Regulation of upper gastrointestinal motility and sensation in health and disease

a thesis submitted by

Christopher Keith Rayner

for the degree of

Doctor of Philosophy

Department of Medicine
University of Adelaide

December 2000
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td>7</td>
</tr>
<tr>
<td>STATEMENT OF ORIGINALITY</td>
<td>12</td>
</tr>
<tr>
<td>ACKNOWLEDGMENTS</td>
<td>13</td>
</tr>
<tr>
<td>PUBLICATIONS ARISING FROM THIS THESIS</td>
<td>15</td>
</tr>
<tr>
<td>CHAPTER 1: MOTOR FUNCTION OF THE STOMACH AND DUODENUM</td>
<td>17</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>17</td>
</tr>
<tr>
<td>REGIONS OF THE STOMACH AND DUODENUM AND THEIR FUNCTION</td>
<td>17</td>
</tr>
<tr>
<td>Proximal stomach</td>
<td>18</td>
</tr>
<tr>
<td>Antrum</td>
<td>19</td>
</tr>
<tr>
<td>Pylorus</td>
<td>21</td>
</tr>
<tr>
<td>Duodenum</td>
<td>21</td>
</tr>
<tr>
<td>Motor Innervation</td>
<td>22</td>
</tr>
<tr>
<td>PATTERNS OF GASTRIC EMPTYING</td>
<td>23</td>
</tr>
<tr>
<td>Non-nutrient liquids</td>
<td>23</td>
</tr>
<tr>
<td>Nutrient liquids</td>
<td>24</td>
</tr>
<tr>
<td>Solids</td>
<td>24</td>
</tr>
<tr>
<td>Pasta</td>
<td>25</td>
</tr>
<tr>
<td>SMALL INTESTINAL FEEDBACK REGULATION OF GASTRIC MOTOR FUNCTION</td>
<td>25</td>
</tr>
<tr>
<td>INTEGRATION OF PROXIMAL GASTRIC, ANTRAL, PYLORIC, AND DUODENAL MOTOR FUNCTION DURING GASTRIC EMPTYING</td>
<td>28</td>
</tr>
<tr>
<td>Integration of proximal and distal gastric motor function</td>
<td>28</td>
</tr>
<tr>
<td>Pyloric function</td>
<td>30</td>
</tr>
<tr>
<td>Relative importance of the &quot;pressure pump&quot; and &quot;peristaltic pump&quot;</td>
<td>30</td>
</tr>
<tr>
<td>Duodenal function</td>
<td>31</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>32</td>
</tr>
<tr>
<td>CHAPTER 2: DISORDERED UPPER GASTROINTESTINAL MOTOR FUNCTION</td>
<td>38</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>38</td>
</tr>
<tr>
<td>AETIOLOGY OF MOTOR DYSFUNCTION</td>
<td>40</td>
</tr>
<tr>
<td>REGIONAL MOTOR ABNORMALITIES</td>
<td>41</td>
</tr>
<tr>
<td>Proximal stomach</td>
<td>41</td>
</tr>
<tr>
<td>Antrum</td>
<td>43</td>
</tr>
<tr>
<td>Pylorus</td>
<td>44</td>
</tr>
<tr>
<td>Duodenum</td>
<td>44</td>
</tr>
<tr>
<td>THERAPY FOR DELAYED GASTRIC EMPTYING</td>
<td>45</td>
</tr>
<tr>
<td>Pharmacological therapies</td>
<td>45</td>
</tr>
<tr>
<td>Non-pharmacological therapies</td>
<td>50</td>
</tr>
<tr>
<td>CHANGES IN GASTRODUODENAL MOTOR FUNCTION ASSOCIATED WITH AGING</td>
<td>51</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>52</td>
</tr>
</tbody>
</table>
CHAPTER 3: SENSORY FUNCTION IN THE UPPER GASTROINTESTINAL TRACT

INTRODUCTION ............................................................................. 55

GUT .................................................................................................. 55
Sensory innervation ...................................................................... 56
Mediators of sensation ................................................................ 57
Characteristics of gastrointestinal stimuli ................................ 58
Gut distension .............................................................................. 58
Chemical and nutrient stimuli .................................................... 59
Interaction between concurrent stimuli ...................................... 60

DISORDERED UPPER GASTROINTESTINAL SENSATION: THE AETIOLOGY OF SYMPTOMS .......................................................................... 61

EFFECTS OF AGING ON GASTROINTESTINAL SENSATION ............. 64

THERAPY FOR SYMPTOMS .............................................................. 65
Prokinetic drugs .......................................................................... 65
Specific mediators of viscerosensitivity ..................................... 66
Gastric pacing .............................................................................. 68

CONCLUSIONS .............................................................................. 69

CHAPTER 4: GASTROINTESTINAL CONTROL OF APPETITE .......... 72

INTRODUCTION ............................................................................. 72
CENTRAL CONTROL OF APPETITE ............................................. 72
GASTRIC DISTENSION .................................................................. 73
SMALL INTESTINAL FEEDBACK ...................................................... 74
MEDIATORS OF NUTRIENT FEEDBACK FROM THE SMALL INTESTINE 75
Neural mediators ........................................................................ 75
Humoral mediators ..................................................................... 76

EFFECT OF VARIATIONS IN THE BLOOD GLUCOSE CONCENTRATION ON APPETITE ......................................................... 79

EFFECT OF AGING ON APPETITE ................................................ 81

CONCLUSIONS .............................................................................. 83

CHAPTER 5: UPPER GASTROINTESTINAL MOTOR AND SENSORY FUNCTION IN DIABETES MELLITUS ......................................................... 87

SUMMARY ................................................................................... 87
INTRODUCTION ............................................................................. 88
MOTOR FUNCTION ........................................................................ 89
Oesophagus ............................................................................... 89
Stomach ...................................................................................... 90
Small intestine .......................................................................... 92

UPPER GASTROINTESTINAL SYMPTOMS IN DIABETES MELLITUS . . . 93

AETIOLOGY OF MOTOR DYSFUNCTION AND SYMPTOMS IN DIABETES 94
MANAGEMENT OF DISORDERED MOTILITY AND SYMPTOMS IN DIABETES MELLITUS ....................................................... 97
Oesophagus ............................................................................... 97
Stomach .................................................................................... 98
Small intestine .......................................................................... 100

CONCLUSIONS ............................................................................ 101

CHAPTER 6: RELATIONSHIPS OF UPPER GASTROINTESTINAL MOTOR AND SENSORY FUNCTION WITH GLYCAEMIC CONTROL . . . 105

INTRODUCTION ........................................................................... 106
EFFECTS OF THE BLOOD GLUCOSE CONCENTRATION ON UPPER GASTROINTESTINAL MOTOR AND SENSORY FUNCTION ........................................... 107
Motor function .................................................................................. 108
Sensory function ................................................................................ 114
Significance of the effects of the blood glucose concentration on upper gastrointestinal sensory function .............................................. 115
Mechanisms mediating the effects of hyperglycemia on gastrointestinal motor and sensory function .................................................. 116
THE CONTRIBUTION OF UPPER GASTROINTESTINAL MOTOR FUNCTION TO POSTPRANDIAL BLOOD GLUCOSE LEVELS ......................................................... 119
Gastric emptying ................................................................................ 119
Small intestinal glucose absorption .................................................. 121
Hepatic glucose production .............................................................. 123
Therapeutic modulation of gastric emptying ..................................... 124
CONCLUSIONS .................................................................................. 125

CHAPTER 7: TECHNIQUES FOR EVALUATION OF UPPER GASTROINTESTINAL MOTOR AND SENSORY FUNCTION IN HUMANS .............................................. 135
INTRODUCTION ............................................................................... 135
METHODS TO STUDY MOTOR FUNCTION ......................................... 136
Flow .................................................................................................. 137
Wall motion ....................................................................................... 142
Gastric electrical activity ................................................................. 147
METHODS TO STUDY SENSATION .................................................. 148
Subjective assessment of perception ............................................... 149
Objective assessment of sensation ................................................ 150
CONCLUSIONS ............................................................................... 153

CHAPTER 8: PHYSIOLOGICAL CHANGES IN BLOOD GLUCOSE DO NOT AFFECT GASTRIC COMPLIANCE AND PERCEPTION IN NORMAL SUBJECTS ................................................................. 158
SUMMARY ....................................................................................... 158
INTRODUCTION ............................................................................... 159
METHODS ....................................................................................... 161
Subjects .............................................................................................. 161
Protocol ............................................................................................. 161
Stabilisation of blood glucose concentrations .................................. 163
Performance of gastric distensions .................................................. 163
Evaluation of sensation ................................................................. 164
Statistical analysis ........................................................................... 164
RESULTS ........................................................................................ 165
Pressure-volume relationships ....................................................... 166
Perception of gastric distension ..................................................... 166
DISCUSSION .................................................................................... 166

CHAPTER 9: PHYSIOLOGICAL CHANGES IN BLOOD GLUCOSE AFFECT APPETITE AND PYLORIC MOTILITY DURING INTRADUODENAL LIPID INFUSION ................................................. 174
SUMMARY ....................................................................................... 174
INTRODUCTION ............................................................................... 175
METHODS ....................................................................................... 177
Subjects .............................................................................................. 177
Protocol ............................................................................................. 177
Outcome Measures ........................................ 179
Statistical Analysis ........................................ 180
RESULTS ..................................................... 181
Appetite .................................................... 181
Antrypyloric pressures ...................................... 182
DISCUSSION ............................................... 183
Appetite .................................................... 184
Antrypyloric Pressures ..................................... 186
Conclusions ............................................... 189

CHAPTER 10: EFFECTS OF CHOLECYSTOKININ ON APPETITE AND PylORIC MOTILITY DURING PHYSIOLOGICAL HYPERGLYCAEMIA .................................................. 196

SUMMARY .................................................. 196
INTRODUCTION ............................................. 197
METHODS .................................................. 199
Subjects ................................................... 199
Protocol .................................................... 199
Stabilisation of blood glucose concentrations ............ 201
Measurement of antrypyloric pressures ...................... 201
Statistical analysis ......................................... 202
RESULTS ................................................... 203
Blood glucose concentrations ............................. 203
Antrypyloric pressures ................................... 203
Hunger, fullness, and nausea ............................... 204
Food intake ............................................... 204
DISCUSSION ................................................. 205

CHAPTER 11: PROXIMAL GASTRIC COMPLIANCE AND PERCEPTION OF DISTENSION IN TYPE 1 DIABETES MELLITUS - EFFECTS OF HYPERGLYCAEMIA .............................................. 214

SUMMARY .................................................. 214
INTRODUCTION ............................................. 215
METHODS .................................................. 217
Subjects ................................................... 217
Protocol .................................................... 218
Stabilisation of blood glucose concentrations .......... 219
Performance of gastric distension ......................... 219
Assessment of perception .................................. 221
Assessment of upper gastrointestinal symptoms and autonomic nerve function ............... 221
Statistical analysis ......................................... 222
RESULTS ................................................... 222
Pressure-volume relationships ............................ 222
Perception .................................................. 224
DISCUSSION ................................................. 225

CHAPTER 12: EFFECTS OF HYPERGLYCAEMIA ON THE CORTICAL RESPONSE TO EOSPHAGEAL DISTENSION IN NORMAL SUBJECTS .................................................. 235

SUMMARY .................................................. 235
INTRODUCTION ............................................. 236
METHODS .................................................. 237
Protocol .................................................... 237
Performance of oesophageal balloon distensions ........ 238
CHAPTER 13: THE STIMULATION OF ANTRAL MOTILITY BY ERYTHROMYCIN IS ATTENUATED BY HYPERGLYCAEMIA

SUMMARY

INTRODUCTION

METHODS

Subjects...

Protocol...

Statistical analysis

RESULTS

Antral pressure waves

Isolated pyloric pressure waves

Basal pyloric pressure

Duodenal pressure waves

DISCUSSION

CHAPTER 14: GASTRODUODENAL, RESPONSES TO SMALL INTESTINAL NUTRIENTS, AND SMALL INTESTINAL GLUCOSE ABSORPTION, IN TYPE 1 DIABETES MELLITUS

SUMMARY

INTRODUCTION

METHODS

Subjects...

Protocol...

Statistical analysis

RESULTS

Upper gastrointestinal symptoms and autonomic nerve function

Blood glucose concentrations

Duration of the postprandial period

Duodenal pressure waves

Plasma GLP-1 concentrations

Perceptions related to intraduodenal nutrient infusion

Plasma 3-OMG concentrations

DISCUSSION

Upper gastrointestinal responses to intraduodenal nutrient...

Small intestinal glucose absorption

CHAPTER 15: EFFECTS OF INTRADUODENAL GLUCOSE AND FRUCTOSE ON ANTEROPYLORIC MOTILITY AND APPETITE IN HEALTHY HUMANS

SUMMARY
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>308</td>
</tr>
<tr>
<td>METHODS</td>
<td>310</td>
</tr>
<tr>
<td>Protocol</td>
<td>310</td>
</tr>
<tr>
<td>Antropyloric pressures</td>
<td>311</td>
</tr>
<tr>
<td>Glucose, insulin, GIP, and GLP-1 concentrations</td>
<td>312</td>
</tr>
<tr>
<td>Appetite</td>
<td>313</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>313</td>
</tr>
<tr>
<td>RESULTS</td>
<td>313</td>
</tr>
<tr>
<td>Antropyloric pressures</td>
<td>313</td>
</tr>
<tr>
<td>Blood glucose, and plasma insulin, GIP, and GLP-1</td>
<td>314</td>
</tr>
<tr>
<td>Appetite</td>
<td>314</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>315</td>
</tr>
<tr>
<td>CHAPTER 16: EFFECTS OF AGE ON PROXIMAL GASTRIC MOTOR AND SENSORY FUNCTION</td>
<td>324</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>324</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>325</td>
</tr>
<tr>
<td>METHODS</td>
<td>325</td>
</tr>
<tr>
<td>Subjects</td>
<td>327</td>
</tr>
<tr>
<td>Protocol</td>
<td>327</td>
</tr>
<tr>
<td>Performance of gastric distensions</td>
<td>329</td>
</tr>
<tr>
<td>Measurement of perception</td>
<td>330</td>
</tr>
<tr>
<td>Measurement of energy intake</td>
<td>330</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>331</td>
</tr>
<tr>
<td>RESULTS</td>
<td>331</td>
</tr>
<tr>
<td>Perception of gastric distension</td>
<td>331</td>
</tr>
<tr>
<td>Fasting pressure-volume relationships</td>
<td>332</td>
</tr>
<tr>
<td>Energy intake at the meal</td>
<td>333</td>
</tr>
<tr>
<td>Proximal gastric tone before and after the meal</td>
<td>333</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>334</td>
</tr>
<tr>
<td>CONCLUSIONS</td>
<td>342</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>349</td>
</tr>
</tbody>
</table>
SUMMARY

The studies presented in this thesis relate to the regulation of upper gastrointestinal motor and sensory function in humans, in both health and disease, with particular emphasis on the impact of acute changes in the blood glucose concentration. The broad areas addressed are (i) the effect of physiological changes in the blood glucose concentration in the regulation of gastroduodenal motor and sensory function, (ii) the effect of acute hyperglycaemia on gastric motor and sensory function in patients with diabetes mellitus and the motor response to prokinetic therapy, (iii) the relationships between small intestinal nutrient exposure, gastrointestinal peptide hormone release, antpyloric motility, and appetite, and (iv) the effect of aging on the proximal gastric response to distension and food intake.

Elevation of the blood glucose concentration within the physiological postprandial range (8 - 9 mmol/L) has recently been shown to slow gastric emptying when compared to euglycaemia (4 - 5 mmol/L), and to increase the sensitivity of some regions of the gut, including the oesophagus and duodenum, to distension. Marked hyperglycaemia (blood glucose ~15 mmol/L) increases proximal gastric compliance, and the perception of gastric distension. To examine whether physiological variations in the blood glucose concentration affect proximal stomach function, isobaric and isovolemic gastric distensions were performed using a barostat in fasting healthy volunteers at blood glucose concentrations of 4 mmol/L and 9 mmol/L. Neither fasting gastric compliance nor the perception of gastric distension were affected by variation of the blood glucose in the physiological range, in contrast to the effects of marked hyperglycaemia. These observations suggest that in the fasting state at least, gut regions differ in their sensitivity to blood glucose fluctuations.
The impact of elevations in the blood glucose concentration on appetite is controversial; in the absence of nutrients in the small intestine, "physiological" hyperglycaemia does not appear to affect satiation. The effects of physiological hyperglycaemia (blood glucose ~8 mmol/L) on antroduodenal motility and perceptions of appetite were examined before and during intraduodenal lipid infusion in healthy volunteers. There was no difference in hunger between the two blood glucose concentrations during fasting, however hunger was less at a blood glucose concentration of 8 mmol/L than 5 mmol/L during intraduodenal lipid infusion. Physiological hyperglycaemia did not affect the number of atrial or phasic pyloric waves, nor basal pyloric pressure, but the pattern of pyloric pressures over time differed from euglycaemia. These observations suggest that physiological elevations of blood glucose act synergistically with nutrients in the small intestine to influence satiation and pyloric motility.

In view of the apparent synergy between physiological hyperglycaemia and the presence of nutrients in the small intestine a study was performed to determine whether physiological elevations of blood glucose modulate the effects of exogenous cholecystokinin on pyloric motility and appetite in healthy volunteers. The suppression of food intake induced by intravenous cholecystokinin did not differ between blood glucose concentrations of 4 mmol/L and 8 mmol/L, but the stimulation of basal pyloric pressure by cholecystokinin was greater at a blood glucose of 8 mmol/L. The study demonstrates a synergistic relationship between physiological hyperglycaemia and the actions of CCK on pyloric motility. However, the interaction between small intestinal nutrients and elevated blood glucose in suppressing hunger is apparently not attributable to an interaction with CCK.

Upper gastrointestinal symptoms occur frequently in patients with diabetes mellitus, but their aetiology is poorly understood. In patients with severe symptoms, during euglycaemia gastric compliance and perception of gastric distension are greater than in healthy controls.
Hyperglycaemia (blood glucose concentration ~ 15 mmol/L) increases gastric compliance and the perception of gastric distension in healthy volunteers. To examine proximal stomach function and the effects of hyperglycaemia in unselected patients with type 1 diabetes mellitus, gastric distensions were performed using a barostat during both euglycaemia (blood glucose 6 mmol/L) and hyperglycaemia (15 mmol/L). Results were compared with those obtained in healthy controls studied during euglycaemia. In the diabetic patients, the perception of gastric distension was greater than in the controls during euglycaemia. Hyperglycaemia increased gastric compliance in the patients. These observations indicate that even uncomplicated diabetes is associated with hypersensitivity to gastric distension, and that changes in proximal stomach motor function may contribute to the delayed gastric emptying associated with hyperglycaemia in patients with diabetes mellitus.

Measurement of cortical evoked potentials, induced by rapid balloon distension or electrical stimulation of a viscous, is an objective method of evaluating visceral sensation. The effects of hyperglycaemia (blood glucose ~ 15 mmol/L) on cortical potentials elicited by rapid balloon distension of the oesophagus were assessed in healthy volunteers. The amplitude of the cortical response to moderate, but not unpleasant, oesophageal distension was greater during hyperglycaemia when compared to euglycaemia. These observations are consistent with the concept of an increased intensity of gut sensation during hyperglycaemia.

Erythromycin, when given acutely during euglycaemia to patients with diabetic gastroparesis, is a potent prokinetic agent. Recent studies have demonstrated that the gastrokinetic effects of erythromycin are attenuated by hyperglycaemia. The motor correlates of this effect are unknown. Antpyloroduodenal pressures were measured in healthy volunteers before and during intraduodenal lipid infusion, at blood glucose
concentration of 5 mmol/L and 15 mmol/L; erythromycin was administered intravenously after intraduodenal lipid infusion had commenced. Hyperglycaemia attenuated the effects of erythromycin on antral motility and the organisation of antral pressure waves, but not on the pylorus or duodenum.

It is not known whether small intestinal feedback on upper gastrointestinal motility and sensation is abnormal in patients with diabetes mellitus, nor whether glucose absorption from the small intestine is increased. Antropyloroduodenal pressures, perceptions of hunger and fullness, and plasma glucagon-like peptide 1 (GLP-1) were measured during and after 30 minutes of intraduodenal nutrient infusion, in patients with type 1 diabetes (studied during euglycaemia) and healthy controls. An intraduodenal bolus of 3-O-methylglucose (3-OMG) was administered after the nutrient infusion, and plasma 3-OMG concentrations were used as an index of glucose absorption. Antropyloroduodenal motility was similar in patients and controls during the nutrient infusion, but antral and duodenal motor activity was greater in the patients following the infusion, with a delayed return of phase III activity. There were no differences in gut perceptions in response to nutrient, nor in GLP-1 concentrations. 3-OMG absorption did not differ between patients and controls, but did correlate with both duodenal motor activity during nutrient infusion, and the blood glucose concentration at the time of 3-OMG administration.

Fructose empties from the stomach more rapidly than glucose, and may suppress food intake more at a subsequent meal. These differential effects may potentially be attributable to the magnitude of small intestinal feedback. The effects of fructose, glucose, and saline given intraduodenally on antropyloric motility and appetite were evaluated in healthy volunteers. The two monosaccharides did not differ in their effects on antropyloric motility, but only fructose suppressed food intake when compared with saline. Intraduodenal glucose increased blood glucose, as well as plasma insulin and gastric inhibitory
polypeptide (GIP), more than intraduodenal fructose, whereas there was no difference in the GLP-1 response. These observations indicate that intraduodenal fructose and glucose have comparable effects on enteroendocrine motility, while only fructose suppresses appetite compared to saline, despite similar GLP-1 and less GIP release than glucose.

Healthy aging is associated with a reduction in food intake that may predispose to malnutrition. The effects of aging on proximal stomach function have not been studied. Distensions of the proximal stomach were undertaken in healthy older men and young male controls using a barostat, and gastric tone was evaluated before and after a meal. In older subjects the perception of gastric distension was much less, in the absence of any difference in gastric compliance, and gastric relaxation in response to a meal was delayed. These observations suggest that diminished sensations arising from the stomach may predispose to impaired regulation of food intake with aging.