Role of the Gastrointestinal Tract in Postprandial Blood Pressure Regulation

Role of the Gastrointestinal Tract in Postprandial Blood Pressure Regulation

A thesis submitted by

Diana Gentilcore

For the Degree of

Doctor of Philosophy

School of Medicine

Discipline of Medicine

University of Adelaide

December 2006

Table of contents

Chapter 1: Pathophysiology of postprandial hypotension

Chapter 2: Blood pressure regulation

Summary

This thesis presents studies relating to the role of the gastrointestinal tract in postprandial blood pressure regulation. The areas that have been addressed include: (i) the methodological approaches to the evaluation of gastric emptying, blood pressure, splanchnic blood flow, intraluminal manometry and gut hormones and (ii) the pathophysiological mechanisms underlying postprandial hypotension, with a particular focus on 'gastric' and 'small intestinal' mechanisms and their potential therapeutic relevance. All of the studies have been either published or manuscripts have been prepared for publication.

While scintigraphy represents the 'gold standard' for the measurement of gastric emptying, recent studies suggest that three-dimensional (3D) ultrasonography may also allow a precise measure of gastric emptying. Concurrent scintigraphic and ultrasonographic measurements of gastric emptying of liquids were performed in healthy young volunteers. There was a good correlation and agreement between scintigraphic measurements of gastric emptying and 3D ultrasonography after ingestion of both low- and high- nutrient drinks, indicating that 3D ultrasonography, provides a valid measure of gastric emptying of liquid meals in normal subjects.

Postprandial hypotension, defined as a fall in systolic blood pressure of ≥ 20mmHg, occurring within two hours of a meal is now recognised as an important clinical problem, particularly in the elderly and in patients with type 2 diabetes. The mechanisms mediating postprandial hypotension are poorly understood. The effects of variations in concentration of intraduodenal glucose on the magnitude of the fall in

blood pressure were evaluated in healthy elderly subjects. Blood pressure fell, and heart rate and blood glucose increased over time during infusions, however, there was no difference in blood pressure, heart rate or blood glucose concentrations between the study days. These observations suggest that glucose induced postprandial hypotension is a load rather, than concentration, dependent phenomenon.

The effect of meal composition has been reported to influence the hypotensive response to a meal and information relating to the effects of triglyceride and protein on blood pressure is inconsistent. The comparative effects of isocaloric and isovolaemic intraduodenal infusions of glucose, triglyceride and protein on the magnitude of the postprandial fall in blood pressure and rise in heart rate and superior mesenteric artery blood flow were evaluated in healthy elderly subjects. There were comparable falls in systolic blood pressure and rises in heart rate, however, the maximum fall in systolic blood pressure occurred later after triglyceride and protein and the stimulation of superior mesenteric artery blood flow was less after protein. These observations suggest that the relatively slower systolic blood pressure response after triglyceride and protein may potentially reflect the time taken for digestion of triglyceride to free fatty acids and protein to amino acids.

Acarbose is an antidiabetic drug that slows both gastric emptying and small intestinal glucose absorption. The effects of acarbose, on blood pressure, heart rate, gastric emptying of, and the glycaemic, insulin, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic-polypeptide (GIP) responses to, an oral sucrose load were

evaluated in healthy elderly subjects. Acarbose attenuated the fall in blood pressure and increase in heart rate induced by oral sucrose. Acarbose slowed gastric emptying and was associated with increased retention in the distal stomach. Stimulation of GLP-1 may contribute to the slowing of gastric emptying and suppression of postprandial glycaemia by acarbose. These findings suggest that acarbose may represent a therapeutic option for the treatment of patients with postprandial hypotension.

Recent studies indicate that gastric distension attenuates the postprandial fall in blood pressure. The effects of gastric distension on blood pressure and heart rate during intraduodenal infusion of glucose at a constant load and concentration were evaluated in healthy elderly subjects. Intragastric administration of water markedly attenuated the falls in systolic and diastolic blood pressure induced by intraduodenal glucose. Heart rate increased, with and without gastric distension, in response to intraduodenal glucose infusion but not after intraduodenal saline infusion. This study suggests that gastric distension may potentially be used as a simple adjunctive treatment in the management of postprandial hypotension.

Studies employing nitric oxide synthase blockers have established, in animals, that nitric oxide mechanisms are important in the regulation of splanchnic blood flow and, hence, may effect postprandial blood pressure. The role of the nitric oxide synthase inhibitor, NG-nitro-L-arginine-methyl-ester (L-NAME), on gastric emptying, postprandial blood pressure, plasma insulin concentration and incretin hormone (ie GIP and GLP-1) release, following an oral glucose load, were evaluated in healthy elderly

subjects. L-NAME attenuated the postprandial fall in blood pressure and increase in heart rate but had no effect on gastric emptying of glucose. L-NAME attenuated the glucose-induced rise in plasma insulin but had no effect on the incretin (GIP and GLP-1) hormone response to oral glucose. The study indicates that the magnitude of the fall in blood pressure and increase in heart rate and stimulation of insulin secretion induced by oral glucose in healthy elderly subjects are mediated by nitric oxide mechanisms by an effect unrelated to changes in gastric emptying, or the secretion of GIP and GLP-1.

Studies utilising 5-hydroxytryptamine (5-HT) infusions in animals have demonstrated regional variations in intestinal blood flow suggesting a role for 5-HT in postprandial haemodynamic responses. The effects of the 5-hydroxytryptamine 3 (5-HT3) antagonist, granisetron, on the blood pressure, heart rate, antropyloroduodenal motility and glycaemic responses to intraduodenal glucose infusion were assessed in healthy elderly subjects. Granisetron had no effect on blood pressure, heart rate or antral and pyloric motor responses but modulated the duodenal motor response, to intraduodenal glucose. This study indicates that while the cardiovascular response to intraduodenal glucose does not appear to be influenced by the stimulation of 5-HT3 receptors, this receptor may be involved in the modulation of the duodenal motor activity.

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 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 being made available in the University Library. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder/s of those works.

_____

Diana Gentilcore

December 2006

Dedication

For my husband Laurie

Your courage is inspirational.

Acknowledgements

Now that I am at the end of what seems like a very, very long road, I would like to thank the following people for the support and help given to me over the last four years.

I would like to start by thanking my supervisors, Dr Karen Jones and Professor Michael Horowitz. Karen, thank you for giving me the opportunity to grow as a person, both personally and professionally and for sticking by me in the good and the very bad times. You are a true friend. It has been an honour to have you as my supervisor and I hope that I have made you proud. Michael, thank you for your support and kindness during my time in the department, especially in the beginning when I needed it the most. Thank you for pushing me to go that one step further even when I wanted to run in the other direction. Thank you both for giving me the opportunity to travel to many parts of this wonderful world - this would not have been possible without your support. Finally, I hope that when you look back and reflect, you are able to see a glimmer of yourselves in me - you have impacted on my life in such a way that you will both be a part of me always.

To my friends in the Discipline of Medicine - and it is a very long list: Antonietta 'Ants' Russo, Julie 'Jules' Stevens, Ixchel 'Spunkette' Brennan, Amelia 'Ballerina' Pilichiewicz, Kate 'Katie' Feltrin, Paul 'Paulie' Cavuoto, Sue 'W-B-W' O'Connor, Sean 'Seanie' Martin, and those of you without nicknames, Kamilia Tai, Reawika Chaikomin and Anne Maddox - thank you for your help, advice and laughs over the years and for brightening up my days.

To my special friend Tanya 'Stuart' Little with whom I have laughed and cried so many times over the last two years. Thank you for your friendship, support, chats and for keeping me company in the evenings while we were both trying to write our theses.

To Natalie Luscombe-Marsh - thank you to such a special and caring friend who has always looked out for me and helped me during challenging times.

Thank you to my friends who have long gone but were so helpful in the early days - Deirdre O'Donovan, Renuka Visvanathan and Barbara Parker.

To the visiting Professors I have worked, chatted and laughed with: Professor Trygve Hausken, my Norwegian friend - you really are 'not that bad'. Only joking, you are really 'the best'. Thanks for practising patience and humour when teaching me ultrasound and for allowing me to visit your beautiful country and department. To Professors André Smout, Melvin Samson and Jim Meyer for spending time sharing wonderful ideas with me.

Thanks to Judith Wishart for analysing my blood samples whenever I needed them 'yesterday!'

To the staff of the Department of Nuclear Medicine, Positron Emission Tomography and Bone Densitometry - there are just too many of you to name. Thanks for your help during my studies and for the chats and hugs.

Thanks to Pauline Francis and staff of the Cardiovascular Investigational Unit for allowing me to use your equipment to test cardiovascular autonomic nerve function.

Many thanks to Justin Lokhurst and Nancy Briggs who provided assistance with statistical analyses.

To my special volunteers: Val, Vic, David, Rose, Max, Betty, Dorothy, Barbara, Frank, Aileen, Donald, Keith, Brian and others whose names don't appear on this list. Thanks for your willingness to participate in my studies and for tolerating all those tubes! Thanks also for all your wonderful words of wisdom.

To the Discipline of Medicine and University of Adelaide for the financial support provided to me, and by my William T Southcott Scholarship in Nuclear Medicine.

To all my fellow co-investigators. Thanks for your help and advice during and after studies.

To my dad Adolfo, mum Alba, sister Julie and brother Tony for always being so proud of me. To my Auntie Silvana 'Zee-zee-van' - for your support over the years and not just the last four.

To the very special children in my life: Dean Bakasetas, Sienna Capone, Jenna Maione and Adrienne 'Princess' and Michael Slavotinek. Your warm smiles and love always brighten up the darkest days.

To my dear friend Nadia 'Nards' Maione. Thanks for being there when I have needed it the most and for asking all the right questions at the right time.

Thanks to my dear friends Cristina Blefari, Silvana Di Ciocco and Patrizia Lim for your understanding and not giving up on me when I haven't returned your many emails, phone calls, Xmas cards, etc!

And last but definitely not least. To my husband Laurie. For your support, love, humour, encouragement and for always being there, and proud of me. But most of all, thanks for being you.

Publications arising from this thesis

Gentilcore, D, Visvanathan, R, Russo, A, Chaikomin, R, Stevens, JE, Wishart, JM, Tonkin, A, Horowitz, M & Jones, KL 2005, 'Role of nitric oxide mechanisms in gastric emptying of, and the blood pressure and glycemic responses to, oral glucose in healthy older subjects', *Am J Physiol Gastrointest Liver Physiol*, vol. 288, no. 6, pp. G1227-G1232.

Gentilcore, D, Bryant, B, Wishart, JM, Morris, HA, Horowitz, M & Jones, KL 2005, 'Acarbose attenuates the hypotensive response to sucrose and slows gastric emptying in the elderly', *Am J Med*, vol. 118, no. 11, pp. 1289.e5-1289.e11.

Gentilcore, D, Jones, KL, O'Donovan, DG & Horowitz, M 2006, 'Postprandial hypotension - novel insights into pathophysiology and therapeutic implications', *Curr Vasc Pharmacol*, vol. 4, no. 2, pp. 161-171.

Gentilcore, D, Doran, S, Meyer, JH, Horowitz, M & Jones, KL 2006, 'Effects of intraduodenal glucose concentration on blood pressure and heart rate in healthy older subjects', *Dig Dis Sci*, vol. 51, no. 4, pp. 652-656.

Gentilcore, D, Hausken, T, Horowitz, M & Jones, KL 2006, 'Measurements of gastric emptying of low- and high-nutrient liquids using 3D ultrasonography and scintigraphy in healthy subjects', *Neurogastroenterol Motil*, vol. 18, no.12, pp. 1062-1068.

Other publications

Gentilcore, D, O'Donovan, D, Jones, KL & Horowitz, M 2003, 'Nutrition therapy for diabetic gastroparesis', *Curr Diab Rep*, vol. 3, no.5, pp. 418-426.

Gentilcore, D, Chaikomin, R, Jones, KL, Russo, A, Feinle-Bisset, C, Wishart, JM, Rayner, CK & Horowitz, M 2006, '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*, vol. 91, no. 6, pp. 2062-2067.