blood glucose, insulin, and incretin concentrations, and energy intake and the relationship between the glycemic response to the drink with GE in lean, overweight, and obese subjects.

MATERIALS AND METHODS

Subjects

A total of 60 male age-matched subjects, including 20 lean [age [median (range)]: 35 (19–60) yr; BMI [median (range)]: 23.4 (19.3–25) kg/m²], 20 overweight [age: 36 (21–60) yr; BMI: 27.5 (25.8–
29.7) kg/m²], and 20 obese [age: 37 (22–59) yr; BMI: 34.5 (30.7–37.6) kg/m²], with the age distribution well balanced across the age range, participated in the study, which conformed to the guidelines set out in the Declaration of Helsinki. Participants were recruited from an existing pool of volunteers, and the study was approved by the Royal Adelaide Hospital Research Ethics Committee. Subjects with significant GI, cardiovascular, or respiratory disease, GI symptoms or surgery (established using screening questionnaires), diabetes mellitus (assessed using fasting blood glucose levels), or epilepsy, subjects using medication known to affect gut function, appetite, or body weight, cigarette smokers, and those consuming >20 g alcohol/day were excluded. Lean subjects were required to be unrestrained eaters, as determined by a score of ≤12 on the eating restraint questionnaire component of the three-factor eating questionnaire (40). This was not used as an exclusion criterion in overweight and obese subjects, given the high prevalence of eating restraint. All subjects provided informed, written consent prior to their inclusion.

Protocol

Subjects were provided with a standard meal (beef lasagna; McCain Foods, Wendouree, Victoria, Australia) to be consumed on the evening prior to each study at 2000 and were instructed to fast overnight from both solids and liquids thereafter before attending the laboratory at 0830. Upon arrival at the Department of Nuclear Medicine, PET, and Bone Densitometry, an intravenous cannula was inserted into a forearm vein to obtain blood samples for the measurement of blood glucose and subsequent analysis of plasma insulin, GLP-1, and GIP concentrations. A baseline blood sample was taken at t = −15 min. Two cobalt markers (1.5 cm in diameter) were taped onto the skin, with one situated in the left hypochondrium at the end of the ninth rib and the other over the left anterior superior iliac spine. These remained in position for the duration of the study as anatomic reference points to correct for movement of the subject in the subsequent data analysis. After a 10-min baseline period (i.e., at t = −5 min), subjects ingested the test drink comprising 500 ml (532 kcal) of Ensure (15% protein, 60% carbohydrate, and 25% fat; Abbott Australasia, Botany, New South Wales, Australia) labeled with 20 MBq 99mTc-Nanocollod. All subjects ingested the drink within −5 min, and the duration of drink ingestion did not differ between lean [median (range): 146 (71–318) s], overweight [132 (80–301) s], and obese [128 (77–298) s] subjects. At t = 0 min (i.e., immediately after the test drink had been consumed), measurement of GE (Genie; GE Healthcare Technologies, Milwaukee, WI) commenced and was continued for 5 h. Static images were acquired in the following way: subjects stood with their backs against the camera for 1 min to obtain an anterior image and then turned around facing the camera, with their abdomen against the gamma camera for 1 min to obtain a posterior image. GE images and 10-ml blood samples were collected in ice-chilled EDTA-treated tubes containing 400 kIU/ml blood aprotinin (Trasylol; Bayer Australia, Pymble, Australia). Venous blood glucose concentrations (mmol/l) were determined immediately by the glucose oxidase method using a portable glucometer (Medisense Precision QID; Abbott Laboratories, Bedford, MA). This technique has a coefficient of variation (CV) between 2.1 and 5.6%. The accuracy of this method has been confirmed in our laboratory using the hexokinase technique (42). Plasma was obtained by centrifugation of blood samples at 3,200 rpm for 15 min at 4°C. Plasma samples were frozen at −70°C for later analysis of insulin, GLP-1, and GIP (42).

Plasma insulin concentrations (mU/l) were measured by ELISA immunoassay (10–1113; Mercodia, Uppsala, Sweden)(42). The intra-assay CV was 2.6%, the interassay CV was 4.9%, and the detection limit was 1 mU/l.

Plasma GLP-1 concentrations (pmol/l) were determined after ethanol extraction, using a radioimmunoassay kit (GLPIT-36HK; Millipore, Billerica, MA) (42). The antibody used (supplied by Prof. S. R. Bloom, Hammersmith Hospital, London, UK) does not cross-react with glucagon, gastric inhibitory peptide, or other gut or pancreatic peptides, and it measures intact GLP-1(7–36) amide, as well as the degraded form, GLP-1(9–36) amide. Intra- and inter-assay (CVs) were 4.2 and 10.5%, respectively. The minimum detectable concentration was 3 pmol/l.

Plasma GIP concentrations (pmol/l) were determined using a modification of the original method (42). The standard curve was prepared in buffer rather than extracted charcoal-stripped serum, and the radioiodinated label was supplied by Perkin-Elmer (Boston, MA). The assay measures both active and degraded GIP. The intra-assay CV was 3.8%, the interassay CV was 9%, and the detection limit was 2 pmol/l.

Insulin resistance. The homeostasis model assessment (HOMA) was used to assess insulin resistance (27), using fasting glucose and insulin concentrations by the following formula: insulin resistance (HOMA) = [fasting glucose (mmol/l)/22.5] × fasting insulin (mU/l). Energy intake. Habitual energy and macronutrient intake were quantified using a validated dietary questionnaire developed by the Cancer Council, Victoria, Australia, to characterize eating habits over the past 12 mo (18).

The amount eaten (g), energy intake (kJ), and macronutrient distribution (g and %) at the buffet meal were quantified as described previously (17).

Statistical Analysis

Data were analyzed using SPSS version 17 (SPSS, Chicago, IL). Repeated-measures analysis of variance (ANOVA) was used to evaluate total, proximal, and distal emptying profiles, blood glucose, insulin, plasma GLP-1, and GIP, with time as within-subject factor and group (lean, overweight, and obese) as between-subject factor. Areas under the curve (AUCs) for glucose and plasma insulin, GLP-1, and GIP were calculated using the trapezoidal rule. One-way ANOVA was used to analyze gastric half-emptying time (T50), mouth-to-cecum transit time, insulin resistance, AUCs for glucose, hormones, energy intake (kJ), amount eaten (g), and macronutrient distribution (g and %) from the buffet meal, and habitual energy (kJ) and macronutrient (g and %) intakes, with group as a factor. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni’s correction, were performed where ANOVAs revealed significant effects. Linear regression analysis was used to evaluate relationships between GE, oro-cecal transit, blood glucose, plasma insulin, GLP-1, and GIP. Statistical significance was accepted at P < 0.05. Data are means ± SE.
groups. Similarly, there was no difference in the amount of drink remaining in the proximal (Fig. 1B) or distal (Fig. 1C) stomach between groups. There was also no difference in oro-cecal transit time (lean: 111 ± 11 min; overweight: 120 ± 15 min; obese: 86 ± 9 min) between groups, although the mean value was lower in the obese.

**Blood Glucose and Plasma Insulin, GLP-1, and GIP Concentrations**

**Blood glucose.** There was no difference in baseline glucose (lean: 5.5 ± 0.1 mmol/l; overweight: 5.6 ± 0.2 mmol/l; obese: 5.9 ± 0.2 mmol/l) between groups (Fig. 2A). In all three groups, blood glucose rose in response to the drink \( (P < 0.001) \) and returned to baseline by \( t = \sim 150 \) min. There was a significant group \( \times \) time interaction for blood glucose concentrations \( (P < 0.001) \) so that blood glucose was greater in the obese between \( t = 45 \) and 90 min compared with the lean \( (P < 0.05) \) and between \( t = 30 \) and 45 min and at \( t = 75 \) min compared with the overweight \( (P < 0.05) \), with no difference between the overweight and lean. Peak blood glucose was also substantially greater in the obese \( (9.3 \pm 0.5 \text{ mmol/l}) \) when compared with the overweight \( (7.8 \pm 0.3 \text{ mmol/l}) \) and the lean \( (8.0 \pm 0.3 \text{ mmol/l}) \) \( (P < 0.05) \). AUC for blood glucose was also greater in the obese \( (1,842 \pm 55 \text{ mmoll}^{-1}\cdot\text{min}) \) when compared with the overweight \( (1,670 \pm 40 \text{ mmoll}^{-1}\cdot\text{min}) \) and lean \( (1,647 \pm 48 \text{ mmoll}^{-1}\cdot\text{min}) \) \( (P < 0.05) \).

**Plasma insulin.** There was a difference in baseline insulin concentrations (lean: 3.7 ± 0.4 mU/l; overweight: 4.4 ± 0.5 mU/l; obese: 10.7 ± 1.5 mU/l) between groups \( (P < 0.001) \) so that plasma insulin was greater in obese when compared with both lean and overweight subjects \( (P < 0.001 \text{ for both}) \). There was a significant group \( \times \) time interaction for insulin \( (P < 0.001; \text{Fig. 2B}) \). Plasma insulin concentrations were much greater in the obese when compared with the lean between \( t = 0 \) and 300 min \( (P < 0.01) \) and compared with the overweight between \( t = 0 \) and 75 min and \( t = 180 \) and 300 min \( (P < 0.05) \), with no difference between the overweight and lean group. In all three groups, plasma insulin had returned to baseline by \( \sim 210 \) min. AUC for plasma insulin was also greater in the obese \( (10,979 \pm 1,434 \text{ mU}^{-1}\cdot\text{min}) \) when compared with the overweight \( (5,532 \pm 995 \text{ mU}^{-1}\cdot\text{min}) \) and lean \( (4,276 \pm 578 \text{ mU}^{-1}\cdot\text{min}) \) \( (P < 0.01) \).

There were also differences in HOMA (lean: 0.9 ± 0.1 min; overweight: 1.1 ± 0.1 min; obese: 2.9 ± 0.5 min) between groups \( (P < 0.001) \) so that HOMA was greater in the obese compared with both the lean and overweight groups (both \( P < 0.001 \)), with no difference between lean and overweight.

**Plasma GLP-1.** There was no difference in baseline GLP-1 concentrations (lean: 21.3 ± 1.7 pmol/l; overweight: 21.9 ± 1.7 pmol/l; obese: 24.7 ± 2.1 pmol/l) between groups (Fig. 2C). There was a significant time effect for plasma GLP-1 concentrations \( (P < 0.001) \). Plasma GLP-1 increased in all groups promptly following the drink. GLP-1 increased between \( t = 15 \) and 30 min and \( t = 60 \) and 90 min in lean, between \( t = 15 \) and 90 min in overweight, and between \( t = 15 \) and 30 min in the obese compared with baseline \( (P < 0.05 \text{ for all}) \), with no differences between groups, although mean values were highest in the obese. In all three groups, plasma GLP-1 had returned to baseline by \( t = \sim 210 \) min. AUC for plasma GLP-1 did not differ between groups (lean: 6,842 ± 395 pmoll^{-1}\cdot\text{min}; overweight: 7,158 ± 442 pmoll^{-1}\cdot\text{min}; obese: 7,934 ± 458 pmoll^{-1}\cdot\text{min}).
Plasma GIP. There was no difference in baseline GIP concentrations (lean: 17.5 ± 1.7 pmol/l; overweight: 18.2 ± 1.3 pmol/l; obese: 20.9 ± 2.3 pmol/l) between groups. There was a significant time effect for plasma GIP concentrations (P < 0.001) (Fig. 2D). Plasma GIP increased promptly in all groups following the test meal. GIP increased between t = 15 and 180 min in lean and obese and between t = 15 and 120 min in overweight subjects (P < 0.05 for all), with no difference between groups. At t = 300 min, there was no difference in plasma GIP concentrations from baseline in any of the groups. AUC for plasma GIP did not differ between groups (lean: 12,467 ± 902 pmol·l⁻¹·min; overweight: 12,665 ± 757 pmol·l⁻¹·min; obese: 12,209 ± 828 pmol·l⁻¹·min).

Energy Intake

Table 1. Habitual energy intake and macronutrient distribution in lean, overweight, and obese subjects

<table>
<thead>
<tr>
<th></th>
<th>Lean</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake, kJ</td>
<td>9,627 ± 712</td>
<td>10,684 ± 1,636</td>
<td>10,564 ± 720</td>
</tr>
<tr>
<td>Fat, g</td>
<td>99 ± 8</td>
<td>109 ± 20</td>
<td>116 ± 8</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>246 ± 22</td>
<td>260 ± 37</td>
<td>242 ± 19</td>
</tr>
<tr>
<td>Protein, g</td>
<td>109 ± 7</td>
<td>135 ± 24</td>
<td>133 ± 9</td>
</tr>
<tr>
<td>Fat, %</td>
<td>37 ± 1</td>
<td>36 ± 2</td>
<td>40 ± 1*</td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>42 ± 1</td>
<td>43 ± 2</td>
<td>38 ± 1*</td>
</tr>
<tr>
<td>Protein, %</td>
<td>20 ± 1</td>
<td>21 ± 1</td>
<td>21 ± 1</td>
</tr>
</tbody>
</table>

Table data are means ± SE (n = 20 lean, 19 overweight, and 18 obese). Subject nos. vary, as questionnaires of some subjects could not be read by the analysis program, and therefore, they could not be analyzed. *Trend for difference from lean and overweight; %energy from fat (P = 0.052), %energy from carbohydrate (P = 0.086).

There were no differences in either habitual energy intake or macronutrient distribution (g) between obese, overweight, and lean subjects (Table 1), although there was a trend for a treatment effect for %energy from fat (P = 0.058) and carbohydrate (P = 0.06) between groups (Table 1). Obese subjects tended to consume a greater percent energy from fat (P = 0.052) and a lower percent energy from carbohydrate (P = 0.086) than lean or overweight subjects, with no difference between lean and overweight. There was no difference in percent energy from protein between groups.

Although there were no differences in energy intake (kJ) or the amount eaten (g) at the buffet meal (Table 2), there was a difference in the percent energy consumed from fat and carbohydrate at the buffet meal (P < 0.05 for both) so that percent energy from fat was slightly greater (P < 0.05) and percent energy from carbohydrate slightly less (P < 0.05) in the obese when compared with the lean and overweight group, with no difference between lean and overweight (Table 2). There was no difference in percent energy from protein consumed at the buffet meal between groups.

Fig. 2. Blood glucose (A), plasma insulin (B), plasma glucagon-like peptide-1 (GLP-1; C), and plasma glucose-dependent insulinotropic peptide (GIP) concentrations (D) following oral ingestion of 500 ml (532 kcal) of Ensure in lean, overweight, and obese subjects. Repeated-measures analyses of variance (ANOVA) with time and treatment as factors were used to determine statistical difference. If ANOVA revealed significant effects, pairwise comparisons were performed. Data are means ± SE (n = 20 lean, 20 overweight, and 20 obese). *P < 0.05 vs. lean; #P < 0.05 vs. overweight.
There was a significant relationship between the magnitude of the rise in GIP concentrations and T50 in all three groups combined. There was also an inverse relationship between the magnitude of the rise in blood glucose concentrations and T50 in all three groups combined or in the lean group. As has been shown to be the case in health (20) and both type 1 and type 2 diabetes (22), there was no relationship between peak blood glucose concentration and T50 in any group or in all three groups combined. There was no significant relationship between peak GIP concentration and T50 in any group or in all three groups combined or in the lean group. 

There was no significant relationship between habitual energy intake with the GE T50 in any group or in all three groups combined. There was no significant relationship between habitual energy intake and GE T50 in any group or in all three groups combined or in the lean group. There was no significant relationship between peak blood glucose concentration with T50 in any of the groups. However, it is important to note that the overweight and obese tended to have slightly higher mean intakes than the lean, and there was substantial interindividual variation within as well as between the three groups. Given the number of subjects that were evaluated (n = 20 in each group), we cannot entirely exclude the possibility of small differences in habitual energy intake between groups, particularly an increase in the obese, which would impact body weight. 

Meal composition has a major effect on GE (46). GE of low-nutrient liquids is dependent primarily on fundic tone, whereas solid GE is characterized by an initial lag phase, which reflects the transit of food from the fundus to the antrum and the time taken for solid food to be reduced to small particles by antral peristalsis, followed by an emptying phase that approximates a linear pattern, at least for the majority of emptying. High-nutrient liquids, as used in this study, empty from the stomach at rates that are comparable with solid meals, although the lag phase is usually short, if not absent (9a), as their emptying is dependent primarily on neural/humoral feedback arising from the interaction of nutrients with the small intestine (28). In addition, their capacity to identify disordered gastric emptying appears to be comparable with that of solid meals, which is not the case with low-nutrient liquids as they empty more rapidly. Hence, our observations with a nutrient liquid, at least as they relate to the rate of emptying, are likely to also apply to solid meals. Small intestinal transit is a determinant of GI hormone and glycemic responses (7), but to date there has been no evaluation of the relationship between the glycemic responses and small intestinal transit in overweight/obese compared with lean subjects. Thus, we assessed small intestinal transit by cecal arrival of a radiolabeled meal. Although this technique is known to have limitations, we observed no significant differences between the groups, although mean transit in the obese as a group appeared to be slightly faster.

Consistent with other studies, the glycemic and insulminemic responses to the drink were substantially higher in the obese compared with the lean and overweight group, and the obese subjects were markedly insulin resistant, as assessed by HOMA (27). The blood glucose concentration is a determinant of GE, which is affected by elevations of blood glucose within the physiologic range such that GE of both solids and liquids is slower at blood glucose concentrations of 8 mmol/l compared to 5 mmol/l. 

### Table 2. Energy intake and macronutrient distribution at the buffet meal (t = 300–330 min) following ingestion of 500 ml (532 kcal) of Ensure 305 min earlier in lean, overweight, and obese subjects

<table>
<thead>
<tr>
<th>Energy intake, kJ</th>
<th>Lean</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount eaten, g</td>
<td>1,053 ± 53</td>
<td>1,116 ± 75</td>
<td>1,105 ± 101</td>
</tr>
<tr>
<td>Fat, g</td>
<td>41 ± 3</td>
<td>43 ± 4</td>
<td>51 ± 3</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>127 ± 7</td>
<td>119 ± 8</td>
<td>131 ± 9</td>
</tr>
<tr>
<td>Protein, g</td>
<td>58 ± 4</td>
<td>61 ± 5</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>Fat, %</td>
<td>32 ± 1</td>
<td>33 ± 1</td>
<td>36 ± 1*</td>
</tr>
<tr>
<td>Carbohydrate, %</td>
<td>47 ± 2</td>
<td>44 ± 2</td>
<td>42 ± 1*</td>
</tr>
<tr>
<td>Protein, %</td>
<td>21 ± 1</td>
<td>22 ± 1</td>
<td>23 ± 2</td>
</tr>
</tbody>
</table>

Data are means ± SE (n = 20 lean, 20 overweight, and 20 obese). *P < 0.05 vs. lean and overweight.

### Discussion

This study has evaluated a number of aspects of GI function relevant to the regulation of energy intake and glycemia, including GE, oro-cecal transit, blood glucose, insulin, GLP-1, GIP, and energy intake following ingestion of a high-nutrient liquid in healthy lean, overweight, and obese male humans. There was no significant difference in previous patterns of energy intake, GE, oro-cecal transit, plasma GLP-1 or GIP, or energy intake between the groups. Blood glucose and plasma insulin responses to the drink were predictably greater in the obese when compared with the lean and overweight, and importantly, the glycemic response was shown to be related to GE in the obese, indicating that GE is an important determinant of postprandial glycemia in this group, as has been shown to be the case in health (20) and both type 1 (21) and type 2 diabetes (22).

Previous studies on the relationship between GE and body weight have yielded inconsistent observations, with GE being reported to be comparable, faster, or slower in obese when compared with lean humans (38). These outcomes are likely to be attributable to a number of interrelated issues, particularly differences in meal composition, methodologies used to assess GE, and, perhaps most importantly, the criteria used to select obese individuals, including age and sex and particularly other factors that may affect GE, such as habitual diet (14, 15). The latter was not quantified in the majority of studies despite persuasive evidence that previous nutrient intake impacts GE (2, 10, 14, 15). For example, the effects of fat on gastric emptying and oro-cecal transit are attenuated following consumption of a high-fat diet so that, in healthy males, consumption of a high-fat, hypercaloric diet for 14 days is associated with marked acceleration of GE and mouth-to-cecum transit of a high-fat, solid test meal when compared with a low-fat diet (14). Moreover, in healthy young (15) and older (2) subjects, short-term glucose supplementation accelerates GE of a glucose drink, whereas fasting slows GE (10). That there were no differences in habitual fat or energy intake between the lean, overweight, and obese groups in our study is not surprising given that all subjects were weight-stable, and this could well account for the absence of any difference in GE between the groups. However, it is important to note that the overweight and obese tended to have slightly higher mean intakes than the lean, and there was substantial interindividual variation within as well as between the three groups. Given the number of subjects that were evaluated (n = 20 in each group), we cannot entirely exclude the possibility of small differences in habitual energy intake between groups, particularly an increase in the obese, which would impact body weight.
with 4 mmol/l (34). Hence, it is possible that GE would have been relatively faster in the obese if they had been studied during euglycemia. However, it should be recognized that, even after a carbohydrate-containing drink, the difference in the glycemic response in the obese was modest (e.g., peak glucose was 9.3 ± 0.5 mmol/l in the obese and 8.0 ± 0.3 mmol/l in the lean), so differences in glycemia appear unlikely to be a confounder. Our study indicates that in the obese, GE is a major determinant of postprandial glycemic excursions, as is known to be the case in health (20), type 1 (21), and type 2 diabetes (22). That a significant relationship between postprandial glycemia with gastric emptying was not evident in the healthy and overweight groups was probably because the rise in glucose in response to this meal was much less in these two groups. We would speculate that obese subjects who have relatively more rapid GE (within the normal range) are at greater risk for postprandial hyperglycemia and type 2 diabetes, as has been suggested to be the case in Hispanics (30a). More rapid gastric emptying may also potentially predispose to greater blood glucose variability, particularly when there is concurrent insulin resistance. These hypotheses warrant exploration.

The outcomes of previous studies relating to the effect of obesity on incretin hormone secretion have been inconsistent. Fasting GLP-1 concentrations have been reported to be reduced (24) or not different (6, 16, 44) and fasting GIP concentrations greater (45) or not different (6, 44) in the obese when compared with lean individuals. Postprandial GLP-1 concentrations have also been reported to be reduced in the obese (6, 24, 44) or not different (16, 45), with no differences in GIP between lean and obese (6) or increased levels in the obese (45). DPP-IV activity appears to be increased in obesity associated with enhanced GIP but not GLP-1 metabolism (6). A major limitation of these studies is that GE was not quantified. We found no differences in GE, and this was associated with comparable GLP-1 and GIP concentrations in lean, overweight, and obese subjects. We have shown that GLP-1 and GIP secretion is highly dependent on the rate of small intestinal carbohydrate delivery in healthy (30), type 2 diabetic (26), and older subjects (43). Moreover, in type 2 diabetic and older subjects, at a particular small intestinal glucose load, GLP-1 and GIP concentrations appear to be comparable with those of healthy, young, lean individuals. Hence, there is no evidence in the BMI range studied that a diminished incretin hormone response is associated with obesity and the predisposition to type 2 diabetes. However, because the insulinotropic property of both GLP-1 and GIP is “glucose-dependent,” the incretin response may be relatively more important for glucose regulation in the obese because of the higher postprandial glucose in these individuals, and GLP-1 and GIP may contribute to the higher postprandial insulin response compared with healthy subjects. For example, in the current study, postprandial peak blood glucose was above the threshold for insulinotropic effects of GIP and GLP-1 in the obese but not the two other groups.

Some strengths and limitations of our study warrant discussion. We included a relatively large number of individuals with a broad age range, and individuals were age-matched across groups, and this was the first study to evaluate the effects of aspects of GI function relevant to energy intake regulation and glycemic control concurrently in a broad range of BMIs. We included only male subjects; thus, we are unable to extrapolate our conclusions to females, although major differences would seem intuitively unlikely. We anticipated differences in energy intake between lean, overweight, and obese groups in response to the drink, and it should be recognized that, in retrospect, the timing of the buffet meal at 5 h was less than optimal given that GE was complete and glucose, GLP-1, and GIP concentrations had returned to baseline.

In conclusion, in the absence of significant differences in habitual energy intake, obesity appears to have no effect on GE or incretin hormone release, and GE is a determinant of postprandial blood glucose.

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DISCLOSURES

None of the authors has a conflict of interest, financial or otherwise, to declare.

AUTHOR CONTRIBUTIONS


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