Pooled-data analysis identifies pyloric pressures and plasma cholecystokinin concentrations as major determinants of acute energy intake in healthy, lean men

Radhika V Seimon, Kylie Lange, Tanya J Little, Ixchel M Brennan, Amelia N Pilichiewicz, Kate L Feltrin, Astrid J Smeets, Michael Horowitz, and Christine Feinle-Bisset

ABSTRACT

Background: The interaction of nutrients with the small intestine modulates gastropyloroduodenal motility, stimulates the release of gut hormones, and suppresses appetite and energy intake.

Objective: We evaluated which, if any, of these variables are independent determinants of acute energy intake in healthy, lean men.

Design: We pooled data from 8 published studies that involved a total of 67 healthy, lean men in whom antropyloroduodenal pressures, gastrointestinal hormones, and perceptions were measured during intraduodenal nutrient or intravenous hormone infusions. In all of the studies, the energy intake at a buffet lunch was quantified immediately after the infusions. To select specific motor, hormone, or perception variables for inclusion in a multivariable mixed-effects model for determination of independent predictors of energy intake, we assessed all variables for collinearity and determined within-subject correlations between energy intake and these variables by using bivariate analyses adjusted for repeated measures.

Results: Although correlations were shown between energy intake and antropyloroduodenal pressures, plasma hormone concentrations, and gastrointestinal perceptions, only the peak number of isolated pyloric-pressure waves, peak plasma cholecystokinin concentration, and area under the curve of nausea were identified as independent predictors of energy intake (all \( P < 0.05 \)), so that increases of 1 pressure wave, 1 pmol/L, and 1 mm · min were

Conclusion: We identified specific changes in gastrointestinal motor and hormone functions (ie, stimulation of pyloric pressures and plasma cholecystokinin) and nausea that are associated with the suppression of acute energy intake. Am J Clin Nutr 2010;92:61–8.

INTRODUCTION

In Western countries, the prevalence of obesity has more than doubled over the past 3 decades (1). Hence, there is an urgent need for effective prevention and treatment strategies. Numerous dietary and pharmacologic treatments for obesity have been developed; however, most of these treatments have limited efficacy, and in the case of drugs, adverse effects occur frequently (2). The available therapies have largely ignored the pivotal role of the gastrointestinal tract in the regulation of appetite and energy intake in humans (3–9).

The modulation of energy intake by the gastrointestinal tract is likely to involve motor and hormonal mechanisms. Although distension of both the proximal and distal stomach increases fullness (10, 11) and suppresses energy intake (4, 12), the antrum may play the dominant role in these functions (4, 10). The presence of nutrients in the small intestine slows gastric emptying potently by decreasing antral motility and stimulating phasic and tonic pyloric-pressure waves (PPWs) and stimulates the release of gastrointestinal hormones, including cholecystokinin, peptide YY (PYY), and glucagon-like peptide 1 (GLP-1) (13, 14), which may mediate the concomitant inhibition of appetite and subsequent energy intake. For example, studies that used the cholecystokinin-1 receptor antagonist loxiglumide established that endogenous cholecystokinin inhibits energy intake (6, 15, 16). Exogenous PYY(3-36) and GLP-1 were also reported to decrease energy intake in some (5, 17) but not all (18–20) studies. We recently reported an inverse relation between the suppression of energy intake and the stimulation of pyloric pressures in response to intravenous cholecystokinin-8 infusion in healthy men, which provided evidence of a link between specific changes in gastrointestinal motor function and the suppression of energy intake in humans (7).

Received November 30, 2009. Accepted for publication April 15, 2010. First published online May 19, 2010; doi: 10.3945/ajcn.2009.29015.
slowing of gastric emptying and the suppression of energy intake reported previously (23). Changes in motility and hormone secretion occur concurrently with changes in appetite, and therefore, it is not surprising that there is little information regarding which, if any, of these factors are independent determinants of energy intake. For example, although cholecystokinin does have a role in the process, this may potentially be mediated indirectly by its effect on motility (7, 19).

During the last few years, we performed a series of studies in our laboratory in healthy men that related to gastrointestinal motor and hormonal functions and appetite and energy intake in response to small intestinal nutrient (8, 24–29) or intravenous hormone administration (7, 19, 30), and a substantial body of data has been accumulated. A focus of this work has been on pyloric motility, given that the pylorus is of pivotal importance to the regulation of gastric emptying (22) but has, hitherto, received inappropriately little attention. Individually, such studies are often limited by small sample sizes so that it is only possible to perform simple correlation or regression analyses between energy intake and physiologic variables that are uncontrolled for other concurrent physiologic changes. Pooling data from these studies enabled us to generate a uniquely large set of data to examine the simultaneous relations between multiple variables and, thus, to determine independent predictors of acute energy intake.

METHODS

Subjects

A total of 67 subjects, with a mean (±SEM) age of 26 ± 1 y and of normal body weights for their heights [body mass index (in kg/m²): 23.3 ± 0.3], participated in the studies (7, 8, 19, 24–30) that were included in this analysis. Of the 67 subjects, 6 subjects participated in 2 studies, 4 subjects participated in 3 studies, and 2 subjects participated in 5 studies. Information relating to the subjects in each study is provided in Table 1. All subjects were unrestrained eaters as determined by a score of <12 on the eating-restraint component of the 3-factor eating questionnaire (31) and were questioned before the study to exclude significant gastrointestinal symptoms or disease, current use of medication known to affect gastrointestinal function or appetite, cigarette smoking, or intake of >20 g alcohol/d. The Royal Adelaide Hospital Research Ethics Committee approved the study protocols, and the studies were initiated between May 2003 to July 2008. All subjects provided informed written consent before their inclusion.

Study design

Data from 8 published studies (7, 8, 19, 24–30), which represented all studies conducted in our laboratory that used identical methodologies and techniques and evaluated the same outcome measures, were pooled for analysis. The data were analyzed by using the same statistical tests that would be appropriate for a full meta-analysis, although it is inappropriate to refer to the current study as such because the included studies were not identified through a systematic review (32).

Study protocols

Each study evaluated the effects of either intraduodenal nutrient infusions (8, 24–29) or intravenous hormone infusions...
on antropyloroduodenal motility, gastrointestinal hormone release, appetite, and energy intake. Intraduodenal or intravenous infusions, rather than oral ingestion, were used in these studies to bypass orosensory and gastric influences on gut function and appetite. Energy intake was assessed at the end of the duodenal nutrient-infusion period or during the final 30 min of the intravenous hormone infusion by using a cold buffet-style meal. The treatments and infusion periods in each of the studies varied, and the protocol details are provided in Table 1.

In all studies, subjects arrived in the laboratory after an overnight fast. A 16-channel catheter (Dentsleeve International Ltd, Mississauga, Canada) for the assessment of pressures in the antropyloroduodenal region was inserted through an anesthetized nostril into the stomach and was allowed to pass into the duodenum by peristalsis (22). Six side holes (channels 1–6) were positioned in the antrum, a 4.5-cm sleeve sensor (channel 7) with 2 channels present on the back of the sleeve (channels 8 and 9) was positioned across the pylorus, and 7 side holes (channels 10–16) were positioned in the duodenum. Side holes were spaced at 1.5-cm intervals. An additional channel, positioned 11.75 cm distal to the pylorus, was used for intraduodenal infusion of nutrients or saline control (8, 24–29). The most distal antral channel (channel 6, 240 mV) and the most proximal duodenal channel (channel 10, 0 mV) were perfused with degassed 0.9% saline so that the position of the catheter could be monitored continuously through measurement of the transmucosal potential difference (22). For this purpose, an intravenous cannula was placed subcutaneously in the left forearm and filled with sterile saline as a reference electrode (22). All other channels were perfused with degassed, distilled water at 0.15 mL/min. For intravenous infusions of saline, cholecystokinin-8 or GLP-1, an intravenous cannula was placed in the right arm (7, 19, 30). A second intravenous cannula was inserted into a left forearm vein for blood sampling, and blood samples were obtained at regular intervals during the studies. Gastrointestinal perceptions were assessed at regular intervals by using a validated visual analog scale (VAS) questionnaire (33). At the end of each infusion, subjects were extubated and offered a cold buffet-style meal to consume freely for ≥30 min until comfortably full. The meal consisted of white and whole-meal breads, cold meats, cheese, lettuce, tomato, cucumber, mayonnaise, butter, apple, banana, yoghurt, chocolate custard, fruit salad, iced coffee, orange juice, and water, and the quantities of food offered were in excess of what the subjects were expected to eat (19).

Data analyses

The variables assessed in each study are detailed in Table 2. Manometric pressures were digitized and recorded on a computer-based system that ran commercially available software (HAD; A/Prof GS Hebbard, Royal Melbourne Hospital, Melbourne, Australia) and stored for subsequent analyses. Antropyloroduodenal pressures were analyzed for 1) the number and amplitude of antral and duodenal pressure waves (PWs) and 2) the basal pyloric pressure and number and amplitude of isolated pyloric PWs (IPPWs) by using previously described criteria (34, 35). Antral and duodenal PWs were expressed as total numbers and mean amplitudes (mm Hg). IPPWs, defined as PWs that occur in the absence of PWs on adjacent antral and...
duodenal channels, were characterized by the peak number during the infusion, the time to peak number (min), number of IPPWs premeal (ie, immediately before the buffet meal), total number, and area under the curve (AUC; calculated by using the trapezoidal rule as a measure over the entire infusion period) (min), and AUC of the amplitude of IPPWs (mm Hg \cdot min). Basal pyloric pressure, or tone, was expressed as the peak pressure (mm Hg), time to peak pressure (min), and AUC (mm Hg \cdot min).

For subsequent analysis of cholecystokinin, PYY, and GLP-1 concentrations, venous blood samples were collected in ice-chilled EDTA-treated tubes containing 400 kIU aprotinin (Trasyol; Bayer Australia Ltd, Pymble, Australia)/mL blood. Plasma was obtained by centrifugation of blood samples at 3200 rpm for 15 min at 4°C, and plasma was frozen at −70°C for subsequent analysis of cholecystokinin (7, 8, 19, 25–29), GLP-1 (8, 19, 26, 28), and PYY (7, 24, 25, 27, 29, 30) concentrations by radioimmunoassays. Plasma cholecystokinin, PYY, and GLP-1 concentrations were expressed as AUC (pmol \cdot min \cdot L^{-1}) and plasma concentrations premeal (pmol/L), and for plasma cholecystokinin concentrations, peak concentrations (pmol/L) and the time to peak concentrations (min) were calculated. The latter were not calculated for plasma PYY and GLP-1 because these did not generally reach a peak, but continued to rise, throughout the infusion periods.

Appetite perceptions were rated by using a validated VAS questionnaire (33). Nausea and bloating were also assessed. Each VAS consisted of a 100-mm horizontal line, where 0 represented a sensation not felt at all and 100 represented that the sensation felt the greatest. Subjects placed a vertical mark along the line to indicate the strength of the sensation felt at that particular time point. All data were expressed as AUC (mm \cdot min). Energy intake (kJ) was quantified by weighing the buffet meal before and after consumption and with the Foodworks 3.01 software program (Xyris Software, Highgate Hill, Australia) (19).

Statistical analyses

Data are reported as means (±SEMs), unless stated otherwise. To assess the strength of the bivariate relations between each motility, hormone, and perception variable with energy intake, within-subject correlations that were adjusted for repeated measures were performed (36). The independent effects of each motility, hormone, and perception variable on energy intake were assessed by entering the variables simultaneously into a multivariable maximum-likelihood linear mixed-effects model that was adjusted for repeated visits per subject and the clustering of subjects within studies (37). This is equivalent to the one-step analysis approach in a meta-analysis of individual participant data (38). All variables were included in the multivariable model except when collinearity (defined as $r > 0.7$) was present. In this case, of the related variables from within the same underlying motility, hormone, or perception variables, only one was selected for inclusion into the model to ensure the robustness of the regression estimates. This variable was selected on the basis of consistency across studies and the strength of bivariate associations with energy intake. Because all variables were not measured in all studies (Table 1), the multivariable analysis was conducted as 3 separate models. Model 1 included variables that were measured in all 8 studies. Model 2 included all variables in model 1 plus PYY (6 studies), and model 3 included all variables from model 1 plus GLP-1 (4 studies). To test for potential selection effects, model 1 was rerun on the 4 studies used in model 3 to ensure that a particular variable was not identified as independent depending on which studies were included in the model and to ensure that no variables were underrepresented. Analyses were conducted with SPSS 17 software (2008; SPSS Inc, Chicago, IL). Significance was determined at $P < 0.05$.

RESULTS

Bivariate correlation analyses

Within-subject correlations between energy intake and each of the measured variables are presented in Table 3. Collinearity was present between a number of variables; thus, only one could be entered into the multivariate model to guarantee a robust estimation of the regression effects. Within the variables characterizing IPPWs, peak number, total number, and AUC of the number were strongly associated with each other (all $r > 0.74$). Of these, the peak number was selected for inclusion in the multivariable model because it exhibited the strongest correlation with energy intake. Of the cholecystokinin variables, the peak concentration was strongly correlated with both AUC and premeal concentrations (both $r > 0.85$), and thus peak concentration was selected because, of those 3 variables, it best characterized the cholecystokinin response. For PYY and GLP-1, premeal concentrations were strongly associated with the corresponding AUCs (both $r > 0.84$); thus, AUCs were included in the multivariable model because they best characterized these hormone profiles. Of the appetite-related scores, hunger, desire to eat, and prospective consumption were strongly correlated with each other (all $r > 0.82$); thus, prospective consumption was included in the model because it showed the strongest correlation with energy intake. All other variables were entered automatically into the multivariable model because of the absence of any multicollinearity.

Multivariable mixed-effects models

In all 3 models, the peak number of IPPWs, peak plasma cholecystokinin concentration, and AUC for nausea were consistently identified as independent predictors of energy intake (all $P < 0.05$; Table 4) so that an increase in each of these variables by 1 PW, 1 pmol/L, and 1 mm \cdot min, while controlling for all other variables, was associated with a reduction in energy intake by $\approx 36$, $\approx 88$, and $\approx 0.4$ kJ, respectively.

In addition, models 1 and 2 indicated that the number of IPPWs premeal was independently associated with energy intake ($P < 0.05$). However, in contrast to the peak number of IPPWs, an increase in the number of IPPWs premeal by 1 PW was associated with an increase in energy intake of $\approx 19$ kJ.

Model 2 further identified the time to peak number of IPPWs and peak basal pyloric pressure, but not the plasma PYY concentration, as significantly associated with energy intake (all $P < 0.05$; Table 4). An increase in the time to peak number of IPPWs by 1 min, while controlling for all other variables, was associated with a reduction in energy intake of $\approx 10$ kJ. In contrast, an increase in the peak basal pyloric pressure by 1 mm Hg increased the energy intake by $\approx 68$ kJ. Finally, model 3 indicated
that the plasma GLP-1 concentration was not an independent predictor of energy intake. The robustness of the results was confirmed by rerunning model 1 (a complete set of variables) on the subset of 4 studies that were used in model 3 (data not shown). Despite the reduction in the number of studies included in the model from 8 to 4, the peak number of pyloric pressures, plasma cholecystokinin concentrations, and nausea were identified as independent determinants of energy intake, which confirmed the results.

**DISCUSSION**

Our study provides evidence of a direct relation between energy intake with specific changes in gastrointestinal motility and gut hormones. When controlling for all other variables, the peak number of isolated pyloric-pressure waves, peak plasma cholecystokinin concentrations, and AUC of nausea were consistently (i.e., in all 3 statistical models) identified as independent predictors of acute energy intake in healthy men.

It has long been assumed that acute changes in gastrointestinal function in response to nutrient ingestion, which serve to optimize digestion and absorption of nutrients, also play a key role in the regulation of energy intake. For example, in dogs, electrical stimulation of the pylorus, which increases both tonic and phasic pyloric pressures, is associated with a suppression of energy intake (39), which agrees with our recent finding of an inverse relation between the stimulation of pyloric pressures and subsequent energy intake (7). Although this latter study did not establish a causal association, the outcome of the extensive statistical analyses performed in the current study strongly supports this concept. Thus, the magnitude of stimulation of IPPWs (specifically the peak number) independently determines the degree of suppression of acute energy intake. Because pyloric stimulation is a major determinant of the slowing of gastric emptying (22), it is possible that prolongation of gastric filling underlies the pyloric effects. However, as in all our studies (7, 8, 19, 24–30), the stomach was empty, so it is clear that pyloric pressures may have a suppressant effect on energy intake, even in the absence of gastric filling. The number of IPPWs premeal and peak basal pyloric pressure indicated that pyloric pressures may have a suppressant effect on energy intake, even in the absence of gastric filling. However, as in all our studies (7, 8, 19, 24–30), the stomach was empty, so it is clear that pyloric pressures may have a suppressant effect on energy intake, even in the absence of gastric filling.

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n²</th>
<th>Mean ± SD</th>
<th>r</th>
<th>P</th>
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<tr>
<td>Antral pressure waves</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Number</td>
<td>88</td>
<td>44.2 ± 79.7</td>
<td>0.12</td>
<td>0.068</td>
</tr>
<tr>
<td>Amplitude (mm Hg)</td>
<td>88</td>
<td>31.0 ± 26.8</td>
<td>0.23</td>
<td>&lt;0.001</td>
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<td>Isolated pyloric-pressure waves</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number premeal/15 min</td>
<td>84</td>
<td>7.5 ± 10.3</td>
<td>−0.06</td>
<td>0.366</td>
</tr>
<tr>
<td>Peak number/15 min</td>
<td>84</td>
<td>20.7 ± 12.9</td>
<td>−0.30</td>
<td>&lt;0.001</td>
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<tr>
<td>Time to peak number (min)</td>
<td>84</td>
<td>25.8 ± 20.0</td>
<td>−0.10</td>
<td>0.166</td>
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<tr>
<td>Total number</td>
<td>88</td>
<td>43.6 ± 60.6</td>
<td>−0.12</td>
<td>0.052</td>
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<tr>
<td>AUC of number (min)</td>
<td>84</td>
<td>793 ± 833</td>
<td>−0.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC of amplitude (mm Hg - min)</td>
<td>84</td>
<td>2296 ± 1622</td>
<td>−0.16</td>
<td>0.015</td>
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<td>Basal pyloric pressures</td>
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<tr>
<td>Peak pressures (mm Hg)</td>
<td>85</td>
<td>4.5 ± 5.2</td>
<td>−0.09</td>
<td>0.197</td>
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<tr>
<td>Time to peak pressures (min)</td>
<td>85</td>
<td>30.2 ± 24.7</td>
<td>0.20</td>
<td>0.005</td>
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<tr>
<td>AUC (mm Hg - min)</td>
<td>86</td>
<td>86 ± 236</td>
<td>−0.23</td>
<td>&lt;0.001</td>
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<td>Duodenal pressure waves</td>
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<tr>
<td>Number</td>
<td>88</td>
<td>450 ± 396</td>
<td>0.29</td>
<td>&lt;0.001</td>
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<tr>
<td>Amplitude (mm Hg)</td>
<td>88</td>
<td>27.0 ± 7.9</td>
<td>0.14</td>
<td>0.029</td>
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<tr>
<td>Plasma cholecystokinin</td>
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<tr>
<td>Premeal (pmol/L)</td>
<td>82</td>
<td>6.9 ± 6.5</td>
<td>−0.42</td>
<td>&lt;0.001</td>
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<tr>
<td>Peak concentration (pmol/L)</td>
<td>82</td>
<td>8.5 ± 8.1</td>
<td>−0.33</td>
<td>&lt;0.001</td>
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<td>Time to peak (min)</td>
<td>82</td>
<td>29.8 ± 28.3</td>
<td>0.02</td>
<td>0.784</td>
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<td>AUC (pmol - min - L⁻¹)</td>
<td>76</td>
<td>647 ± 800</td>
<td>−0.38</td>
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<td>Plasma peptide YY</td>
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<tr>
<td>Premeal (pmol/L)</td>
<td>59</td>
<td>114.7 ± 136.4</td>
<td>−0.23</td>
<td>0.005</td>
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<tr>
<td>AUC (pmol - min - L⁻¹)</td>
<td>59</td>
<td>6933 ± 10,458</td>
<td>−0.22</td>
<td>0.006</td>
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<tr>
<td>Plasma GLP-1</td>
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<td></td>
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<td></td>
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<tr>
<td>Premeal (pmol/L)</td>
<td>38</td>
<td>21.3 ± 17.3</td>
<td>−0.24</td>
<td>0.012</td>
</tr>
<tr>
<td>AUC (pmol - min - L⁻¹)</td>
<td>38</td>
<td>1936 ± 1424</td>
<td>−0.20</td>
<td>0.041</td>
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<td>Gastrointestinal perceptions (mm - min)</td>
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<td></td>
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<tr>
<td>AUC hunger</td>
<td>84</td>
<td>−853 ± 1838</td>
<td>0.21</td>
<td>0.001</td>
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<tr>
<td>AUC desire to eat</td>
<td>84</td>
<td>1044 ± 1910</td>
<td>0.24</td>
<td>&lt;0.001</td>
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<td>AUC prospective consumption</td>
<td>84</td>
<td>1065 ± 1777</td>
<td>0.31</td>
<td>&lt;0.001</td>
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<tr>
<td>AUC fullness</td>
<td>84</td>
<td>1745 ± 1838</td>
<td>−0.12</td>
<td>0.080</td>
</tr>
<tr>
<td>AUC nausea</td>
<td>84</td>
<td>297 ± 968</td>
<td>−0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUC bloating</td>
<td>84</td>
<td>838 ± 1447</td>
<td>−0.28</td>
<td>&lt;0.001</td>
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</table>

¹ AUC, area under the curve; GLP-1, glucagon-like peptide 1.
² Variations in the number of subjects (n) for the various variables due to missing data.
The peak stimulation of both IPPWs and plasma cholecystokinin occurred 15–30 min after commencement of the intraduodenal nutrient or intravenous hormone infusions (8, 19, 24–30), and these responses had diminished by the time energy intake was assessed, which is consistent with the concept that the information was encoded in the brain and translated into a suppression in energy intake even after a temporal delay, yet still inversely proportional to the maximum pyloric and cholecystokinin stimulation that occurred 60–90 min earlier. This relation clearly warrants further investigation in prospective studies, but the finding offers initial insights as to how information on the extent of peripheral nutrient or hormonal stimulation may be conveyed to and then used by the brain to determine subsequent energy intake.

The effects of PYY (3–36), the active metabolite of PYY, on energy intake have been the subject of much debate, with a number of studies (5, 43) that reported profound suppressant effects of ~30% in lean and obese humans, whereas extensive studies (18) in rodents showed no such effects. A study by Degen et al (44) provided a conceivable explanation for this major discrepancy by showing that the suppressant effect of PYY (3–36) on energy intake in humans is only apparent at pharmacologic doses and coincides with the induction of nausea. Thus, our finding that PYY is not an independent predictor of energy intake is not surprising, particularly because the vast majority of individuals did not experience overt nausea or other adverse effects during any of the treatment conditions. The fact that cholecystokinin stimulates the release of PYY (30), an
action mediated by cholecystokinin-1 receptors (45), may explain, at least in part, why PYY was not identified as an independent predictor of energy intake. Data relating to the role of GLP-1 in the regulation of energy intake are also inconsistent. Although many studies (17, 46, 47) observed that intravenous infusion of GLP-1 suppresses energy intake, other studies (19, 20, 48, 49) showed no effect. We did not identify plasma GLP-1 concentrations as an independent predictor of energy intake. Other gut peptides, including ghrelin and pancreatic polypeptides, have also been reported to modify energy intake in humans (50, 51). We were unable to identify the potential contribution of these peptides.

Our findings of correlations between appetite perceptions and subsequent energy intake confirm data from a previous study (33) in young and older subjects and are not surprising. In contrast, our analyses indicated that appetite perceptions are not determinants of energy intake. Perhaps this result can be explained by our study design: intraduodenal infusion of nutrients or intravenous administration of gut peptides may not elicit the same feelings of fullness and satisfaction compared with oral meal ingestion, because both orosensory and gastric mechanisms are bypassed. Alternatively, it may suggest that the degree of hunger preceding a meal is not a good predictor of the amount consumed at that meal. Nausea was identified as an independent predictor of energy intake. We cannot entirely exclude the possibility that nausea occurred as a result of the direct intraduodenal nutrient or intravenous hormone administrations used in all of our studies, but it is important to emphasize that, on average, nausea scores did not increase by \( >\) 10%. Hence, the statistical outcome of nausea as an independent predictor of energy intake is based on very modest changes and suggests that energy intake may be regulated, at least in part, by subtle feelings of nausea that were only perceived subconsciously by the subjects. That said, our analyses also indicated that the contribution of nausea to the suppression of energy intake was very small, particularly when compared with the effects of prilocic stimulation and cholecystokinin. More research is required to determine how nausea may be part of the spectrum of appetite perception.

Some limitations of the study need to be recognized. Because all of our studies were performed in healthy, lean men, we cannot draw any firm conclusions regarding outcomes in women, increasing body weight, or age. Only subsets of studies evaluated plasma PYY and GLP-1 concentrations, which may have influenced the statistical outcomes; however, the SEs for these variables remained within reasonable limits, which indicated a sufficient statistical power, and the main outcomes were confirmed when model 1 was repeated including only the 4 studies included in model 3. Although the studies were performed over a number of years, the techniques, equipment, and calibration methods that were used were identical, and the within-subject reproducibility of our techniques is very good (52). Moreover, interindividual variations in responses were taken into account by using a multivariable mixed-effects model that is appropriate for this type of data analysis.

In conclusion, our findings provide strong evidence that pyloric pressures, plasma cholecystokinin concentrations, and nausea are independent predictors of acute energy intake in healthy men. The evaluation of these variables as determinants of energy intake and their potential as screening tools for the appetite-suppressant potency of novel, gut-focused, therapeutic agents in prospective studies would be of interest. Strategies modulating these gastrointestinal functions to regulate energy intake have the potential to lead to novel approaches for the prevention and management of obesity.

The authors’ responsibilities were as follows—RVS, KL, and CF-B: study design, statistical analysis, data interpretation, and drafting of the manuscript; TJL and MH: data interpretation and drafting of the manuscript; AJS: data analysis; RVS, TJL, IMB, ANP, KLF, MH, and CF-B: performance of the original studies; and CF-B: overall responsibility for the study. None of the authors had a personal or financial conflict of interest.

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