Factors Involved in the Regulation of Gastrointestinal Motility, Hormone Release, Symptoms and Energy Intake in Health and Patients with Functional Dyspepsia

A thesis submitted by

Amelia Pilichiewicz

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LIST OF ABBREVIATIONS

1.33/50	1.33 kcal/min lipid infusion for 50 min
1.33/150	1.33 kcal/min lipid infusion for 150 min
4/50	4 kcal/min lipid infusion for 50 min
5HT	5-Hydroxy-tryptamine
APD	antropyloroduodenal
ALE	artichoke leaf extract
ANOVA	analysis of variance
AUC	area under the curve
BMI	body mass index
CCK	cholecystokinin
CHO	carbohydrate
CV	coefficient of variation
EAT	Eating Attitudes Test
EPQ	Eysenck Personality Questionnaire
FD	functional dyspepsia
G1	1 kcal/min glucose infusion
G2	2 kcal/min glucose infusion
G4	4 kcal/min glucose infusion
GIP	glucose-dependent insulinotropic polypeptide
GIS	gastrointestinal symptom
GLP-1	glucagon-like peptide-1
HAD	Hospital Anxiety and Depression
H pylori	Helicobacter pylori

HS	healthy subject
IBS	irritable bowel syndrome
IPPW	isolated pyloric pressure wave
IL0.25	0.25 kcal/min lipid infusion
IL1.5	1 kcal/min lipid infusion
Il4	4 kcal/min lipid infusion
MI	motility index
MDP	minimal distending pressure
MMC	migrating motor complex
NDI	Nepean Dyspepsia Index
NS	not significant
NWLRC	Northwest Lipid Research Clinic
PWs	pressure waves
PWSs	pressure wave sequences
PYY	peptide tyrosine tyrosine
RMP	resting membrane potential
TFEQ	Three Factor Eating Questionnaire
THL	tetrahydrolipstatin
TMPD	transmucosal potential difference
VAS	visual analogue scale

THESIS SUMMARY

This thesis presents studies relating to effects of different macronutrients, predominantly fat and carbohydrate, on gastrointestinal motility, hormone release/suppression, appetite and energy intake in healthy subjects, and on symptom generation in patients with functional dyspepsia. The three broad areas that have been investigated in these studies are: (i) the effect of load, and duration, of small intestinal nutrient exposure on gastric motility, gastrointestinal hormone release/suppression, appetite and energy intake in healthy subjects, (ii) the dietary factors that may contribute to symptom generation in patients with functional dyspepsia, through analysis of diet diaries and acute nutrient challenges, and (iii) the effects of the herbal medication, Iberogast®, on gastric motility in healthy subjects.

The ingestion of nutrients, triggers a number of gastrointestinal responses, including the modulation of antropyloroduodenal motility, gastrointestinal hormone release/suppression, and the suppression of appetite and energy intake, resulting in a slowing of gastric emptying to an average rate of 1 - 3 kcal/min, which is required for efficient nutrient digestion and absorption. Additionally, the rate at which glucose enters the small intestine influences postprandial glycaemia and incretin responses. These responses have been demonstrated in animals to be dependent on the length, and region, of the small intestine exposed to fat and glucose, however, this has not been directly investigated in humans.

Functional dyspepsia is a clinical condition, characterised by chronic upper abdominal symptoms, such as nausea, bloating and early fullness, without a known cause, which

affects approximately 11 - 29 % of the population. Many studies have reported that disturbed gastric motor activity may be the cause of these symptoms, but patients frequently experience symptoms following ingestion of food, and some patients report to eat smaller meals more frequently and avoid fatty and spicy foods. In addition, laboratory-based studies have indicated that functional dyspepsia patients may be hypersensitive to fat, but not carbohydrate. To date, the treatments used to reduce symptoms are frequently directed at the normalisation of gastroduodenal motility, using prokinetics. However, the beneficial effect of these drugs is relatively small and variable, and their adverse effects can be substantial. Herbal drug preparations have recently received considerable interest as an alternative treatment option in functional dyspepsia. A commercially available herbal preparation, Iberogast® which contains nine plant extracts, has been reported to improve upper abdominal symptoms in functional dyspepsia and to decrease fundic tone, increase antral contractility and decrease afferent nerve sensitivity in experimental animals. The effects of Iberogast® in the human gastrointestinal tract have not been investigated.

The first three studies presented in this thesis have focused on the effects of delivering fat and glucose into the small intestine at different loads (Chapter 5, 6 and 7), lower, comparable to, and higher than gastric emptying normally occurs, and at different durations of infusion (but still at similar caloric loads - Chapter 5, fat only), on gastrointestinal motility, plasma hormone release/suppression, glycaemia, and energy intake in healthy male subjects.

The study in Chapter 5 demonstrated that antral pressure waves and pressure wave sequences were suppressed, and basal pyloric pressure, isolated pyloric pressure waves,

and plasma cholecystokinin and peptide YY stimulated, during both the low (1.33 kcal/min for 50 min: 67 kcal/min), and high (4 kcal/min for 50 min: 200 kcal), loads of lipid. The effect of the 4 kcal/min load was sustained so that the suppression of antral pressure waves and pressure wave sequences and increase in peptide YY remained evident after cessation of the infusion. The prolonged lipid infusion (1.33 kcal/min for 150 min: 200 kcal) suppressed antral pressure waves, stimulated cholecystokinin and peptide YY and basal pyloric pressure and tended to stimulate isolated pyloric pressure waves when compared with saline throughout the entire infusion period. These results indicate that both the load, and duration, of small intestinal lipid have an influence on antropyloroduodenal motility and patterns of cholecystokinin and peptide YY release.

Chapter 6 demonstrated that lipid loads lower than gastric emptying normally occurs (0.25 kcal/min for 50 min: 12.5 kcal) transiently stimulated isolated pyloric pressure waves and cholecystokinin release and suppressed pressure wave sequences and hunger scores. Loads comparable to (1.5 kcal/min for 50 min: 75 kcal) and higher (4 kcal/min for 50 min: 200 kcal), than the normal rate of gastric emptying, were required to stimulate basal pyloric tone and peptide YY release and suppress antral and duodenal pressure waves. Only the 4 kcal/min load suppressed energy intake. The effects of lipid on all parameters, with the exception of hunger, were load-dependent. In addition, there were relationships between antropyloroduodenal motility and cholecystokinin and peptide YY concentrations with energy/food intake.

The study in Chapter 7 demonstrated that loads of glucose lower than (1 kcal/min for 120 min: 120 kcal), comparable to (2 kcal/min for 120 min: 240 kcal) and higher than (4 kcal/min for 120 min: 480 kcal) the rate gastric emptying normally occurs, stimulated

blood glucose, plasma insulin, glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide and cholecystokinin concentrations and suppressed the number of antral pressure waves, 2 and 4 kcal/min loads were required for the suppression of duodenal pressure waves and pressure wave sequences and the stimulation of basal pyloric pressure and suppression of energy intake only after the 4 kcal/min loads. There were also relationships between glucagon-like peptide-1 and glucose-dependent insulinotropic peptide with basal pyloric tone, and food/energy intake with pyloric pressures.

The studies presented in the subsequent three chapters investigated the contribution of dietary factors on the generation of symptoms in patients with functional dyspepsia when compared with healthy subjects (Chapter 8 and 9) and the effect of Iberogast® on motility in the healthy gastrointestinal tract (Chapter 10). The effects of equi-caloric high-carbohydrate vs. high-fat yoghurt preloads on symptom generation, plasma hormone concentrations, antral area and energy intake were compared between functional dyspepsia patients and healthy subjects (Chapter 8). Nausea and pain were greater in patients after the high-fat, when compared with high-carbohydrate and control, preloads and with healthy subjects. Discomfort was greater after all preloads in patients when compared with healthy subjects. Fasting cholecystokinin and stimulation of cholecystokinin by the high-fat preload were greater in patients, while fasting and postprandial peptide YY were lower in patients than in healthy subjects, with no differences in fasting, or postprandial, plasma ghrelin between patients and healthy subjects. Fasting antral area was greater in patients, with no differences postprandially between patients and healthy subjects. There were no differences in energy intake between the two groups. The relationship between the effect of dietary intake and

eating behaviour over a 7-day period on the occurrence and severity of abdominal symptoms was compared between patients and healthy subjects (Chapter 9). The symptoms experienced by the patients included nausea, fullness discomfort, bloating and upper abdominal, and epigastric, pain, of a modest severity, which occurred within 30 min of eating. The number of "meals" ingested was significantly less in functional dyspepsia patients and there was a trend for total energy and fat intake to be less. The occurrence of these symptoms was also statistically related to the ingestion of fat and energy intake. The results of these studies indicate that diet, particularly the ingestion of fat, influences the development of symptoms in a subgroup of patients with functional dyspepsia.

The study in Chapter 10 evaluated the effect of the herbal drug Iberogast® on gastric motility in the gastrointestinal tract. Iberogast® increased proximal gastric volume, increased antral pressure waves without affecting pyloric or duodenal pressures, and slightly increased the retention of liquid in the total stomach, but had no effect on gastric emptying of solids or intragastric distribution. These results demonstrate that Iberogast® affects gastric motility in humans, and the stimulation of gastric relaxation and antral motility may contribute to the reported therapeutic efficacy of Iberogast® in functional dyspepsia.

The studies reported in this thesis provide new information about the regulation of gastric motility, hormone release/suppression, appetite and energy intake, by varying the loads of lipid and glucose infused into the small intestine in healthy subjects, which may have implications in patients with altered gastric motor functions, such as obese, type-2 diabetes and functional dyspepsia patients. In addition, studies in functional

dyspepsia patients revealed that diet, in particular the ingestion of fat, contribute to the cause of their symptoms, and these findings may have important implications for the development of diet-based therapies for the treatment of functional dyspepsia. Furthermore, functional dyspepsia patients with impaired gastric relaxation and antral dysmotility may benefit from the effects of Iberogast® as demonstrated in the healthy gastrointestinal tract.

DECLARATION OF ORIGINALITY

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, expect where due reference has been made in the text.

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Amelia Pilichiewicz

January 2008

DEDICATION

To all my rocks…

You know who you are…

I am forever grateful…

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PUBLICATIONS ARISING FROM THIS THESIS

The data presented in this thesis has formed the basis for the publications listed below:

Pilichiewicz, AN, Little, TJ, Brennan, IM, Meyer, JH, Wishart, JM, Otto, B, Horowitz, M, Feinle-Bisset, C 2005, 'Effects of load, and duration, of duodenal lipid on antropyloroduodenal motility, plasma CCK and PYY, and energy intake in healthy men', *Am J Physiol,* vol. 290, no. 3, pp. R668-677.

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Pilichiewicz, AN, Feltrin, KL, Horowitz, M, Holtmann, G, Wishart, JM, Jones, KL, Talley, NJ, Feinle-Bisset, C 2007, 'In functional dyspepsia oral carbohydrate and fat differentially modulate symptoms, gut hormones and antral area', *Am J Gastroenterol* (submitted).

Pilichiewicz, AN, Horowitz, M, Russo, A, Maddox, AF, Jones, KL, Schemann, M, Holtmann, M, Feinle-Bisset, C 2007, 'Effects of Iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men', *Am J Gastroenterol*, vol. 102, no. 6, pp. 1276-1283.