Gastrointestinal mediation of glucose homeostasis and postprandial cardiovascular risk

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A thesis submitted by

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THESIS SUMMARY

In the majority of patients with type 2 diabetes, who have reasonably good glycemic control (HbA_1C ~7.5% or less), it is postprandial glycemia which predominates over fasting blood glucose in contributing to HbA_1C; postprandial glycemia may therefore represent an independent risk factor for diabetic complications and adverse cardiovascular events (Monnier et al., 2003). Also, at the same HbA_1C level, subjects with larger fluctuations in the blood glucose levels postprandially carry a higher cardiovascular risk (Del Prato, 2002b). The magnitude of postprandial glycemic excursions is largely determined by the rate of gastric emptying of nutrients to the small intestine which in turn regulates various metabolically important neurohumoral responses set off mainly by the release of incretin hormones from the enteroendocrine cells of the intestine. Conversely, acute glycemic excursions can regulate gastric emptying through feedback mechanisms. This thesis highlights the pivotal role of the upper gastrointestinal tract in the regulation of postprandial glycemia and attendant cardiovascular risks in health and type 2 diabetes, and the capacity for interventions aimed at modulation of upper gut function to be effective in the treatment of diabetes. Following is a brief outline of the experimental studies described in this thesis:

1. Changes in meal composition and duration affect postprandial endothelial function in healthy humans

Impaired endothelial function is now well-recognized as a forerunner of atherosclerosis (Juonala et al., 2004), and is predictive of long-term adverse cardiovascular outcomes (Vogel, 2001). The endothelial dysfunction after an oral glucose load is related to the degree of rise in blood glucose in both health and type 2 diabetes (Title et al., 2000, Kawano et al., 1999), with the duration of dysfunction being greater in the latter (Akbari et al., 1998). The rate of gastric emptying is a major determinant of postprandial glycemic increments (Chaikomin et al., 2006, Marathe et al., 2013) and modulating gastric emptying and/or nutrient absorption from the upper gut can be achieved non-pharmacologically by modifying the composition of a meal, for example by adding soluble fiber such as guar gum (Holt et al., 1979, Torsdottir et al., 1989), or by decreasing the rate of meal ingestion (Zhu et al., 2013). Though the effects of such dietary manipulations on glycemia have been described previously, their influence on postprandial endothelial function had not been investigated. We therefore evaluated the effects of dietary modifications designed to slow gastric emptying and/or small intestinal nutrient absorption on postprandial endothelial function in healthy humans.

2. The glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, inhibits small intestinal motility, flow, transit and absorption of glucose in health and type 2 diabetes: a randomised controlled trial.

The presence of glucose in the small intestine stimulates the release of several peptides, including glucagon-like peptide-1 (GLP-1) (Schirra et al., 1996); the latter has a critical role in determining postprandial insulin and glycemic responses, mainly via its ability to slow gastric emptying and regulate nutrient delivery to the small intestine, though other factors such as its insulinotropic property could also be involved. Lately, GLP-1 receptor agonists have been used widely in the treatment of patients with type 2 diabetes, (Holst and Gromada, 2004, Elahi et al., 1994). Exenatide belongs to this class of medications and is resistant to degradation by the plasma enzyme di-peptidyl peptidase-IV (DPP-IV) that rapidly degrades endogenous GLP-1. Previous studies in healthy humans have demonstrated that intravenous exogenous GLP-1 slows gastric emptying (Little et al., 2006b, Nauck et al., 1997b), but the effects of GLP-1, or agonists of its receptor, on small intestinal flow events and transit have not yet been evaluated in humans. Data from animal studies have shown that exogenous GLP-1 inhibits small intestinal motility and transit (Tolessa et al., 1998b, Tolessa et al., 1998a), which could represent an additional mechanism in the lowering of postprandial glycemia. This chapter describes the effects of the GLP-1 receptor agonist, exenatide on duodenal pressure waves, flow events, small intestinal transit time, and the rate of small intestinal glucose absorption in healthy humans as well as in those with type 2 diabetes.

3. Effects of glucagon-like peptide-1 (GLP-1) receptor agonist, exenatide, on blood pressure and heart rate in response to intraduodenal glucose infusion in type 2 diabetes: a randomised controlled trial.

It is well recognised that the magnitude of postprandial hypotension depends largely on the rate of gastric emptying (Trahair et al., 2012b); hence glucagon-like peptide-1 (GLP-1) receptor stimulation, which slows gastric emptying, could potentially be used as a treatment for postprandial hypotension. As exogenous GLP-1 has been found to increase blood pressure in some human studies, albeit not consistently (Edwards et al., 1998, Halbirk et al., 2010, Bharucha et al., 2008), and attenuate the hypotensive effect of both oral (Trahair et al., 2015) and intraduodenal (Trahair et al., 2014b) glucose loads, mechanisms other than just slowing of gastric emptying could potentially be involved. In this chapter, we present the effects of an intravenous infusion of a GLP-1 receptor agonist, exenatide, on systolic, diastolic and mean arterial blood pressure, and heart rate, measured in the course of Study 2 (above), during and after the intraduodenal glucose infusion.

4. Effects of hydroxycitrate (HCA) on intestinal glucose absorption and incretin release in healthy subjects and in type 2 diabetes.

It is now well-recognised that patients with greater fluctuations in blood glucose carry a greater cardiovascular risk than those with lesser excursions, even if HbA_1C levels are similar (Del Prato, 2002a). Therefore, there has been an emerging interest in exploring the therapeutic potential of inhibiting/delaying postprandial small intestinal carbohydrate absorption in order to dampen the glycemic spikes (Qualmann et al., 1995). Extracts from the fruit *Garcinia cambogia*, in which hydroxycitric acid (HCA) is the active ingredient, have been widely marketed for weight loss, but may also reduce postprandial

glycemia. The latter claim is based mainly on findings from rodent studies, where HCA was associated with a delay in glucose absorption, and stimulation of GLP-1 release from the distal gut. In this chapter, we describe the effects of small intestinal pre-treatment with HCA on glucose absorption and incretin release in healthy humans and in patients with diet-controlled type 2 diabetes.

5. Effects of 5 weeks resveratrol supplementation on GLP-1 secretion, gastric emptying, and postprandial glycemia in patients with type 2 diabetes.

Resveratrol, a phytoalexin, found in plant foods including red grapes, improves glycemic control in experimental animals with type 2 diabetes by uncertain mechanisms (Vang et al., 2011) and could be attractive as a potential therapy for type 2 diabetes in humans because it is safe and relatively inexpensive. In a high fat diet mouse model of diabetes, supplementation with resveratrol for 5 weeks was associated with a reduction in the glycemic excursion after an oral glucose tolerance test, together with an enhanced insulin response and substantially increased concentrations of GLP-1 in the portal vein (Dao et al., 2011), as well as increases in the proglucagon mRNA and GLP-1 content in the colon. However, effects of resveratrol on GLP-1 secretion have not previously been evaluated in humans with diabetes. This chapter describes the effects of 5 weeks of resveratrol supplementation on GLP-1 secretion, gastric emptying, and postprandial glycemia in patients with diet-controlled type 2 diabetes.

6. Comparative effect of intraduodenal and intrajejunal glucose infusion on the gut-incretin axis response in healthy males

Bariatric surgical procedures such as the Roux-en-Y gastric bypass are known to result in improvements in glycemic control in patients with type 2 diabetes, which is associated with an enhanced incretin response. In this chapter, we examined whether bypassing the duodenum would elicit a greater response of the gut-incretin axis to small intestinal glucose infusion, by comparing plasma GLP-1, GIP, insulin and glucagon, and blood glucose responses to a standardised glucose infusion into the proximal jejunum and duodenum in healthy humans.

7. Mechanism of increase in plasma intact GLP-1 by metformin in type 2 diabetes: stimulation of GLP-1 secretion or reduction in plasma DPP-4 activity?

The critical role of GLP-1 in glucose homeostasis is being increasingly recognised. In this chapter, we describe the effects of the widely used anti-diabetic medication, metformin, on total and intact GLP-1 concentrations, and on the activity of plasma dipeptidyl peptidase -4 (DPP-4), the enzyme responsible for the degradation of GLP-1, before and during an intraduodenal glucose infusion in patients with type 2 diabetes.

DECLARATION

Name: **Sony Sebastian Thazhath** ***Program:*** **Doctor of Philosophy**

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PUBLICATIONS ARISING FROM THE THESIS

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Statements of Authorship

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