Gastrointestinal motility and glycaemic control in diabetes

A Thesis submitted by

Dr Reawika Chaikomin
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THESIS SUMMARY

Gastric emptying, and small intestinal glucose exposure and absorption, are potentially important determinants of postprandial blood glucose homeostasis and energy intake. The studies presented in this thesis were designed to provide novel insights into the interrelationships of upper gastrointestinal function with glycaemia and appetite in both health and type 2 diabetes. The issues which were addressed relate in particular to: (i) the physiology, regulation and measurement of gastric and small intestinal motility, (ii) the relationships between small intestinal glucose exposure, incretin hormone release, antropyloroduodenal motility and appetite, and (iii) the impact of gastric and small intestinal motility on glycaemia.

The study reported in chapter 4 evaluated the effect of variations in small intestinal glucose delivery on blood glucose, plasma insulin, and incretin hormone (GLP-1 and GIP) concentrations in healthy subjects. While initially rapid, and subsequently slower, duodenal glucose delivery potentiated incretin and insulin responses when compared to constant delivery of an identical glucose load, the overall glycaemic excursion was not improved. These observations add to the rationale for the use of dietary and pharmacological strategies designed to reduce postprandial glycaemic excursions in health and type 2 diabetes by slowing gastric emptying, rather than initially accelerating it.

Fat is a potent inhibitor of gastric emptying. In chapter 5, the acute effect of slowing gastric emptying by fat, on postprandial glycaemia in type 2 diabetes, has

been evaluated. Ingestion of a small amount of olive oil, as a 'preload' 30 min before a carbohydrate meal, was shown to markedly slow gastric emptying, affect intragastric meal distribution, delay the postprandial rises in blood glucose, plasma insulin, and GIP, and stimulate GLP-1. In contrast, the effects of including the same amount of oil within the meal, on gastric emptying, as well as glycaemic and incretin responses, were relatively modest. As blood glucose levels had not returned to baseline by 210 min (the end of each experiment), effects on the overall glycaemic (or insulinaemic) response could not be determined; this represents a priority for future studies.

The energy content of a meal is a major determinant of its rate of gastric emptying. The study reported in chapter 6 demonstrated that the substitution of an artificial sweetener ("diet" mixer) for sucrose ("regular" mixer) in a mixed alcoholic beverage has a major impact on the rate of gastric emptying and alcohol absorption in healthy adults. - A low calorie alcohol-containing drink (made with "diet" mixer) emptied from the stomach much more rapidly and resulted in higher blood alcohol concentrations when compared with a relatively high calorie alcoholic drink (made with "regular" mixer). These observations highlight the need for community awareness of factors, other than the alcohol content of a beverage, which should be taken into account in considering safe levels of consumption and the potential for inebriation.

Upper gastrointestinal motor function and incretin hormone (GLP-1 and GIP) secretion are known to be major determinants of postprandial glycaemia and

insulinaemia, however, the impact of small intestinal flow events on glucose absorption and incretin release has not been evaluated. In the study reported in chapter 7, intraduodenal pressures and impedance signals were recorded simultaneously in healthy humans, while glucose was infused into the duodenum in the presence and absence of the anticholinergic drug, hyoscine butylbromide. The frequency of duodenal flow events (evaluated by impedance) was suppressed by hyoscine much more than that of duodenal pressure waves, or propagated pressure wave sequences (evaluated by manometry). Blood glucose and plasma 3-OMG concentrations (the latter provide an index of glucose absorption) were lower during hyoscine than saline. Plasma insulin, GLP-1, and GIP concentrations were initially lower during hyoscine. The disparity between impedance measurements and manometry in detecting alterations in flow during hyoscine infusion was marked and, accordingly, supports the potential utility of small intestinal impedance monitoring to evaluate alterations in gastrointestinal transit in various disease states. The observations also indicate that the frequency of small intestinal flow events is a determinant of both glucose absorption and incretin release.

Intraduodenal administration of the local anaesthetic, benzocaine, has been shown to attenuate the release of cholecystokinin (CCK) by small intestinal lipid, and the perceptions of fullness, discomfort, and nausea induced by gastric distension during small intestinal lipid infusion, implying that local neural mechanisms may regulate CCK release in response to intraduodenal nutrients. In chapter 8, the effects of intraduodenal administration of benzocaine on: (i) blood glucose, incretin hormone and insulin concentrations (ii) antropyloroduodenal motility, and (iii) gut

sensations and appetite, in response to an intraduodenal glucose infusion, were evaluated in healthy subjects. Benzocaine attenuated the perceptions of abdominal bloating and nausea, but had no effect on antro-pyloro duodenal motility, blood glucose concentrations, or incretin responses. These observations indicate that the induction of sensations by small intestinal glucose is mediated by local neural pathways.

GLP-1 is released from L-cells whose density is greatest in the distal jejunum and ileum, GIP predominantly from duodenal K cells, and cholecystokinin (CCK) from I cells, which appear confined to the duodenum and jejunum. The study reported in chapter 9 evaluated the effects of infusion of glucose into different gut regions (mid-jejunal vs duodenal) on incretin hormones, CCK, appetite and energy intake in healthy subjects. There was no difference in the incretin responses between infusion at the two sites (85 cm apart), however the stimulation of CCK and suppression of hunger and energy intake, were greater with the duodenal compared to the jejunal infusion. These observations indicate that the site of small intestinal glucose exposure is a determinant of CCK release and appetite.

Both glucose and fat are known to be potent stimuli for incretin secretion, but the effect of protein is uncertain. Protein may also stimulate insulin secretion directly via absorption of amino acids. In the study reported in chapter 10, gastric emptying, and the blood glucose, insulin and incretin responses, alter a 300 mL drink containing 50 g glucose, 25 g protein, or both 50 g glucose and 25 g protein, were evaluated in healthy subjects. This study established that the addition of

protein to an oral glucose load improved the glycaemic response, predominantly by slowing gastric emptying. However, protein also stimulated incretin and insulin secretion. These observations have implications for the use of protein in the dietary management of type 2 diabetes.

The relationship between glycaemia, incretin hormones, appetite suppression and modulation of antropyloroduodenal motility with duodenal glucose delivery is poorly defined. In chapter 11, the effects of intraduodenal glucose infusions at different caloric rates (of 1 kcal/min, 2 kcal/min and 4 kcal/min, or control (saline)) on antropyloroduodenal motility, plasma GLP-1, GIP and CCK, appetite and energy intake have been evaluated in healthy subjects. While there was a rise in blood glucose in response to all the intraduodenal glucose loads, there was no significant difference in the response to infusions at 2 kcal/min and 4 kcal/min. An initial, transient, small rise in GLP-1 was evident, in response to all glucose loads, but a sustained and progressive rise only occurred with the 4 kcal/min infusion. In contrast, a load-dependent stimulation of GIP occurred in response to all glucose infusions. The stimulation of CCK was much greater in response to the 4 kcal/min infusion. While antral pressures were suppressed by all rates of glucose infusion, the stimulation of basal pyloric pressure was load-dependent. Energy intake was suppressed only by the 4 kcal/min infusion. This may potentially reflect the substantially greater stimulation of CCK, consistent with the observations reported in chapter 9. This study establishes that there is a substantial discordance in the acute effects of small intestinal glucose on glycaemia, incretin hormones, CCK, motility and appetite. It is planned to perform measurements of plasma insulin on

the stored samples - these results were, unfortunately, not available at the time of the submission of this thesis and are critical to the overall interpretation of the data.

STATEMENT OF ORIGINALITY

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.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Reawika Chaikomin

December 2006

DEDICATION

To my mother, my father, my grandmother, my father - in - law, my mother - in - law, my sisters, and my husband. - Without their support and ongoing encouragement this would not have been undertaken successfully.

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Completion of this thesis would not have been possible without the support and encouragement of many people. I am sincerely grateful to my supervisors, Professor Michael Horowitz, Dr Karen Jones, and Dr Chris Rayner for their sustained encouragement, patience and intellectual inspiration. All of them undertook the painstaking task of reading this thesis carefully, to minimise the number of errors in my English grammar and spelling, and their contributions to all aspects of my research programme and this thesis have been invaluable. As a result of their guidance, I have learned much about the process of research, as well as the importance of critical thinking and this has also been associated with personal development in many areas.

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This acknowledgement would be incomplete if I omitted to mention some of the numerous experiences (both positive and negative) that occurred during the 3 years and 6 months that I was a PhD student in Adelaide. I knew that the challenges associated with the decision to pursue a PhD and come to Adelaide would be substantial, particularly as I had been married for only 8 months. I was aware that to come to a new country, to interact with new people and in a new environment, successfully, without the support of my family and with relatively poor English skills, would be very difficult. I soon realised that this task would be much harder than I had imagined, but not impossible to achieve if I worked diligently. While a PhD student, I have been treated warmly and supported by many people. There have been unique professional opportunities, including an oral presentation during the 2005 Australian Gastroenterology Week meeting in Brisbane, which was

exciting and terrifying at the same time! It proved very difficult and stressful for me to obtain a visa to visit the USA, but in the end I was successful and was able to present some of my research during the Digestive Diseases Week meeting in Los Angeles and the American Motility Society meeting in Boston (both in 2006). It was very interesting to visit large American cities, but I would not want to live in them! - I had a delicious lobster, and my first clam chowder, in Boston which were very nice, but not as good as the big fish (bream) I caught by myself fishing in a river on Kangaroo Island. While in Adelaide, I also had the chance to go horse riding with my friend Alena, attend the opera (3 times!) and go to a number of classical music concerts with Michael and his family. I was surprised that I enjoyed the music so much, as if was very different to what I knew. I also went to the gym and played squash regularly with my friends, Yan and Niva. - So my life was never boring!

I plan to apply the knowledge and experience that I have gained as a PhD student, to develop my academic and personal skills further. My English has improved a lot (I now don't have difficulty in understanding the majority of jokes in English, which is a good test!) and I have promised myself to make it improve further. I am still very worried about giving lectures in English, but I also know that I can do it. I hope that Adelaide is a place that I can come back again …. and again.

As the American baseball coach/comedian, Yogi Berra, said: "Prediction is very hard, especially when it is about the future".

PUBLICATIONS ARISING FROM THIS THESIS

The material in this thesis formed the basis for the publications list below:

Chaikomin R, Doran S, Jones KL, Feinle-Bisset C, O'Donovan D, Rayner CK, Horowitz M. Initially more rapid small intestinal glucose delivery increases plasma insulin, GIP, and GLP-1 but does not improve overall glycemia in healthy subjects. *Am J Physiol Endocrinol. Metab*. 2005 Sep; 289(3): E504-7.

Gentilcore D, Chaikomin R, Jones KL, Russo A, Feinle-Bisset C, Wishart JM, Rayner CK, Horowitz M. Effects of fat on gastric emptying of and the glycemic, insulin, and incretin responses to a carbohydrate meal in type 2 diabetes. *J Clin Endocrinol Metab.* 2006 Jun; 91(6): 2062-7.

Wu KL, Chaikomin R, Doran S, Jones KL, Horowitz M, Rayner CK. Artificially sweetened versus regular mixers increase gastric emptying and alcohol absorption. *Am J Med*.2006 Sep; 119(9): 802-4.

Chaikomin R, Rayner CK, Jones KL, Horowitz M. Upper gastrointestinal function and glycemic control in diabetes mellitus. *World J Gastroenterol*. 2006 Sep 21; 12(35): 5611-21.

Chaikomin R, Wu KL, Doran S, Jones KL, Smout AJPM, Renooij W, Meyer JH, Holloway RH, Horowitz M, Rayner CK. Concurrent duodenal manometric and impedance recording to evaluate the effects of hyoscine on motility and flow

events, glucose absorption, and incretin hormone release. *Am J Physiol Gastrointest Liver Physiol*. 2007 Jan 4; [Epub ahead of print]

Chaikomin R, Doran S, Jones KL, Horowitz M, Rayner CK. Effects of intraluminal local anesthetic on duodenal glucose sensing in humans. (Submitted for publication).

Chaikomin R, Wu KL, Doran S, Meyer JH, Jones KL, Horowitz M, Rayner CK. Effects of mid-jejunal compared to duodenal glucose infusion on gut hormone release and appetite. (Submitted for publication).

Karamanlis A, Chaikomin R, Doran S, Bellon M, Bartholomeusz FD, Wishart JM, Jones KL, Horowitz M, Rayner CK. Effects of protein on glycemic and incretin responses, and gastric emptying, after oral glucose in healthy subjects. (Submitted for publication).