Gastric and Small Intestinal Determinants of Postprandial Blood Pressure and Glycaemia

Thesis by

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Now the world is upside down,

I'm heading straight for the clouds…

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THESIS SUMMARY

This thesis presents clinical research studies relating to the roles of the stomach and small intestine in determining postprandial blood pressure (BP) and glycaemic responses in different patient groups. Postprandial hypotension (PPH), defined as a fall in systolic BP ≥ 20 mmHg within two hours of a meal, is an important clinical problem in older individuals, which may lead to syncope and falls and is associated with increased mortality. PPH occurs when mechanisms responsible for the homeostatic maintenance of BP (including baroreceptor activation), are unable to compensate adequately for the shift in blood volume to the splanchnic circulation induced by meal ingestion. The gastrointestinal tract is also pivotal to the regulation of postprandial glycaemia. Postprandial glycaemia depends on the rate at which carbohydrate is delivered from the stomach to be absorbed from the small intestine, glucose disposal, and endogenous glucose production. The rate of gastric emptying (GE) is known to be a determinant of both the hypotensive and glycaemic responses to carbohydrate ingestion, so that when GE is relatively faster, the fall in BP and rise in blood glucose are more substantial. The broad focus of the work presented in this thesis, underlying the hypothesis of each chapter, is to achieve important insights into the physiology of the gastrointestinal tract with respect to the regulation of BP and glycaemia.

The prevalence of PPH is believed to be approximately 30% in individuals aged over 65 years, and even higher in patients with autonomic dysfunction,

hypertension or multiple co-morbidities. Estimates of the prevalence of PPH, however, are for the main part, derived from clinical studies in small, heterogenous cohorts and no study has been undertaken to determine the prevalence of PPH in otherwise healthy individuals. Furthermore, given the wide range of 'normal' GE, it is likely that relatively more rapid GE may be a risk factor for PPH. In the study reported in **Chapter 5**, we aimed to determine the prevalence of PPH, as well as the relationships between BP responses with GE, in a cohort of 88 healthy older volunteers, in response to a standardised 75 g oral glucose tolerance test (OGTT) 'meal'. In our cohort, the prevalence of PPH was ~13% and in patients with PPH, GE was faster. These findings are consistent with the concept that relatively more rapid GE may be a 'risk' factor for PPH, and that dietary and/or pharmacological strategies that slow GE may prove beneficial in the management of PPH.

The 75 g OGTT is regarded as the 'gold standard' for the diagnosis of impaired glucose tolerance and diabetes, but is subject to considerable variability which is likely to be accounted for, in part, by variations in GE. Furthermore, recent studies have questioned the diagnostic value of blood glucose at 60 min, used as an alternative to, or in conjunction with, the traditional 120 min value. We sought to determine the impact of GE on both 'early' and 'late' blood glucose responses to an OGTT in healthy older volunteers with and without impaired glucose tolerance. We obtained concurrent measurements of blood glucose, serum insulin and 'incretin' hormones (glucagon-like peptide-1 (GLP-1), and gastric inhibitory polypeptide (GIP)) in the cohort of older volunteers studied and reported in

Chapter 5. These results are presented in **Chapter 6**. Subjects were classified according to their glucose tolerance as either impaired glucose tolerance (IGT) or normal glucose tolerance (NGT). In both NGT and IGT, insulin sensitivity and GE were demonstrated to be independent, yet complimentary, determinants of the blood glucose response at both the 'early' and 'late' time points. These findings indicate that the inter-individual variability of the OGTT can be accounted for, in part, by differences in GE and insulin sensitivity. Furthermore, individuals with an overall faster rate of GE may potentially be at greater risk of developing IGT and type 2 diabetes.

Exposure of the gut lumen to nutrients results in the secretion of a number of hormones, including cholecystokinin (CCK), GIP and GLP-1. CCK and GIP are secreted from I- and K-cells, respectively, located in the proximal small intestine, whereas GLP-1 is released from L-cells located predominantly in the distal small intestine and colon. The mechanisms by which GLP-1 is released from the small intestine are incompletely understood; there appears to be a minimum threshold of nutrient delivery, above which GLP-1 is secreted, and the diversion of nutrients to the distal small intestine can potentiate GLP-1 secretion. We sought to determine region-specific effects of glucose exposure on gut hormone release by measuring the glycaemic, insulinaemic and incretin hormone responses to a duodenal glucose infusion in proximal (12 – 60 cm beyond the pylorus), distal (> 70 cm beyond the pylorus), and proximal and distal combined, small intestinal segments. This study is reported in **Chapter 7**. The findings from this study suggest the importance of the distal small intestine for GLP-1, and to a lesser extent GIP

and CCK, secretion. Therapies which target GLP-1 release in the distal small intestine may, therefore, potentially be more effective in blood glucose regulation than those that have a non-specific regional effect throughout the small intestine.

The pathophysiology of PPH is poorly defined. Although the gastrointestinal tract is important in the pathophysiology of PPH, a fall in BP must ultimately be regarded as an inadequate cardiovascular response to compensate for meal-related splanchnic blood pooling. Conversely, gastric distension, either nutrient or non-nutrient, stimulates sympathetic output and has the capacity to attenuate the fall in BP. The information relating to the effects of nutrients on cardiovascular function is limited and inconsistent, and no study of patients with PPH has employed echocardiography to assess postprandial cardiovascular changes. In the study reported in **Chapter 8**, we measured postprandial cardiovascular haemodynamics with echocardiography in response to drinks of water or glucose in individuals with and without PPH. We found that the fall in postprandial BP was greater in PPH but there were no differences in cardiac parameters. Interestingly, the hypotensive response to glucose and the hypertensive response to water were shown to be related. As the pressor response to water drinking is maintained and probably exaggerated in PPH, this represents a potential therapeutic target.

While delayed GE is a sequela of Parkinson's disease, the prevalence of delayed GE is uncertain, as is the impact of this phenomenon on postprandial BP and glycaemia. PPH is likely to occur frequently in Parkinson's disease,

particularly in cases with impairment of the autonomic nervous system. In healthy individuals, the postprandial fall in BP is related to the increase superior mesenteric artery (SMA) blood flow, but this has not been investigated in Parkinson's disease. In **Chapter 9**, we present the results of a cross-sectional study in which GE, BP, SMA blood flow and glycaemia were measured following an OGTT, in individuals with mild-to-moderate Parkinson's disease. Gastric emptying was delayed in 14% of these patients and 38% had PPH. Gastric emptying was related to autonomic dysfunction and a determinant of the glycaemic, but not apparently the hypotensive, responses to meal ingestion in this population. There was also no relationship between the rise in SMA blood flow and fall in BP.

GLP-1, by slowing GE and altering mesenteric blood flow, may potentially affect postprandial BP. The slowing of GE by GLP-1 is potent, so that it is the primary mechanism by which GLP-1 lowers postprandial glycaemia. GLP-1 and GLP-1 receptor agonists may affect BP, but clinical trials of GLP-1 receptor agonists have, for the main part, not discriminated between fasting and postprandial BP. We evaluated the effects of GLP-1 on postprandial BP in two studies, reported in **Chapters 10 and 11.** In **Chapter 10**, we report the effects of exogenous GLP-1 on the BP, heart rate, SMA blood flow and glycaemic responses to an intraduodenal glucose infusion in healthy older subjects. In **Chapter 11**, the effects of exogenous GLP-1 in response to an oral glucose load, in healthy older subjects and patients with type 2 diabetes, are reported. The findings of both of these studies suggest GLP-1 receptor agonists may be effective in the management of PPH; one potential

mechanism is through the slowing of GE, although GLP-1 was shown to attenuate the fall in BP during intraduodenal glucose infusion so other factors are also involved. It is clear that clinical trials that report the effects of GLP-1 and GLP-1 receptor agonists on BP should differentiate between the fasting and postprandial states.

When glucose is infused intraduodenally at rates spanning the normal range of GE, the increase in SMA blood flow and heart rate occurs in parallel with secretion of GIP, not GLP-1. A potential role for GIP in the regulation of the cardiovascular response to meal ingestion is suggested by the outcomes of the study reported in **Chapter 12**. We report the effects of sitagliptin (a dipeptidyl peptidase-4 inhibitor, which increases circulating levels of GLP-1 and GIP), on BP and heart rate during an intraduodenal glucose infusion at a rate of 2 kcal/min, where GIP is the major incretin in the circulation. Our findings suggest a potential role of GIP in the regulation of postprandial cardiovascular function but more studies are warranted.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, 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 in my name, 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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Signature: Date: February 2016

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PUBLICATIONS ARISING FROM THESIS

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