

**Gastrointestinal motor and sensory function,
and hormone secretion – implications for
postprandial blood glucose regulation
in type 2 diabetes mellitus**

A thesis submitted by

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To my dearest parents, Junbao and Cui'e, and wife Lifang

Thank you for your selfless love and support,

I couldn't have done this without you.

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THESIS SUMMARY

This thesis focuses on the role of gastrointestinal motor and sensory function, and gut hormone secretion, in postprandial blood glucose regulation in health and type 2 diabetes. The key themes relate to: 1) evaluation of the effects of potential dietary and/or pharmacological strategies on gastric emptying, secretion of ‘incretin’ hormones (i.e. glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)), and postprandial glycaemia, 2) effects of intraluminal bile acids on GLP-1 secretion and blood glucose homeostasis, and 3) the role of the sweet taste sensing pathway in gastrointestinal motor, secretory, and absorptive function in health and type 2 diabetes.

Macronutrient ‘preloads’ taken before a meal can stimulate endogenous GIP from the proximal gut, and GLP-1 from the distal gut, slow gastric emptying, and reduce postprandial glycaemic excursions, but entail additional energy intake. The study reported in Chapter 4 evaluates the effects of 1) 3-O-methylglucose (a non-metabolised substrate of sodium glucose co-transporter-1) and 2) a mixture of poorly absorbed tagatose and isomalt, when given as preloads in healthy humans. Since the incretin hormones are rapidly degraded by the enzyme, dipeptidyl peptidase 4 (DPP-4), the study in Chapter 5 evaluates whether the effects of a D-xylose preload (a poorly absorbed, low-energy pentose) could be further optimised by concurrent DPP-4 inhibition with sitagliptin, in patients with type 2 diabetes.

It was recently established that a small dose of lauric acid, delivered to a long segment of distal gut via enteric-coated pellets, can stimulate GLP-1 and attenuate postprandial glycaemia in well controlled type 2 patients. The study reported in Chapter 6 evaluates the glucose-lowering effect of these pellets in less well-controlled type 2 patients, when given concurrently with sitagliptin.

The effects of DPP-4 inhibition on the incretin hormone, glycaemic, and gastrointestinal motor responses to intraluminal glucose have not been well characterised in obesity and type 2 diabetes. It has been suggested that metformin has the capacity to augment plasma GLP-1 concentrations, and may synergise with DPP-4 inhibitors to improve glycaemia in type 2 diabetes. The study described in Chapter 7 examines the effects of sitagliptin on glycaemia and antropyloroduodenal motility in response to intraduodenal glucose infusion in health, obesity, and type 2 diabetes treated with or without metformin.

It is emerging that bile acids function as important signalling molecules, and are essential in blood glucose regulation. In animal models, intraluminal bile acids have been shown to stimulate GLP-1 and peptide YY (PYY) via activation of the TGR5 receptor. The study reported in Chapter 8 evaluates the effects of rectally administered taurocholic acid (TCA) on the release of GLP-1 and PYY in healthy humans. In Chapter 9, the effects of intrajejunal TCA on blood

glucose, GLP-1 and insulin responses to intrajejunal glucose infusion are evaluated.

The mechanisms underlying nutrient detection in the small intestine and consequent stimulation of incretin hormone release are poorly understood. Emerging data support the involvement of intestinal sweet taste receptors (STR) in carbohydrate sensing. In rodents, intestinal STR transcript and protein levels are rapidly down-regulated upon acute luminal exposure to glucose or artificial sweeteners. In Chapter 10, the capacity for the non-caloric artificial sweeteners, sucralose and acesulfame potassium, to stimulate GLP-1 release, slow gastric emptying, and modify postprandial glycaemia when given with oral glucose is evaluated. In Chapter 11, the modulation of duodenal STR expression in response to acute changes in luminal and systemic glucose exposure in healthy humans is assessed, and comparison is made to patients with type 2 diabetes. Furthermore, relationships between STR expression, glucose absorption and gut hormone secretion are examined in both groups.

DECLARATION

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Program: Doctor of Philosophy

I 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. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Wu T, Bound MJ, Standfield SD, Jones KL, Horowitz M, Rayner CK. Effects of taurocholic acid on glycaemic, glucagon-like Peptide-1, and insulin responses to small intestinal glucose infusion in healthy humans. *J Clin Endocrinol Metab.* 2013 Apr;98(4):E718-22.

Wu T, Bound MJ, Standfield SD, Bellon M, Young RL, Jones KL, Horowitz M, Rayner CK. Oral ingestion of artificial sweeteners before glucose has no effect on gastric emptying, glucagon-like peptide-1, postprandial glycaemia, or appetite sensations in healthy humans. *Diabetes Care.* 2013. (In press)

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By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the Paper	TW was involved in study design and coordination, subject recruitment, data collection and interpretation, statistical analysis, and drafting of the manuscript.		
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Name of Co-author	Michelle J Bound		
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Name of Co-author	Max Bellon		
Contribution to the Paper	MB performed gastric emptying analysis.		
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Name of Co-author	Karen L Jones		
Contribution to the Paper	KLJ was involved in conception of the study and data interpretation.		
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Name of Co-author	Michael Horowitz		
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Name of Co-author	Christopher K Rayner		
Contribution to the Paper	CKR was involved in conception and design of the study, data analysis and interpretation and review of the manuscript, and had overall responsibility for the		

	study.		
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Chapter 7.

Title of Paper	Effects of sitagliptin on glycaemia, incretin hormones, and antropyloroduodenal motility in response to intraduodenal glucose infusion in healthy lean and obese humans, and patients with type 2 diabetes treated with or without metformin.
Publication Status	<input type="checkbox"/> Published, <input type="checkbox"/> Accepted for Publication, <input checked="" type="checkbox"/> Submitted for Publication, <input type="checkbox"/> Publication style
Publication Details	Wu T, Ma J, Bound MJ, Checklin H, Jones KL, Horowitz M, Rayner CK. Effects of sitagliptin on glycaemia, incretin hormones, and antropyloroduodenal motility in response to intraduodenal glucose infusion in healthy lean and obese humans, and patients with type 2 diabetes treated with or without metformin. (submitted for publication)

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Name of Co-author	Helen L Checklin		
Contribution to the Paper	HLC assisted data collection.		
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Name of Co-author	Carolyn F Deacon		
Contribution to the Paper	CFD performed plasma glucagon, GLP-1 and GIP assays, and was involved in data interpretation.		
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Contribution to the Paper	KLJ was involved in conception of the study, data interpretation and review of the manuscript		
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Name of Co-author			
Contribution to the Paper	MH was involved in conception of the study, data interpretation and review of the manuscript.		
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Contribution to the Paper	CKR was involved in conception and design of the study, data analysis and interpretation, and review of the manuscript, and had overall responsibility for the study.		
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Chapter 8.

Title of Paper	Effects of rectal administration of taurocholic acid on glucagon-like peptide-1 and peptide YY secretion in healthy humans.
Publication Status	<input checked="" type="checkbox"/> Published, <input type="checkbox"/> Accepted for Publication, <input type="checkbox"/> Submitted for Publication, <input type="checkbox"/> Publication style
Publication Details	Wu T, Bound MJ, Standfield SD, Gedulin B, Jones KL, Horowitz M, Rayner CK. Effects of rectal administration of taurocholic acid on glucagon-like peptide-1 and peptide YY secretion in healthy humans. <i>Diabetes Obes Metab.</i> 2013 May;15(5):474-7.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the Paper	TW was involved in study design and coordination, subject recruitment, data collection and interpretation, statistical analysis, and drafting of the manuscript.		
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Contribution to the Paper	MJB assisted data collection.		
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Name of Co-author	Scott D Standfield		
Contribution to the Paper	SDS performed GLP-1 and PYY assays.		
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Contribution to the Paper	KLJ was involved in conception of the study, data interpretation and review of the manuscript		
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Name of Co-author	Michael Horowitz		
Contribution to the Paper	MH was involved in conception of the study, data interpretation and review of the manuscript.		
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Name of Co-author	Christopher K Rayner		
Contribution to the Paper	CKR was involved in conception and design of the study, data analysis and interpretation and review of the manuscript, and had overall responsibility for the study.		
Signature		Date	22 July 2013

Chapter 9.

Title of Paper	Effects of taurocholic acid on glycaemic, glucagon-like Peptide-1, and insulin responses to small intestinal glucose infusion in healthy humans.
Publication Status	<input checked="" type="checkbox"/> Published, <input type="checkbox"/> Accepted for Publication, <input type="checkbox"/> Submitted for Publication, <input type="checkbox"/> Publication style
Publication Details	Wu T, Bound MJ, Standfield SD, Jones KL, Horowitz M, Rayner CK. Effects of taurocholic acid on glycaemic, glucagon-like Peptide-1, and insulin responses to small intestinal glucose infusion in healthy humans. J Clin Endocrinol Metab. 2013 Apr;98(4):E718-22.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

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Contribution to the Paper	TW was involved in study design and coordination, subject recruitment, data collection and interpretation, statistical analysis, and drafting of the manuscript.		
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Contribution to the Paper	KLJ was involved in conception of the study, data interpretation and review of the manuscript.		
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Contribution to the Paper	CKR was involved in conception and design of the study, data analysis and interpretation and review of		

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	the manuscript, and had overall responsibility for the study.		
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Chapter 10.

Title of Paper	Oral ingestion of artificial sweeteners before glucose has no effect on gastric emptying, glucagon-like peptide-1, postprandial glycaemia, or appetite sensations in healthy humans.
Publication Status	<input type="checkbox"/> Published, <input checked="" type="checkbox"/> Accepted for Publication, <input type="checkbox"/> Submitted for Publication, <input type="checkbox"/> Publication style
Publication Details	Wu T, Bound MJ, Standfield SD, Bellon M, Young RL, Jones KL, Horowitz M, Rayner CK. Oral ingestion of artificial sweeteners before glucose has no effect on gastric emptying, glucagon-like peptide-1, postprandial glycaemia, or appetite sensations in healthy humans. Diabetes Care. 2013 (accepted)

Author Contributions

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Candidate	Tongzhi Wu
Contribution to the Paper	TW was involved in study design and coordination, subject recruitment, performing the study, data interpretation, statistical analyses, and drafting of the manuscript.

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Name of Co-author	Scott D Standfield		
Contribution to the Paper	SDS performed insulin and GLP-1 assays.		
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Contribution to the Paper	RLY was involved in study design, data interpretation and review of the manuscript.		
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Contribution to the Paper	KLJ was involved in conception of the study, data interpretation and review of the manuscript		

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Name of Co-author	Michael Horowitz		
Contribution to the Paper	MH was involved in conception of the study, data interpretation and review of the manuscript.		
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Name of Co-author	Christopher K Rayner		
Contribution to the Paper	CKR was involved in conception and design of the study, data analysis and interpretation, and review of the manuscript, and had overall responsibility for the study.		
Signature		Date	22 July 2013

Chapter 11.

Title of Paper	Disordered control of intestinal sweet taste receptor expression in type 2 diabetes.
Publication Status	<input checked="" type="checkbox"/> Published, <input type="checkbox"/> Accepted for Publication, <input type="checkbox"/> Submitted for Publication, <input type="checkbox"/> Publication style
Publication Details	Young RL, Chia B, Isaacs NJ, Ma J, Khoo J, Wu T, Horowitz M, Rayner CK. Disordered control of intestinal sweet taste receptor expression in type 2 diabetes. Diabetes. 2013 Jun 12. [Epub ahead of print]

Author Contributions

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Candidate	Tongzhi Wu	
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Name of Co-author	Joan Khoo		
Contribution to the Paper	JK assisted in study design, acquired data and critically reviewed the manuscript.		
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Contribution to the Paper	BC acquired data and provided technical support.		
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Name of Co-author	Nicole J Isaacs		
Contribution to the Paper	BC acquired data and provided technical support.		
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Name of Co-author	Michael Horowitz		
Contribution to the Paper	MH designed the study, interpreted data and critically reviewed the manuscript.		
Signature		Date	22 July 2013

Name of Co-author	Richard L Young		
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Contribution to the Paper	RLY conceived, designed and supervised the study, obtained funding, acquired data, undertook statistical analyses and interpreted data, drafted and critically reviewed the manuscript; he is one of the guarantors of this work.		
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Name of Co-author	Christopher K Rayner		
Contribution to the Paper	CKR conceived, designed and supervised the study, obtained funding, acquired data, undertook statistical analyses and interpreted data, drafted and critically reviewed the manuscript; he is one of the guarantors of this work.		
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