The role of gastric and small intestinal mechanisms in postprandial hypotension

A thesis submitted by

Lora Vanis

For the degree of

Doctor in Philosophy

School of Medicine

Discipline of Medicine

The University of Adelaide

Centre of Clinical Research Excellence in Nutritional Physiology, Interventions & Outcomes

September 2010

Table of contents

Chapter 4: Common methodologies

Chapter 5: Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycaemia and GLP-1 release in healthy older subjects

Chapter 6: Comparative effects of glucose and xylose on blood pressure, gastric emptying and incretin hormones in healthy older subjects

Chapter 7: Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects

Thesis abstract

Postprandial hypotension, defined as a fall in systolic blood pressure of ≥ 20 mmHg, within two hours of a meal, leading to syncope, falls, dizziness and angina, occurs frequently in the elderly and is now recognised as an important clinical problem. In healthy young and older individuals, meal ingestion is associated with a rapid rise in heart rate indicative of normal baroreflex function which appears to prevent a significant fall in blood pressure. However, in patients with postprandial hypotension, this response is inadequate to maintain blood pressure. Current approaches to the management of postprandial hypotension are suboptimal and there is a need for novel therapeutic strategies. Recent studies have established that the magnitude of the fall in blood pressure is dependent on the rate of delivery of nutrients from the stomach into the small intestine, while gastric distension attenuates the postprandial fall in blood pressure.

The overall aims of the studies described in this thesis were to investigate the pathophysiology of postprandial hypotension, with the particular focus on gastric and small intestinal mechanisms and their potential therapeutic relevance. In this thesis, studies were carried out in healthy older subjects (age 65 - 80 years) and were designed to evaluate the following: i) the effects of small intestinal glucose load on blood pressure, heart rate and superior mesenteric artery blood flow, ii) the comparative effects of two carbohydrates, glucose and xylose, on blood pressure, heart rate and gastric emptying, iii) the effects of gastric distension, using a barostat, on blood pressure, heart rate and superior mesenteric artery blood flow in response to intraduodenal glucose infusion, iv) the effects of variations in gastric volume, using a barostat, on blood pressure, heart rate and superior

mesenteric artery blood flow during intraduodenal glucose infusion, v) the effects of the oligosaccharide, alpha (α) – cyclodextrin, on blood pressure and heart rate, vi) the effects of acarbose on the blood pressure, heart rate and splanchnic blood flow responses to intraduodenal sucrose. All of the studies have either been published or manuscripts prepared and submitted for publication.

The effects of meal composition on the magnitude of the postprandial fall in blood pressure have been inconsistent. Of the macronutrients, the ingestion of carbohydrate, in particular glucose, was believed to have the greatest effect on blood pressure, with the effects of protein and fat being inconsistent. The fall in blood pressure following intraduodenal glucose appears to be load dependent rather than concentration dependent. A recent study demonstrated that when intraduodenal glucose is administered at a rate of 3 kcal/min, the fall in blood pressure and rise in heart rate were substantially greater compared to a 1 kcal/min glucose infusion. A limitation of this study was that there was no control arm, and because only two intraduodenal glucose loads were evaluated, it could not be determined whether the relationship between the fall in blood pressure and the duodenal glucose load is linear, this was addressed in **Chapter 5**.

There is relatively little information about the effect of different carbohydrates on postprandial blood pressure. Information relating to the effect of xylose on blood pressure is inconsistent, with previous studies showing xylose to have little or no effect. However, in these studies gastric emptying was not measured and it is known that differences in the rate of gastric emptying can affect the magnitude of

the fall in blood pressure. Blood pressure and the rate of gastric emptying of oral glucose and xylose was studied in healthy older subjects in the study reported in **Chapter 6.**

Previous studies have established that the magnitude of the postprandial fall in blood pressure is attenuated by gastric distension, however, it is unknown whether this effect is caused by the change in intragastric pressure **(Chapter 7)** or intragastric volume **(Chapter 8).** Gastric distension at predefined volumes and/or pressures can be achieved using a barostat device. Gastric distension at a pressure of 8 mmHg above minimal distending pressure using a barostat, increased mean arterial pressure, heart rate and total peripheral arterial resistance in healthy subjects. No studies have hitherto evaluated the effects of gastric distension, using a barostat, on the hypotensive response to small intestinal nutrients, and this was addressed in **Chapter 7.**

Intragastric distension with 500 ml water was shown to markedly attenuate the magnitude of the fall in systolic blood pressure in response to intraduodenal glucose. However, a limitation of this study was that during intraduodenal glucose infusion, gastric emptying was markedly attenuated, so that it reached a plateau at 300 ml and little information could be determined in relation to the minimum volume required to attenuate the hypotensive response to glucose, therefore, this was evaluated in **Chapter 8**.

Cyclodextrins inhibit pancratic amylase activity and are poorly digested in the small intestine. α- and beta (β)- cyclodextrins have been reported to reduce the postprandial glycaemic and insulinaemia responses to a starch meal. However, a limitation of these studies was that the rate of gastric emptying was not measured, hence it remains to be determined whether the observed effects were related to gastric emptying and/or intestinal glucose absorption. In the study reported in **Chapter 9**, the effects of α-cyclodextrin on the rate of gastric emptying and hypotensive response to an oral sucrose drink were evaluated.

Acarbose has been used in the treatment of type 2-diabetes for many years by suppressing postprandial glycaemia and slowing of small intestinal digestion and absorption of carbohydrate. Previous studies have illustrated that acarbose has the capacity to slow gastric emptying and attenuate the hypotensive response to carbohydrate meals. The effects of acarbose on postprandial blood pressure and heart rate when administered intraduodenally i.e. in the absence of an effect on gastric emptying, have not been evaluated. Intraduodenal infusion allows the 'intragastric' mechanisms related to changes in gastric emptying to be 'bypassed', which have been evaluated in **Chapter 10**.

Declaration 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 to Lora Vanis 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 made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

_____

Lora Vanis

September 2010

Dedication

To my dear family,

Thank you for your continual love and support,

You have been truly inspirational,

I couldn't have done this without you

Acknowledgements

After almost three and a half roller-coaster years, the end of this very long road has finally come. I can't not believe how much I have achieved during this time. I would like to thank the following people for their support.

To my supervisors, Associate Professor Karen Jones, Professor Michael Horowitz and Associate Professor Chris Rayner, thank you for your continual support, guidance, patience and encouragement, in helping me to overcome all the challenges that I have faced. I hope that I have made you proud. Karen, thank you for being my 'PhD mum'. You have given me the opportunity to grow both professionally and personally and have pushed me to achieve great things. Thank you for giving me the opportunity to travel the world to present my work and learn new techniques and for reviewing my chapters whilst on maternity leave. Michael, it was an absolute pleasure and privilege to work with you more closely in the final months of my PhD. I have learnt so much from you, and I am forever grateful. To my 'unofficial supervisor', Dr Diana Gentilcore, thank you for taking me under your wing and mentoring me. Your patience and the occasional glove flick, has taught me so much of what I know today!! I am very thankful for your advice and that our friendship has continued to blossom. Also, to Associate Professor Christine Feinle-Bisset and Dr Natalie Luscombe-Marsh, thank you for your continued advice and guidance, and always having your office door open for a quick chat.

Thank you to everyone I have shared an office with. Firstly, to Jing Ma, Yan Lam, George Hatzinikolas and Paul Kuo, you all welcomed me to the department with

open arms and helped me settle in; I am very thankful. I then moved to the ‘cool’ office and enjoyed so many chats, debates, laughs, footy banter and ‘choc-chip Friday’s’ with Diana Gentilcore, Radhika Seimon, Paul Cavuoto, Ixchel Brennan, Kylie Lange, Lisa Philp, and Amy Ryan. Thank you for the fun times and memories. For those still in the office, I wish you all the best in completing your PhD. An extra thank you to Radhika for being a special and caring friend, helping me through challenging times, and of course, for proof reading my thesis!!!

To all my other friends in the department (this is a very long list), both past and present, thanks for all the chats, laughs and fun memories we have shared. Good luck with your future endeavours.

Thank you to all the visiting professors that I have been so very fortunate to collaborate with and learn from, both here and abroad. Professor Trygve Hausken, thank you for all your help teaching me ultrasound, the slaps on the back for encouragement, and welcoming me into your house in Bergen to eat reindeer, I know that I have learnt from the best. To Professor Odd Helge Gilja, Professor Chris Mathias, Professor Jim Meyer and Professor John Morley, thank you for your ideas, stimulating conversation and advice on my PhD and beyond.

A big thank you to all my study volunteers, there is too many of you to name. I would like to thank you for giving up your time to participate in my studies and in particular, for enduring the much dreaded barostat bag. I am glad to see the end of the barostat bag as much as you!!! I have enjoyed working with you and all the

conversations we have had while waiting for tubes to get into position!!! Without you, there would be no thesis.

Thank you to all my fellow study co-investigators for your support, advice and help in ensuring all my studies ran as smoothly as possible. To Mrs Rachael Tippett and Ms Michelle Bound, thank you for being my second pair of hands!!

To the Discipline of Medicine, The University of Adelaide and The Centre of Clinical Research Excellence (CCRE) in Nutritional Physiology, Interventions & Outcomes, thank you for the financial support you have provided to me.

To Kylie Lange, thank you for all your assistance with statistical analysis, in particular all those correlations right towards the end, and putting up with all my other statistical questions!!!

Thank you to Judith Wishart for analysing my blood samples.

Thank you to the staff of the Department of Nuclear Medicine, Positron Emission Tomography and Bone Densitometry and the Cardiovascular Investigational Unit for allowing me to use your equipment for my studies.

To my high school girls: Kim Poland, Clare van Eyk, Jennifer Lynch, Vilija Sabeckis, Jennifer Watts and Joanne Bennett, thank you for putting up with me during my PhD, and for always being there to enjoy a glass of wine together.

To my ‘CSIRO’ girls: Dr Denise Furness, Dr Sasja Beestra-Hill and Dr Bianca Benassi-Evans. I have finally joined the Dr’s club!!! Thank you for the regular catch-up lunches, that were always filled with gossip and so many laughs. I look forward to continuing them in the future.

To David, thank you for always being there for me, and knowing how to put a smile on my face during the tough times. Your belief in me, as well as your continual love, support and encouragement has got me through, I hope I have made you proud.

Last but no least, to my very special family, my dad Terry, mum Evelyn and brother Paul, I know I don’t say it enough, thank you for your love and support, not only during my PhD, but also through my whole life. You have always been there for me whenever I have needed help and I know I can always count on you. I hope I have made you just that little bit more proud.

Publications arising from thesis

Vanis L, Gentilcore D, Hausken T, Pilichiewicz A, Lange K, Rayner CK, Feinle-Bisset C, Meyer JH, Horowtiz M, Jones KL (2010). "Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects." *Am J Physiol Regul Integr Comp Physiol* 299:R960-967.

Vanis L, Hausken T, Gentilcore D, Rigda RS, Rayner CK, Feinle-Bisset C, Horowitz M, Jones KL. "Comparative effects of glucose and xylose, on blood pressure, gastric emptying and incretin hormones in healthy older subjects." *BJN* (accepted).

Vanis L, Gentilcore D, Rayner CK, Horowitz M, Feinle-Bisset C, Jones KL. "Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycemia and GLP-1 release in healthy older subjects." *Am J Physiol Regul Integr Comp Physiol* (submitted).

Accepted in abstract form: *JNHA*, 2009;13(Suppl 1):S478 and *JNHA* 2009;13(Suppl 2):S17.

Vanis L, Gentilcore D, Hausken T, Rayner CK, Feinle-Bisset C, Meyer JH, Horowtiz M, Jones KL. "Effects of variations in intragastric volume, on blood pressure and superior mesenteric artery blood flow during intraduodenal glucose infusion in healthy older subjects." *Am J Physiol Gastrointest Liver Physiol* (submitted).

Gentilcore D, **Vanis L**, Teng JC, Wishart JM, Buckley JD, Rayner CK, Horowitz M, Jones KL. "Effects of the oligosaccharide, alpha (a)-cyclodextrin, on gastric emptying of, and the glycemic and blood pressure responses to, oral sucrose in healthy older subjects." *BJN* (submitted).

Accepted in abstract form: *JNHA* 2009;13(Suppl 1):S478.

Gentilcore D, **Vanis L,** Wishart JM, Rayner CK, Horowitz M, Jones KL. "Effects of intraduodenal acarbose on blood pressure, heart rate and splanchnic blood flow in healthy older subjects." *J Hypertens* (submitted).

Accepted in abstract form: *JAGS*, 2010; 58(Supp 1):S280.

Other manuscripts

Gentilcore D, Nair NS, **Vanis L,** Rayner CK, Meyer JH, Hausken T, Horowitz M, Jones KL (2009). "Comparative effects of oral and intraduodenal glucose on blood pressure, heart rate and splanchnic blood flow in healthy older subjects." *Am J Physiol Regul Integr Comp Physiol* 297:R716-722.

Gentilcore D, Nair NS, Kuo P, **Vanis L,** Buckley JD, Rayner CK, Horowitz M, Jones KL. "Effects of aerobic exercise on gastric emptying of, and the glycemic and cardiovascular responses to, oral glucose in healthy older subjects." (manuscript in preparation).

Accepted in abstract form: *Neurogastroenterol Motil* 2008;20:83.