ORAL AND SMALL INTESTINAL SENSITIVITY
TO FATS IN LEAN AND OBESE HUMANS:
IMPLICATIONS FOR ENERGY INTAKE REGULATION IN OBESITY

A thesis submitted by

Radhika Seimon

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The research presented in this thesis focuses on the complex and interrelated oral and gastrointestinal mechanisms involved in the regulation of appetite and energy intake in lean and obese individuals. The three broad areas of research that have been investigated in the thesis include: i) the gastrointestinal motor and hormonal functions involved in the regulation of energy intake in healthy individuals; ii) the effects of oral and intraduodenal nutrients on gastrointestinal motility and hormone release, appetite and energy intake in obese compared with lean individuals; and iii) the effects of acute and prolonged energy restriction on gastrointestinal function, appetite and energy intake.

Following ingestion of a meal, the interaction of nutrients with receptors in the small intestinal lumen modulates gastropyloroduodenal motility, stimulates the release of gastrointestinal hormones, and suppresses appetite and energy intake. It appears that modulation of gastrointestinal functions, that is, gastrointestinal motility and hormone release/suppression, mediate the regulation of appetite and acute energy intake in humans, at least in part. Changes in motility and hormone secretion occur concurrently with changes in appetite; however, there is little information regarding which, if any, of these factors are independent determinants of energy intake. In the study presented in Chapter 5, we determined independent predictors of energy intake and identified specific changes in gastrointestinal motor and hormone functions (i.e. stimulation of
Abstract

pyloric pressures and plasma cholecystokinin) that are associated with the suppression of acute energy intake in healthy lean males.

The incidence of obesity is rapidly increasing and, currently, the therapies used for the prevention and management of obesity have limited long-term benefits. In addition, the available therapies have largely ignored the pivotal role of the gastrointestinal tract in the regulation of appetite. 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.

There is also evidence that previous patterns of energy intake, in excess or in restriction, even when sustained for short periods, have the capacity to modify gastrointestinal function and energy intake. For example, in humans following a high fat diet for two weeks, gastric emptying and mouth-to-caecum transit in response to a high fat test meal were faster. In contrast, fasting had the opposite effect and a four-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.
Abstract

Although many studies have addressed aspects of gastrointestinal function in the obese, there is a lack of studies that have evaluated gastric emptying and gastrointestinal hormone release specifically GLP-1 and GIP, given the risk of diabetes in obesity, as well as previous patterns of nutrient intake concurrently. In the study presented in Chapter 6, we evaluated the effects of oral ingestion of a nutrient liquid on gastric emptying, oro-caecal transit, plasma GLP-1 and GIP, appetite and energy intake, as well as, habitual energy and fat intake in lean, overweight and obese individuals. We reported no differences in gastric emptying, intragastric distribution or oro-caecal transit between the lean, overweight and obese groups. After the drink, blood glucose and plasma insulin were greater in the obese, when compared with both the lean and overweight groups, however, there were no differences in plasma GLP-1 or GIP concentrations, appetite and energy intake at the buffet meal or habitual energy intake between the groups. In the obese, the magnitude of the rise in blood glucose was inversely related to the gastric emptying, suggesting that obesity per se, in the absence of differences in habitual energy intake, has no effect on gastric emptying or incretin hormone release and that gastric emptying influences postprandial blood glucose in the obese.

In Chapter 7, we investigated the hypothesis that gastrointestinal and oral sensitivity to fat is compromised in the obese and directly related to their high fat/energy consumption. For this purpose, we investigated the effects of an intraduodenal infusion (to bypass gastric emptying), of a fatty acid (oleic acid) on gastrointestinal function, appetite and energy intake, and relationships with habitual energy intake and oral fatty acid detection threshold in lean and obese individuals. We report that pyloric pressure,
which plays a major role in the regulation of gastric emptying, was lower in response to intraduodenal oleic acid infusion, with trends for reduced cholecystokinin stimulation and energy intake responses in the obese compared with lean. Oral fatty acid detection thresholds were higher in obese compared with lean subjects, and obese subjects also had greater habitual energy and fat intakes than lean subjects. The results suggest that the ability to detect fats both orally and within the gastrointestinal tract is compromised in obese males, probably due to their increased fat consumption.

In the study presented in Chapter 8, we evaluated the hypothesis that in obese individuals, the effects of duodenal fat on gastrointestinal motor and hormone function, and appetite would be enhanced by a short period on a very low calorie diet. We demonstrated that following a 70% four-day very low calorie diet there was a significant increase in pyloric pressure and the stimulation of PYY and suppression of ghrelin was greater during an intraduodenal lipid infusion. In addition, following the four-day very low calorie diet, appetite perceptions and energy intake in response to intraduodenal lipid were reduced, indicating that gastrointestinal function, appetite and energy intake in obese can be enhanced over a short period.

Given that gastrointestinal function is sensitive to changes even over short periods of dietary restriction, it is important to determine whether these changes are maintained in the long term in order to determine the efficacy of energy restriction therapies for obesity. To maintain dietary restriction and weight loss in the longer term, we used a 30%, as opposed to 70%, energy-restricted diet. In the study presented in Chapter 9, we evaluated the effects of an acute (in lean and obese) and prolonged (in obese only)
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30% energy restriction on gastrointestinal function and appetite in response to an intraduodenal lipid infusion. In contrast to the previous 70% very low calorie diet study, there were no differences in gastrointestinal motor or hormonal function in the obese following the acute or prolonged 30% dietary restriction period, although there was a trend for energy intake to be reduced. However, in the lean, there was a decrease in plasma CCK and an increase in ghrelin concentrations following the acute period of dietary restriction with no differences in gastrointestinal motility or energy intake, suggesting that a 30% energy-restricted diet diminishes gastrointestinal hormone responses in lean, but not obese, which may suggest that obese are less sensitive to this caloric restriction.

These observations will contribute to the advances in basic appetite physiology and will have clinical implications for further development of dietary interventions for the treatment of obesity.
Declaration of Originality

I, Radhika Seimon, certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Radhika Seimon

March 2012
Publications Arising from This Thesis

The data presented in this thesis have formed the basis for the publications listed below:


Dedication

To my late mother and to my father.

For your unconditional love and sacrifices,

For your continual support and encouragement, and

For your selflessness,

I am forever grateful.
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The studies reported in this thesis were performed in the Discipline of Medicine, University of Adelaide and the Department of Nuclear Medicine, PET and Bone Densitometry at the Royal Adelaide Hospital. While conducting this research, I was financially supported by a Dawes Postgraduate Research Scholarship (2009–2012), jointly provided by the Royal Adelaide Hospital and the University of Adelaide.

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<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>APD</td>
<td>antropyloroduodenal</td>
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<td>AUC</td>
<td>area under the cure</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>CCK</td>
<td>cholecystokinin</td>
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<td>carbohydrates</td>
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<td>CV</td>
<td>coefficient of variation</td>
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<td>MI</td>
<td>motility index</td>
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<tr>
<td>MMC</td>
<td>migrating motor complex</td>
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<td>MSG</td>
<td>monosodium glutamate</td>
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<td>PVN</td>
<td>paraventricular nuclei</td>
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<tr>
<td>PW</td>
<td>pressure waves</td>
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<tr>
<td>PWS</td>
<td>pressure wave sequences</td>
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<td>PYY</td>
<td>peptide tyrosine tyrosine</td>
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<tr>
<td>TEI</td>
<td>total energy intake</td>
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<tr>
<td>Acronym</td>
<td>Definition</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</td>
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<td>VLCD</td>
<td>very low calorie diet</td>
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