



**Relationships Between Motor and Sensory
Function in the Proximal Gut, Appetite, &
Nutrients In Healthy Human Subjects**

A Thesis submitted by

Jane Mary Andrews

For the Degree of

Doctor of Philosophy

In the

**Department of Medicine
University of Adelaide**

December 1999

TABLE OF CONTENTS

| | |
|---|---|
| Summary..... | 1 |
| Statement of Originality..... | 4 |
| Dedication..... | 4 |
| Acknowledgments..... | 5 |
| Publications Arising From the Thesis..... | 7 |

Chapter 1**The Role of the Gut in Appetite Regulation**

| | |
|---|----|
| 1.1 INTRODUCTION..... | 9 |
| 1.2 PREABSORPTIVE MECHANISMS IN APPETITE REGULATION..... | 11 |
| 1.2.1 Oral effects..... | 11 |
| 1.2.2 Gastric effects..... | 12 |
| 1.3 ABSORPTIVE MECHANISMS IN APPETITE REGULATION..... | 14 |
| 1.3.1 Role of the Small Intestine..... | 14 |
| 1.3.2 Putative Satiety Factors/Mechanisms..... | 17 |
| 1.4 POSTABSORPTIVE MECHANISMS IN APPETITE REGULATION..... | 23 |
| 1.4.1 Effects of portal and intravenous nutrients..... | 23 |
| 1.4.2 Central nervous system (CNS) appetite regulation..... | 24 |
| 1.5 ASSESSMENT OF APPETITE..... | 24 |
| 1.5.1 Questionnaire/Visual Analogue Scales (VAS)..... | 25 |
| 1.5.2 Spontaneous report..... | 26 |
| 1.5.3 Observation..... | 26 |
| 1.5.4 Diet diary..... | 26 |
| 1.5.5 Dietary recall..... | 27 |
| 1.6 SUMMARY..... | 27 |

Chapter 2**Human Gastroduodenal Motor Function and its Assessment**

| | |
|---|----|
| 2.1 INTRODUCTION..... | 30 |
| 2.2 FUNCTIONS OF GASTRODUODENAL MOTOR ACTIVITY..... | 30 |

| | |
|---|----|
| 2.3 GASTRODUODENAL ANATOMY..... | 30 |
| 2.4 STRUCTURE OF MUSCULAR LAYERS..... | 31 |
| 2.5 ELECTRICAL CONTROL OF MUSCULAR LAYERS..... | 32 |
| 2.6 OBSERVED MOTOR PATTERNS..... | 34 |
| 2.6.1 Tonic and phasic motor events..... | 35 |
| 2.6.2 Lumen-occlusive vs non lumen-occlusive phasic motor events..... | 35 |
| 2.6.3 Individual contractions..... | 36 |
| 2.6.4 Commonly recognised phasic motor patterns..... | 36 |
| 2.6.5 Global outcomes..... | 37 |
| 2.7 ASSESSMENT OF MOTOR FUNCTION..... | 38 |
| 2.7.1 Techniques for detection of contraction(s)..... | 39 |
| 2.7.2 Techniques for detection of wall motion..... | 39 |
| 2.7.3 Techniques for detection of changes in intraluminal pressure..... | 41 |
| 2.7.4 Techniques for detection of movement of contents..... | 43 |
| 2.8 SUMMARY..... | 45 |

Chapter 3

Human Gastroduodenal Sensory Function and its Assessment

| | |
|--|----|
| 3.1 INTRODUCTION..... | 46 |
| 3.2 PURPOSE OF GASTRODUODENAL SENSORY FUNCTION..... | 47 |
| 3.3 ANATOMY OF SENSORY FUNCTION..... | 48 |
| 3.4 GUT SENSING MECHANISMS..... | 49 |
| 3.4.1 Chemical mechanisms..... | 50 |
| 3.4.2 Mechanical mechanisms..... | 51 |
| 3.5 LOCAL RESPONSES..... | 52 |
| 3.6 CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT..... | 52 |
| 3.7 PERCEPTION..... | 53 |
| 3.8 ASSESSMENT OF SENSORY FUNCTION IN HUMANS..... | 54 |
| 3.8.1 Barostat..... | 54 |
| 3.8.2 Questionnaires/Visual analogue scales (VAS)..... | 55 |
| 3.8.3 Spontaneous report, descriptive..... | 55 |
| 3.8.4 Quantified stimuli, threshold/tolerance levels..... | 55 |
| 3.8.5 Evoked potentials, spinal & cerebral..... | 56 |
| 3.8.6 Techniques measuring blood flow and/or metabolism..... | 56 |
| 3.9 SUMMARY..... | 56 |

Chapter 4**Effects of Small Intestinal Nutrients on Gastroduodenal Motor and Sensory Function**

| | |
|---|----|
| 4.1 INTRODUCTION..... | 58 |
| 4.2 EFFECTS OF NUTRIENTS ON MOTOR FUNCTION..... | 59 |
| 4.2.1 Major outcomes..... | 59 |
| 4.2.2 Effects of intraluminal as compared to intravenous nutrients..... | 61 |
| 4.2.3 Variation of motor effects between macronutrient classes..... | 63 |
| 4.2.4 Adaptation of motor response to dietary changes..... | 64 |
| 4.2.5 Mechanisms implicated in small intestinal nutrient exposure mediated regulation of gastroduodenal motor function..... | 65 |
| 4.3 EFFECTS OF NUTRIENTS ON CONSCIOUS GASTRODUODENAL SENSATION..... | 68 |
| 4.3.1 Modulation of sensations by intraluminal nutrients..... | 68 |
| 4.3.2 Modulation of sensations by intravenous nutrients..... | 69 |
| 4.4 EFFECTS OF NUTRIENTS ON APPETITE REGULATION..... | 69 |
| 4.5 SUMMARY..... | 70 |

Chapter 5**Effects of Ageing on Appetite Regulation and Gastroduodenal Motor and Sensory Function in Humans**

| | |
|--|----|
| 5.1 INTRODUCTION..... | 72 |
| 5.2 APPETITE..... | 74 |
| 5.3 MOTOR FUNCTION..... | 75 |
| 5.4 SENSORY FUNCTION..... | 77 |
| 5.5 ABSORPTIVE FUNCTION..... | 78 |
| 5.6 POTENTIAL GASTROINTESTINAL MECHANISMS IN “ANOREXIA OF AGEING”..... | 78 |
| 5.7 CONFOUNDING FACTORS IN ASSESSING THE “ANOREXIA OF AGEING”..... | 79 |
| 5.7.1 Taste/Oral function..... | 79 |
| 5.7.2 Activity..... | 80 |

| | |
|--|----|
| 5.7.3 Intercurrent Illness/Medication | 80 |
| 5.7.4 Social and psychological aspects | 81 |
| 5.8 SUMMARY | 81 |

Chapter 6

The Relationships Between Gastrointestinal Pressures/Contractions and Flows

| | |
|--|----|
| 6.1 INTRODUCTION | 83 |
| 6.2 TEMPOROSPATIAL RESOLUTION AND ITS SIGNIFICANCE | 84 |
| 6.2.1 Temporal resolution | 84 |
| 6.2.2 Spatial resolution | 86 |
| 6.3 PROXIMAL GASTRIC PRESSURE/FLOW RELATIONSHIPS | 87 |
| 6.4 ANTRAL PRESSURE/FLOW RELATIONSHIPS | 88 |
| 6.5 PYLORIC PRESSURE/FLOW RELATIONSHIPS | 90 |
| 6.6 DUODENAL PRESSURE/FLOW RELATIONSHIPS..... | 91 |
| 6.7 SMALL INTESTINAL PRESSURE/FLOW RELATIONSHIPS..... | 92 |
| 6.8 DESIRABLE CHARACTERISTICS FOR AN INSTRUMENT TO MEASURE INTRALUMINAL FLOWS | 93 |
| 6.9 SUMMARY | 93 |

Chapter 7

Methodologies Used in Multiple Studies.

| | |
|---|----|
| 7.1 INTRODUCTION | 94 |
| 7.2 ESTABLISHED METHODS | 95 |
| 7.2.1 Nasoenteric tube insertion..... | 95 |
| 7.2.2 Water perfused manometry..... | 95 |
| 7.2.3 Monitoring of transmucosal potential difference (TMPD)..... | 96 |
| 7.2.4 Gastric barostat..... | 96 |
| 7.2.5 Blood glucose & insulin measurement | 97 |
| 7.2.6 Intraduodenal (ID) nutrient infusion | 97 |
| 7.2.7 Visual analogue scales (VAS's)..... | 98 |

| | |
|---|----|
| 7.3 SHARED MANOMETRIC RECORDING AND ANALYSIS TECHNIQUES.. | 98 |
| 7.3.1 Recordings..... | 98 |
| 7.3.2 Scoring of Pressure Events..... | 98 |
| 7.3.3 Statistical Analysis..... | 99 |

Chapter 8

Effects of Intraduodenal Nutrients on Appetite and Antropyloric Motility: Role of Gastrointestinal Hormones, Nutrient Class, Dietary Adaptation and Ageing

| | |
|-----------------------|-----|
| 8.1 INTRODUCTION..... | 102 |
| 8.2 CONCLUSION..... | 143 |

8A Appetite Suppression By Intraduodenal Nutrients

| | |
|---|-----|
| 8A.1 INTRODUCTION..... | 104 |
| 8A.2 METHODS..... | 104 |
| 8A.2.1 Subjects..... | 104 |
| 8A.2.2 Experimental design..... | 105 |
| 8A.2.3 Blood measurements..... | 106 |
| 8A.2.4 Statistical analysis..... | 108 |
| 8A.3 RESULTS..... | 109 |
| 8A.3.1 ID Glucose vs. ID Saline..... | 109 |
| 8A.3.2 Effect of octreotide on responses to ID glucose..... | 110 |
| 8A.4 DISCUSSION..... | 113 |

8B Comparison of Effects of Intraduodenal Glucose vs Lipid and Dietary Glucose Supplementation

| | |
|----------------------------------|-----|
| 8B.1 INTRODUCTION..... | 116 |
| 8B.2 METHODS..... | 116 |
| 8B.2.1 Subjects..... | 116 |
| 8B.2.2 Experimental design..... | 117 |
| 8B.2.3 Outcome measures..... | 118 |
| 8B.2.4 Statistical analyses..... | 119 |

| | |
|--|-----|
| 8B.3 RESULTS..... | 119 |
| 8B.3.1 Plasma glucose and insulin concentrations..... | 119 |
| 8B.3.2 Appetite ratings..... | 120 |
| 8B.3.3 Antropyloric pressures..... | 120 |
| 8B.4 DISCUSSION..... | 121 |
| 8B.4.1 Appetite..... | 122 |
| 8B.4.2 Pyloric motility..... | 124 |
| | |
| 8C Appetite Regulation In The Elderly | |
| 8C.1 INTRODUCTION..... | 127 |
| 8C.2 METHODS..... | 128 |
| 8C.2.1 Subjects..... | 128 |
| 8C.2.2 Experimental design..... | 128 |
| 8C.2.3 Assessment of appetite..... | 129 |
| 8C.2.4 Measurement of plasma CCK, GLP-1 and PYY..... | 129 |
| 8C.2.5 Measurement of antropyloric pressures..... | 130 |
| 8C.2.6 Statistical analyses..... | 130 |
| 8C.3 RESULTS..... | 131 |
| 8C.3.1 Appetite..... | 131 |
| 8C.3.2 Gastrointestinal hormones..... | 132 |
| 8C.3.3 Antropyloric motility..... | 134 |
| 8C.3.4 Relationships between gastrointestinal hormones and appetite..... | 135 |
| 8C.3.5 Relationships between gastrointestinal hormones and pyloric pressures.... | 136 |
| 8C.4 DISCUSSION..... | 137 |
| 8C.4.1 Appetite..... | 138 |
| 8C.4.2 Gastrointestinal hormones..... | 139 |
| 8C.4.3 Pyloric pressures..... | 141 |
| 8C.4.4 Relationships among CCK, GLP-1, PYY, appetite and pyloric pressures... | 141 |

Chapter 9

Effects of Physiological Hyperglycaemia on Gastric Motility, Compliance and Perception

| | |
|-----------------------|-----|
| 9.1 INTRODUCTION..... | 145 |
| 9.2 CONCLUSION..... | 159 |

9A Physiological Hyperglycaemia, Antropyloric Motility &

Appetite

| | |
|------------------------------------|-----|
| 9A.1 INTRODUCTION | 146 |
| 9A.2 MATERIALS AND METHODS | 146 |
| 9A.2.1 Subjects..... | 146 |
| 9A.2.2 Experimental design..... | 146 |
| 9A.2.3 Outcome measures..... | 147 |
| 9A.2.4 Statistical analysis | 148 |
| 9A.3 RESULTS..... | 148 |
| 9A.3.1 Appetite..... | 148 |
| 9A.3.2 Antropyloric pressures..... | 149 |
| 9A.4 DISCUSSION..... | 150 |
| 9A.4.1 Appetite..... | 150 |
| 9A.4.2 Antropyloric Pressures..... | 152 |

9B Physiological Hyperglycaemia, Proximal Gastric Compliance & Perception Of Distension

| | |
|---|-----|
| 9B.1 INTRODUCTION | 154 |
| 9B.2 MATERIALS AND METHODS | 154 |
| 9B.2.1 Subjects..... | 154 |
| 9B.2.2 Experimental design..... | 154 |
| 9B.2.3 Performance of gastric distension | 155 |
| 9B.2.4 Evaluation of sensation and appetite..... | 156 |
| 9B.2.5 Statistical analysis | 156 |
| 9B.3 RESULTS..... | 156 |
| 9B.3.1 Pressure-volume relationships..... | 157 |
| 9B.3.2 Perception of gastric distension and appetite..... | 157 |
| 9B.4 DISCUSSION..... | 157 |

Chapter 10**Effect of a Lacto-ovo Vegetarian Diet on Fasting Small Intestinal Motility**

| | |
|---|-----|
| 10.1 INTRODUCTION..... | 160 |
| 10.2 MATERIALS AND METHODS..... | 161 |
| 10.2.1 Subjects..... | 161 |
| 10.2.2 Experimental design..... | 162 |
| 10.2.3 Dietary assessment..... | 162 |
| 10.2.4 Manometric data..... | 163 |
| 10.2.5 Statistical analyses..... | 163 |
| 10.3 RESULTS..... | 164 |
| 10.3.1 Dietary data..... | 164 |
| 10.3.2 Fasting small intestinal motility..... | 165 |
| 10.4 DISCUSSION..... | 166 |
| 10.5 CONCLUSION..... | 170 |

Chapter 11**High Resolution Manometry of the Human Duodenum During Fasting and Lipid Infusion**

| | |
|--|-----|
| 11.1 INTRODUCTION..... | 171 |
| 11.2 METHODS..... | 173 |
| 11.2.1 Subjects..... | 173 |
| 11.2.2 Protocol..... | 173 |
| 11.2.3 Positioning of the Manometric Assembly..... | 173 |
| 11.2.4 Manometric Recordings..... | 174 |
| 11.2.5 Data Analysis..... | 174 |
| 11.3 RESULTS..... | 176 |
| 11.3.1 Number of PW sequences..... | 177 |
| 11.3.2 Frequency of PW sequence lengths..... | 177 |
| 11.3.3 Site of PW sequences..... | 177 |
| 11.3.4 Direction of PW sequences..... | 178 |
| 11.4 DISCUSSION..... | 178 |

Chapter 12**Validation of a Novel Luminal Flow Velocimeter With Video Fluoroscopy and Manometry in the Human Oesophagus**

| | |
|--|-----|
| 12.1 INTRODUCTION..... | 185 |
| 12.2 MATERIALS AND METHODS..... | 186 |
| 12.2.1 Design of the Velocimeter System..... | 186 |
| 12.2.2 Bench testing..... | 188 |
| 12.2.3 Safety Assessments..... | 189 |
| 12.2.4 Human Study..... | 190 |
| 12.3 RESULTS..... | 193 |
| 12.3.1 Bench testing..... | 193 |
| 12.3.2 Human study..... | 193 |
| 12.4 DISCUSSION..... | 196 |

Chapter 13

| | |
|------------------------|------------|
| Conclusion..... | 200 |
|------------------------|------------|

| | |
|------------------------|------------|
| REFERENCES..... | 206 |
|------------------------|------------|



SUMMARY

The motor and sensory interactions between nutrients and the proximal gut in humans are not well understood, despite the pivotal importance of these interactions on appetite, absorption and thus, nutrition. In part, this lack of knowledge results from technical difficulties in studying motor function in the human gut. In particular, the inability to continuously measure intraluminal flow with any degree of temporal resolution, has impeded progress in this field. The studies described in this thesis focus on nutrient-gut interactions; and the development of novel methodologies aimed at advancing our understanding and interpretation of the relationships between intraluminal pressures and flows.

Nutrient-Gut Interactions

To examine the roles of insulin and other gastrointestinal hormones in mediating appetite suppression in response to intraduodenal (ID) infusion of glucose, subjects received either ID glucose, ID saline or ID glucose with intravenous octreotide (somatostatin analogue) during euglycaemic hyperinsulinaemia. It was confirmed that ID glucose suppressed appetite and decreased intake compared to ID saline. Moreover, the suppression of appetite did not appear to be due to elevation of plasma insulin, and was abolished by octreotide implying a role for other gastrointestinal hormones in the production of satiety.

Different macronutrients may vary in their effects on gastrointestinal motor and sensory function. The relative potencies of ID lipid and glucose in suppressing appetite and stimulating pyloric motility was therefore compared. In young healthy subjects (18-40 yrs), lipid was found to be more potent at both suppressing appetite and stimulating pyloric motility.

As there is substantial evidence to suggest that regulation of appetite is impaired with ageing, this comparison was repeated in healthy older subjects (65-80 yrs). In the elderly, the two nutrients did not differ in their effects on appetite or intake. The older subjects were less hungry at baseline and had an enhanced phasic pyloric response to lipid, compared to the young. In addition, the elderly had both a higher fasting level of cholecystinin (CCK) and a greater incremental CCK response to ID lipid. All of which is consistent with dysregulation of appetite with ageing.

Usual diet, and modification of intake are known to influence the gut's subsequent handling of meals containing the nutrient whose intake was altered. The motor mechanisms by which dietary changes influence proximal gut function are unknown. Whether regulation of appetite is likewise affected by changes in diet is also unknown. To determine whether motor modifications occur by "nutrient specific" mechanisms, and to determine whether appetite changes occur at all, pyloric motility and appetite (in response to separate ID infusions of glucose and lipid) were evaluated before and after dietary supplementation with glucose. The motor adaptation which occurred was nutrient specific; in that pyloric tone in response to glucose decreased after supplementation, whilst the motor response to lipid was not substantially altered. Dietary modification did influence appetite, but this change occurred across macronutrient class, with attenuation of the appetite suppressant effects of ID lipid seen after dietary glucose supplementation, whilst perception of appetite in response to ID glucose did not change.

Given the changes found in motor responses to nutrients after dietary manipulation, the effect of diet on fasting motility was then examined. Fasting small intestinal motility was evaluated in longstanding lacto-ovo vegetarian and omnivorous subjects, and also in omnivores who consumed a lacto-ovo vegetarian diet for a 14 day period. No differences in fasting motility were found between long-term vegetarian and control subjects; although when control subjects acutely adopted a vegetarian diet, their interdigestive motor cycle length decreased by approximately one third, due a shortening of phase II. This change was unrelated to total dietary fibre intake. Dietary change may therefore be capable of also modifying fasting motility.

Plasma glucose concentrations in the pathological range (such as seen in diabetes mellitus) are well documented to affect both motor and sensory function in the proximal gut. It is less clear whether plasma glucose within the physiological postprandial range has any effect, and whether physiological levels of hyperglycaemia interact with the presence of small intestinal nutrients. Gastric motor and sensory function were therefore studied at ~4-5 mmol/L (fasting level) and at ~8-9 mmol/L (physiological hyperglycaemia). Physiological hyperglycaemia increased the perception of fullness during fasting and decreased hunger during ID lipid infusion. It also suppressed antral pressure waves, and altered the temporal patterning of phasic pyloric pressures, but had no effect on proximal gastric compliance, or perception of distension. Thus, although physiological hyperglycaemia does affect some proximal gastrointestinal functions, others are spared.

Novel Methodology

To better define the spatiotemporal patterning of duodenal pressures, high resolution manometry along the length of the human duodenum was performed during fasting and 3 different rates of ID lipid infusion. The overwhelming majority of pressure wave (PW) sequences were short (1.5-4.5 cm). ID lipid was associated with a dose-related suppression of the number of PW sequences and regional variation along the duodenum in the patterning of PW sequences compared to fasting. Under all conditions, a greater proportion of sequences were antegrade than retrograde. Further interpretation of the mechanical significance of the temporospatial patterning of duodenal pressures, will require concurrent measurement of intraluminal flows. To date this has not been achievable in human subjects.

In order to concurrently measure intraluminal pressures and flows, a novel laser-Doppler velocimeter was developed. Fibre-optic technology was used to quantify particle speed within the gut lumen and this was implanted in a manometric assembly to enable concurrent pressure measurements. The initial human validation study of this instrument was performed in the oesophagus with concurrent assessment of flow by barium fluoroscopy. The onset of the flow signal from the velocimeter correlated well, particularly in the distal oesophagus, with the occurrence of flow documented fluoroscopically. In analysing data from this study, technical and timing problems with the instrument were discovered. Consideration of these matters has led to further refinements of the instrument being proposed.