Investigations into the gastrointestinal factors involved in the regulation of appetite and energy intake

A thesis submitted by
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Chapter 4: Common methodologies

Thesis summary

The research presented within this thesis has focused on the complex and interrelated gastrointestinal mechanisms involved in the regulation of appetite and energy intake. The suppression of appetite and energy intake is mediated, at least in part, by a number of gastrointestinal factors, including gastric distension, the modulation of gastric emptying, gastrointestinal motility and gastrointestinal peptides, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY) and ghrelin. An understanding of these mechanisms is important to determine the pathophysiology of obesity and to allow the identification of targets for the treatment of obesity.

The effects of the fat on gastrointestinal function and appetite are dependent upon the digestion of fat to free fatty acids. Animal studies indicate that the effects of free fatty acids on energy intake are more potent than those of triglycerides. The comparative effects of a free fatty acid and a triglyceride on gastric emptying, appetite and energy intake were assessed in healthy lean male subjects. Free fatty acids slowed gastric emptying, stimulated the secretion of CCK, suppressed hunger, increased fullness and suppressed energy intake more potently than triglyceride (Chapter 5). These observations suggest that small amounts of free fatty acids in the small intestine potently modulate gastrointestinal function and energy intake.

We had previously demonstrated that intraduodenal infusion of the free fatty acid, lauric acid (C12) (at 0.375 kcal/min, 106 mM), stimulates isolated pyloric pressure waves (IPPWs), inhibits antral and duodenal pressure waves (PWs),

stimulates the release of cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1), and suppresses energy intake, and that these effects are much greater than those seen in response to isocaloric decanoic acid (C10) infusion. However, C12 was associated with nausea, confounding interpretation of these results. In order to determine whether the effects we had observed were physiological, or related to nausea, we assessed the effects of a range of doses of C12 (0.1 – 0.4 kcal/min) on the above parameters. Intraduodenal infusion of very small amounts of C12, potently modulate gastrointestinal motility, gut hormone secretion and suppresses energy intake at a subsequent meal in a dose-dependent fashion, in the absence of nausea (Chapter 6). However, as both the load and the concentration of the infusions varied, it was unclear whether these effects were load-, or concentration-, dependent. We, therefore, examined the independent effects of load, and concentration, of C12 on these variables, and demonstrated that the effects of C12 on gastrointestinal motility, gut hormone release and energy intake are dependent upon the load, but not the concentration of C12 administered to the small intestine in humans (Chapter 7).

Animal studies have indicated that the effects of nutrients on gastrointestinal function and energy intake are dependent upon the length of small intestine exposed to nutrient. In humans, we demonstrated that the modulation of gastrointestinal motility and gut hormone secretion by small intestinal glucose is dependent upon the length of small intestine exposed to nutrient, specifically, the suppression of antral motility, the release of GLP-1 and the suppression of plasma ghrelin concentrations is dependent upon greater than 60 cm of the small intestine being exposed to glucose (Chapter 8).

The inhibitory action of glucagon-like peptide-1 (GLP-1) on gastric emptying GE is likely to be important in mediating its effects on glycaemia, appetite and upper gastrointestinal symptoms. In healthy subjects (i) the slowing of solid and liquid gastric emptying by exogenous GLP-1 is associated with increased retention of both solid and liquid in the distal stomach and, even when administered in a "low" dose can induce "gastroparesis" and (ii) the effects of GLP-1 on postprandial glycaemic and insulinaemic responses are predictable on the basis of its effect on gastric emptying, supporting the concept that gastric emptying is a major target mechanism for the clinical use of incretin mimetics (Chapter 9). The feeding inhibitory effects of GLP-1 are likely to relate to the increased antral meal retention, as a close relationship has previously been demonstrated between antral area (and content) with the perception of fullness and subsequent energy intake.

An understanding of the physiological adaptations that occur in obesity is essential to enable the development of successful therapies for this condition. There is increasing evidence that consumption of a high-fat diet is associated with the development of obesity. The precise mechanisms by which this occurs are unclear, however, studies in animals suggest that adaptations in the gastrointestinal mechanisms involved in the regulation of appetite and energy intake occur, and may, therefore, predispose to obesity. In particular, studies have demonstrated that the acute effects of exogenous CCK, a hormone that potently suppresses energy intake, are attenuated following exposure to a high-fat diet in rats. In our study, healthy lean male volunteers were exposed to a high-fat

diet for a period of 3 weeks, following which the effects of an intravenous infusion of CCK on gastrointestinal motility and energy intake were evaluated. Fasting concentrations of CCK were greater following the high-fat diet, however, we did not demonstrate any differences in the antropyloroduodenal motility or energy intake response to exogenous CCK following ingestion of either diet, suggesting, that at least in the short-term, in healthy lean male subjects consumption of a high-fat diet does not alter the sensitivity to the effects of CCK on antropyloroduodenal motility and energy intake (Chapter 10).

The studies reported in this thesis have provided new insights into the mechanisms by which nutrients present within the gastrointestinal tract modulate gastrointestinal function and energy intake. Future studies in obese subjects will be required to determine whether sensitivity of the gastrointestinal tract to nutrients is modulated in the obese state.

Statement of originality

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Tanya J. Little

Dedication

I dedicate this thesis to my parents, Janet and Brian Little. For your love, support and encouragement throughout these years, I will be 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:

Little TJ, Feltrin KL, Horowitz M, Smout AJPM, Rades T, Meyer JH, Pilichiewicz AN, Wishart J, Feinle-Bisset C. Dose-related effects of lauric acid on antropyloroduodenal motility, gastrointestinal hormone release, appetite and energy intake in healthy men. Am J Physiol Regul Integr Comp Physiol 289 (4): R1090 – R1098 (2005).

Little TJ, Horowitz M, Feinle-Bisset C. Role of cholecystokinin in appetite control and body weight regulation. Obesity Reviews 6: 297 - 306 (2005).

Little TJ, Pilichiewicz AN, Russo A, Phillips L, Jones KL, Nauck MA, Wishart J, Horowitz M, Feinle-Bisset C. Effects of intravenous GLP-1 on gastric emptying and intragastric distribution in healthy subjects – relationships with postprandial glycemic and insulinemic responses. J Clin Endocrinol Metab 91: 1916 - 1923 (2006).

Little TJ, Doran S, Meyer JH, Smout AJPM, O'Donovan DG, Wu KL, Jones KL, Wishart J., Rayner CK, Horowitz M, Feinle-Bisset C. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent on the length of small intestine exposed. Am J Physiol Endocrinol Metab 291: E647-E655 (2006).