Gastric and small intestinal motor function in health and disease – implications for glucose absorption, incretin hormone release, and postprandial blood glucose regulation

A thesis submitted by

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Table of contents

Summary

Declaration

Acknowledgements

Publications arising from this thesis

Chapter 1: Normal physiology of the upper gut

1.1 Introduction

1.2 Motor function of the stomach and proximal small intestine
   1.2.1 Proximal stomach
   1.2.2 Distal stomach
   1.2.3 Pylorus
   1.2.4 Duodenum
   1.2.5 Gastric emptying and its regulation
   1.2.6 Transpyloric flow
   1.2.7 Small intestinal transit
   1.2.8 Gastroduodenal motility
      1.2.8.1 Fasting motility
      1.2.8.2 Postprandial motility

1.3 Neurohormonal regulation of upper gut function
   1.3.1 The brain-gut axis
      1.3.1.1 The enteric nervous system
      1.3.1.2 Nitric oxide
   1.3.2 Incretin hormones
Chapter 2: Gastroduodenal function in diabetes

2.1 Introduction 54
2.2 Glycaemic control and diabetic complications 55
2.3 Upper gut function in diabetes mellitus 56
  2.3.1 Influence of gastric emptying on postprandial glycaemia 58
  2.3.2 Influence of glycaemia on upper gut function 60
2.4 Incretin hormones in diabetes 63
2.5 Diabetic gastropathy 65
  2.5.1 Definition 65
  2.5.2 Pathophysiology 66
  2.5.3 Clinical manifestations 68
  2.5.4 Investigations 70
    2.5.4.1 Measurements of gastric emptying 71
  2.5.5 Management 74
    2.5.5.1 Dietary modification 74
    2.5.5.2 Medical therapy 75
    2.5.5.3 Gastric electrical stimulation 86
    2.5.5.4 Gastrostomy/jejunostomy 88
    2.5.5.5 Surgical therapy 88
2.6 Conclusion 89
Chapter 3: Exocrine pancreatic insufficiency, gastric emptying, and glycaemic control in cystic fibrosis

3.1 Introduction 92
3.2 Pancreatic enzyme replacement therapy 93
3.3 Gastric emptying in cystic fibrosis 96
3.4 Cystic fibrosis-related diabetes 97
  3.4.1 Definition 97
  3.4.2 Pathogenesis 98
  3.4.3 Glucose tolerance 99
  3.4.4 Prognostic implications 100
  3.4.5 Treatment 102
3.5 Relationships between gastric emptying, pancreatic enzyme replacement, and glycaemic control 103
3.6 Conclusion 105

Chapter 4: Techniques in assessing upper gut function

4.1 Introduction 106
4.2 Gastric emptying 106
  4.2.1 Scintigraphy 106
  4.2.2 Three-dimensional ultrasound 108
4.3 Antropyloroduodenl motility 111
  4.3.1 Manometry 111
4.4 Flow events 114
  4.4.1 Impedance monitoring 114
4.5 Upper gut symptom questionnaire 118
  4.5.1 Visual analogue scale (VAS) 118
4.6 Conclusion 118
Chapter 5: Methodologies

5.1 Introduction 119
5.2 Subjects 119
5.3 Ethical approval 120
5.4 Study environment 121
5.5 Drugs 121
  5.5.1 metoclopramide 121
5.6 Glycaemic clamp 122
5.7 Autonomic function testing 123
5.8 Biochemical/hormonal measurements 124
  5.8.1 Blood glucose 125
  5.8.2 Incretin hormones 125
    5.8.2.1 GLP-1 125
    5.8.2.2 GIP 126
  5.8.3 Insulin 126
  5.8.4 3-O-methyl glucose 126
  5.8.5 14C-3-O-methyl glucose 127
5.9 Statistical analysis 127
5.10 Conclusion 128

Chapter 6: Validation of 14C-3-O-methylglucose as a measure of intestinal glucose absorption in humans

6.1 Summary 129
6.2 Introduction 130
6.3 Methods 131
  6.3.1 Subjects 131
  6.3.2 Protocol 131
  6.3.3 Measurements 132
  6.3.4 Statistical analysis 133
6.4 Results

6.4.1 Blood glucose concentrations

6.4.2 Plasma 3-O-methylglucose (3-OMG) and $^{14}$C-3-O methylglucose ($^{14}$C-3-OMG)

6.4.3 Correlations between plasma 3-OMG concentrations, plasma $^{14}$C-3-OMG activities, and blood glucose concentrations

6.5 Discussion

Chapter 7: Transient, early release of glucagon-like peptide-1 during low rates of intraduodenal glucose delivery

7.1 Summary

7.2 Introduction

7.3 Methods

7.3.1 Subjects

7.3.2 Protocol

7.3.3 Measurements

7.3.4 Statistical analysis

7.4 Results

7.4.1 Blood glucose, insulin, GLP-1 and GIP concentrations

7.5 Discussion

Chapter 8: Effects of metoclopramide on duodenal motility and flow events, glucose absorption, and incretin hormone release, in response to intraduodenal glucose infusion

8.1 Summary

8.2 Introduction
Chapter 9: Effects of physiological hyperglycaemia on duodenal motility and flow events, glucose absorption, and incretin hormone secretion in healthy humans

9.1 Summary 174
9.2 Introduction 175
9.3 Methods 177
  9.3.1 Subjects 177
  9.3.2 Protocol 177
  9.3.3 Measurements 179
  9.3.4 Statistical analysis 182
9.4 Results 182
  9.4.1 Blood glucose concentrations 183
  9.4.2 Duodenal pressure waves 183
  9.4.3 Duodenal flow events 183
  9.4.4 $^{14}$C-3-OMG, insulin, GLP-1 and GIP concentrations 184
9.4.5 Relationships between plasma $^{14}$C-3-OMG, insulin, GLP-1, and GIP concentrations 186

9.5 Discussion 187

Chapter 10: The nitric oxide (NO) synthase inhibitor, NG-nitro-L-arginine-methyl-ester (L-NAME), attenuates the delay in gastric emptying induced by hyperglycaemia in healthy humans

10.1 Summary 196
10.2 Introduction 197
10.3 Methods 199
  10.3.1 Subjects 199
  10.3.2 Protocol 199
  10.3.3 Measurements 201
  10.3.4 Statistical analysis 204
10.4 Results 205
  10.4.1 Blood pressure and heart rate 205
  10.4.2 Gastric emptying and intragastric distribution 206
  10.4.3 Antral pressure waves 207
  10.4.4 Duodenal pressure waves 208
  10.4.5 Isolated pyloric pressure waves and basal pyloric Pressures 209
  10.4.6 Plasma insulin and GIP concentrations 209
10.5 Discussion 210
Chapter 11: Gastric emptying in cystic fibrosis – implications for management of exocrine pancreatic insufficiency and postprandial glycaemia

11.1 Summary 222
11.2 Introduction 223
11.3 Methods 225
  11.3.1 Subjects 225
  11.3.2 Protocol 226
  11.3.3 Measurements 227
  11.3.4 Statistical analysis 229
11.4 Results 230
  11.4.1 Gastric emptying 231
  11.4.2 Blood glucose 232
  11.4.3 Plasma insulin, GLP-1, and GIP concentrations 234
  11.4.4 Gastrointestinal symptoms 237
11.5 Discussion 238

Chapter 12: conclusions 249

Bibliography 254
Thesis summary

The human digestive tract is a complex system that, in addition to the digestion and absorption of nutrients, serves an important neuroendocrine role. The focus of this thesis is to examine how changes in the motor function of the gastroduodenal region influence glucose absorption, gut hormone secretion, and postprandial blood glucose regulation, in different human populations, including the healthy young and those with cystic fibrosis. The studies included utilise a mix of established and novel techniques to evaluate gastroduodenal motor function and glucose absorption, and provide insights into the function of the human gut.

Strict overall glycaemic control dramatically reduces the incidence and progression of micro-, and probably macrovascular, complications associated with type 1 and type 2 diabetes. Postprandial glycaemia is now recognised as an important determinant of overall glycaemia, as indicated by the glycated haemoglobin (HbA1c). The rate of glucose absorption after a meal has a major influence on postprandial glycaemia and has, therefore, been a focus of increasing research interest in recent years. Postprandial blood glucose concentrations are a poor indicator of glucose absorption due to peripheral glucose uptake and hepatic glucose release. The glucose analogue 3-O-methylglucose (3-OMG) is absorbed in the small intestine by the same mechanism as glucose, but is not metabolised, and its plasma concentrations are widely used as an index of glucose absorption. However, analysis of plasma 3-OMG concentrations requires chromatographic
methods which are labour-intensive and costly. By labeling 3-OMG with the $^{14}\text{C}$ radioisotope, plasma $^{14}\text{C}$-3-OMG activity can be measured by the rapid and inexpensive method of liquid scintillation counting. In Chapter 6, plasma $^{14}\text{C}$-3-OMG activity was shown to correlate closely to plasma concentrations of 3-OMG, after concomitant oral administration. $^{14}\text{C}$-3-OMG therefore represents a convenient alternative to 3-OMG, for measuring enteral glucose absorption.

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted by the L and K cells in the intestines respectively, in response to nutrient-gut interactions. Their main function is the augmentation of glucose-induced insulin release from the pancreas, the so-called “incretin effect”. GLP-1 also possesses a potent inhibitory effect on gastric emptying, arguably the dominant mechanism through which GLP-1 lowers postprandial blood glucose. However, unlike GIP, the release of which is roughly proportional to the amount of glucose entering the small intestine, a caloric threshold of 1.8 kcal/min has been reported to exist for the release of GLP-1, below which the GLP-1 secretory mechanism is not stimulated. In the study described in Chapter 7, by performing a retrospective analysis of data collated from several studies performed previously, a transient, early release of GLP-1, in response to intraduodenal glucose delivery at the rate of 1 kcal/min, was demonstrated. While the functional significance of this observation remains uncertain, this early release of GLP-1 might serve the role of “priming” the glucose-regulatory system, in anticipation for the subsequent arrival of a larger nutrient
load. Furthermore, the mechanism for this early, transient release of GLP-1 remains to be further investigated, as the GLP-1 secreting intestinal L-cells are located most densely in the distal, rather than the proximal, small intestine.

It is established that differences in the rate of gastric emptying contribute to approximately one-third of the variation in the initial rise in postprandial glycaemia, but the contribution made by duodenal motor activity is much less well defined. An increase in duodenal motility, as measured by the number of pressure waves and propagated pressure wave sequences, has been shown to be associated with increased glucose absorption. More recently, using a combined manometry and impedance monitoring technique, it has been demonstrated that duodenal flow events may be a more important determinant of glucose absorption than pressure waves. Impedance monitoring is capable of measuring intraluminal movement of both fluid and air, and can be used in the proximal small intestine to measure the flow of intraluminal chyme. Compared to manometry, impedance monitoring correlates better with fluoroscopy, for measuring movement of small intestinal intraluminal content. In Chapter 8, it was demonstrated that despite stimulating duodenal pressure waves pharmacologically, using the prokinetic agent metoclopramide, there was no concomitant increase in the number of duodenal flow events, as measured by impedance monitoring, and no associated change in glucose absorption. These findings are consistent with those of a previous study using the anti-motility agent, hyoscine butylbromide, and both reinforce the importance of duodenal flow events in determining glucose
absorption, and highlight the value of combining impedance monitoring with manometry in assessing small intestinal motor function and nutrient absorption.

Delayed gastric emptying affects up to 50% of outpatients with long-standing type 1 and type 2 diabetes, often causing persistent upper gut symptoms that are difficult to manage. Acute hyperglycaemia, in a dose-dependent manner, exerts a number of reversible effects on upper gut motor function, including relaxation of the gastric fundus, suppression of antral motility, stimulation of pyloric contractions, and slowing of gastric emptying. In contrast to gastric motor function, data regarding the effects of hyperglycaemia on small intestinal motor function are scarce. Furthermore, there is little information regarding the effects of hyperglycaemia on incretin hormone release and intestinal glucose absorption. The study described in Chapter 9, using the combined manometry and impedance monitoring technique, demonstrated that acute hyperglycaemia in the physiological postprandial range (~9 mmol/L) had minimal impact on duodenal pressure waves and flow events, but reduced fasting plasma GLP-1 concentrations, and increased postprandial GIP secretion and small intestinal glucose absorption. The mechanism for these observations remains to be determined, but may involve changes in the small intestinal mucosa related to hyperglycaemia.

Nitric oxide is a major inhibitory neurotransmitter in the gut, and an increase in its availability has effects on gastropyloric motility and gastric emptying that are
similar to those observed during acute hyperglycaemia. Therefore, nitric oxide may be a mediator of the effects of hyperglycaemia on upper gut motor function. Using the specific nitric oxide synthase inhibitor, NG-nitro-L-arginine-methylester (L-NAME), the study described in Chapter 10 demonstrated that the delay in gastric emptying induced by acute hyperglycaemia (~15 mmol/L) was indeed mediated by nitric oxide, and may involve the modulation of tonic pyloric activity. In addition, nitric oxide may be involved in the release of insulin.

Cystic fibrosis (CF) affects approximately 1 in 2,500 live births in western societies, and the life-expectancy of these patients has risen dramatically as a result of improved medical care. However, this is accompanied by a rapid rise in many long term co-morbidities such as diabetes, which affects ~75 % of all CF patients by the age of 30. Cystic fibrosis-related diabetes (CFRD) is distinct from type 1 and type 2 diabetes, and is characterised by postprandial, rather than fasting, hyperglycaemia. Persistent fat malabsorption occurs in up to 20 % of CF patients, despite pancreatic enzyme supplementation, and fat malabsorption is known to accelerate gastric emptying in both healthy subjects and type 2 diabetes patients. The breakdown of fat is also required to stimulate the release of incretin hormones from the gut. Therefore, fat digestion in CF may be an important factor in determining the rate of gastric emptying and incretin hormone secretion, and consequently, postprandial glycaemia. The study described in Chapter 11 demonstrated that without pancreatic enzyme supplementation, CF patients had more rapid gastric emptying, reduced incretin hormone secretion, and exaggerated
postprandial glycaemic excursions compared to healthy subjects, after a solid high fat, high carbohydrate meal, and that these abnormalities were either substantially improved or normalised by pancreatic enzyme supplementation. Furthermore, the failure of enzyme supplementation to normalise GIP secretion, as opposed to the complete restoration of the GLP-1 response, suggests that mixing of enzymes with food in the proximal small intestine, where GIP-secreting K cells are predominantly located, is suboptimal. Therefore, strategies to optimise mixing between food and enzymes in the proximal small intestine, or incretin-based approaches such as the administration of GIP analogues, represent potential novel approaches in the management of postprandial hyperglycaemia and diabetes in CF.

The recent rapid rise in the prevalence of type 2 diabetes, and the importance of good overall glycaemic control in reducing the long term complications of diabetes, has prompted intense research into new ways to optimise diabetes management. Gastroduodenal motor function has a major influence on glucose absorption, incretin hormone secretion, and postprandial glycaemia, and thus represents an ideal therapeutic target, illustrated by the recent development of GLP-1-based therapies (such as the GLP-1 analogue exenatide, and the DPP-IV inhibitor sitagliptin) for the treatment of type 2 diabetes. However, many areas are still incompletely understood. Further studies are warranted to investigate the relationships between gastroduodenal motor function, glucose absorption, and
incretin hormone secretion, and their impact on postprandial blood glucose regulation.
Declaration

Name……………………………………. .... Program………………………………

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.

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