Evaluation of appetite regulation in lean and obese individuals

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Ixchel Maya Brennan

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<table>
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<th>Full Form</th>
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<tbody>
<tr>
<td>3-D</td>
<td>three-dimensional</td>
</tr>
<tr>
<td>AP</td>
<td>adequate-protein</td>
</tr>
<tr>
<td>APD</td>
<td>antropyloroduodenal</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>CCK</td>
<td>cholecystokinin</td>
</tr>
<tr>
<td>CHO</td>
<td>carbohydrate</td>
</tr>
<tr>
<td>CV</td>
<td>coefficient of variation</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
</tr>
<tr>
<td>HC</td>
<td>high-carbohydrate</td>
</tr>
<tr>
<td>HF</td>
<td>high-fat</td>
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<tr>
<td>HP</td>
<td>high-protein</td>
</tr>
<tr>
<td>IPPWs</td>
<td>isolated pyloric pressure waves</td>
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<td>intravenous</td>
</tr>
<tr>
<td>LH</td>
<td>luteinizing hormone</td>
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<tr>
<td>LOX</td>
<td>loxiglumide</td>
</tr>
<tr>
<td>LP</td>
<td>low-protein</td>
</tr>
<tr>
<td>MMC</td>
<td>migrating motor complex</td>
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<td>pressure waves</td>
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<tr>
<td>PWSs</td>
<td>pressure wave sequences</td>
</tr>
<tr>
<td>PYY</td>
<td>peptide YY</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
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<tr>
<td>TMPD</td>
<td>transmucosal potential difference</td>
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<tr>
<td>VAS</td>
<td>visual analogue scale questionnaire</td>
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<td>VLCD</td>
<td>very-low calorie diet</td>
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THESIS SUMMARY

The research presented within this thesis has focussed on the complex and interrelated postprandial gastrointestinal mechanisms involved in the regulation of appetite and energy intake. The three broad areas that have been investigated include: (i) the effect of gastrointestinal hormones on gastric motility, gastrointestinal hormone release/suppression, appetite and energy intake in healthy lean subjects, (ii) the effect of oral macronutrients on appetite and energy intake in both lean and obese subjects and (iii) the effects of acute energy restriction on gastrointestinal motility, gastrointestinal hormone release, appetite and energy intake in obese subjects.

Following meal ingestion, the presence of nutrients in the small intestine stimulate small intestinal receptors that trigger a number of gastrointestinal mechanisms within ~ 15 minutes; these include the modulation of gastric emptying and gastrointestinal motility and the release, or suppression, of gastrointestinal hormones i.e. cholecystokinin (CCK), peptide-YY (PYY), glucagon-like peptide-1 (GLP-1) and ghrelin. Hence, it is conceivable that interactions occur between one or more of these stimuli. The study in Chapter 5 assessed possible interactions between intravenous CCK (1.8 pmol/kg/min) and GLP-1 (0.9 pmol/kg/min) that may modulate ghrelin and PYY release. At the doses evaluated, exogenous CCK-8 and GLP-1 had discrepant effects on the secretion of ghrelin and PYY; CCK-8
markedly suppressed ghrelin whereas GLP-1 had no effect, and the stimulation of PYY by CCK-8 was attenuated markedly by GLP-1.

Of the gastrointestinal hormones modulated following nutrient ingestion, CCK and its role in appetite regulation has been studied the most comprehensively. A recent study from our laboratory using exogenous CCK-8 suggested that the ability of CCK to suppress appetite and energy intake were mediated, at least in part, by its actions on the gastrointestinal tract. However, the plasma CCK concentrations resulting from this study were moderately supraphysiological and infusion of CCK-8 was associated with an increase, albeit modest, in nausea. The effects of increasing doses of CCK-8 on gastrointestinal motility, gut hormone release and the relationships between these effects with those on hunger and energy intake had not hitherto been assessed in humans. In Chapter 6, exogenous CCK-8 stimulated pressures in the pylorus, increased plasma PYY concentrations and suppressed desire-to-eat and energy intake in a dose-dependent manner, while all CCK-8 doses equally suppressed ghrelin. There were relationships between plasma CCK with basal pyloric pressure and isolated pyloric pressure waves, and energy intake with isolated pyloric pressure waves.

The prevalence of obesity is rapidly increasing, the cause of which is related, in part, to the readily available supply of high-fat, energy-dense foods. Recent data indicate that there are more than 250 million obese people worldwide, representing ~ 7 % of the adult population. There is evidence that gastrointestinal function in obesity is modified, which may be the result of the eating habits of obese
individuals, and in turn, may also contribute to the maintenance of obesity by causing insufficient suppression of energy intake. However, much of the literature relating to gastrointestinal function in the obese is inconclusive and controversial. A better understanding of any adaptations that occur in obesity is important, particularly in regards to treatment approaches for weight loss.

Protein is considered to be the most satiating macronutrient and studies have demonstrated that consumption of dietary protein reduces appetite and *ad libitum* energy intake when compared with either carbohydrate or fat. One option in the dietary management of obesity has been to replace some carbohydrate in the diet with protein, which has been demonstrated to facilitate loss of fat and blunt loss of lean mass. However, there are discrepancies in the ranking of macronutrients and not all studies demonstrate that protein is more satiating than carbohydrates or fat. Furthermore, studies that have demonstrated effects of high-protein preloads on appetite and energy intake have often used preloads consisting of ~ 60 % protein. Thus, it is plausible that the observed effects may have been due to excessive amounts of protein in the test meal; such meals would be less palatable, which may also lead to reduced energy intake. Since there may be differences in the regulation of gastrointestinal motor function, gastrointestinal hormone release, appetite and energy intake between lean and obese individuals, it is likely that ingestion of individual macronutrients may also have different effects on these parameters, which might have implications for the dietary treatment of obesity.
The study in Chapter 7 evaluated the effects of high-protein, high-fat and high-carbohydrate test meals, and increasing amounts of protein in a test meal, on appetite and energy intake in lean and obese subjects. In addition, the study compared these responses between lean and obese subjects. In lean, but not obese, subjects, hunger was less, and fullness increased, following ingestion of the HF and HP meals. In addition, energy intake was reduced in lean subjects following the HF and HP meals when compared with the HC meal, while in obese subjects, the HP and AP meals reduced energy intake when compared with the HF and HC meals, and HC meal, respectively. When these responses were compared, the percentage change in energy intake between the HF and AP test meals was significantly different between lean and obese, suggesting that obese subjects may be less sensitive to the satiating effects of fat.

The studies presented in the subsequent two chapters (Chapters 8 and 9) investigated the contribution of factors that may influence the effects of oral macronutrients on gastrointestinal function, appetite and energy intake. While young, lean males are the subject group most capable of adjusting their energy intake in response to caloric manipulation, it has been observed that significant inter-individual variation occurs within this group. Therefore, it was important to evaluate whether there was a day-to-day variability in gastrointestinal function, including gastric emptying and gastrointestinal hormone secretion, and if so, how these variations influenced temporal changes in appetite and energy intake. The study in Chapter 8 demonstrated that, in a laboratory setting, appetite perceptions and energy intake in response to a nutrient preload in healthy lean men were
highly reproducible, and that this consistency in energy intake was associated with reproducible patterns of gastric emptying and insulin and CCK secretion.

A major reason that females are used less frequently than males in research studies assessing gastrointestinal function, appetite and energy intake is the perceived confounding effect of the menstrual cycle on these parameters. There is evidence that fluctuations in hormone levels over the menstrual cycle affect energy intake, such that hunger and energy intake are less during the follicular phase and increased during the luteal phase. How this modulation of appetite and energy intake would be related to changes in gastrointestinal function, i.e. gastric emptying and gastrointestinal hormone release, remained unclear. The study described in Chapter 9 demonstrated that gastric emptying was slower, and glycaemia, plasma GLP-1 and insulin responses, hunger and energy intake were less, during the follicular when compared with the luteal phase. Moreover, energy intake and the glucose, plasma GLP-1 and insulin responses were related to gastric emptying. In addition, these parameters were reproducible when assessed twice within the follicular phase of the menstrual cycle.

There is evidence that both previous patterns of macronutrient intake and fasting affect gastrointestinal function. In the context of obesity, both are of relevance. For example, in humans after a high-fat diet for 2 weeks, gastric emptying and mouth-to-caecum transit in response to a high-fat test meal were faster. In contrast, fasting has the opposite effect and a 4-day fast slowed gastric emptying of a glucose drink in both lean and obese subjects, suggesting that a reduction in
nutrient exposure may increase the sensitivity of gastrointestinal responses to nutrients in the obese. The study in Chapter 10 demonstrated that following a four-day very-low calorie diet (VLCD) there was a significant increase in basal pyloric pressure and the number and amplitude of isolated pyloric pressure waves, and a decrease in the number of antral and duodenal pressure waves and pressure wave sequences, during a 120 minute intraduodenal lipid infusion. In addition, following the four-day VLCD, hunger and prospective consumption scores were lower, and energy intake was reduced, indicating that gastrointestinal function, appetite and energy intake in the obese can be modified over a short period of time.

The studies reported in this thesis provide new information relating to the regulation of appetite and energy intake by gastrointestinal motor function and hormone release and/or suppression, in healthy lean and obese subjects. These observations will contribute to advances in basic appetite physiology and have clinical implications for further development of dietary interventions for successful treatment of obesity.
STATEMENT OF ORIGINALITY

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Ixchel Brennan
June 2009
DEDICATION

This thesis is dedicated to
my mother, Kathleen Winifred Brennan
and to
my grandmother, Winifred Royal Brennan.

My first teachers.

I am indebted to your selfless, extraordinary commitment to my education. I am forever grateful to you both for giving me the courage to think for myself, for helping me learn to persevere and work hard to succeed and achieve my goals, and for instilling within me the confidence that I am capable of doing anything I put my mind to.
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PUBLICATIONS ARISING FROM THESIS


OTHER PUBLICATIONS


