EFFECTS OF PROTEIN ON GASTROINTESTINAL FUNCTION AND APPETITE REGULATION

A thesis submitted by

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Table of Contents

List of Figures

List of Tables

Abstract

The prevalence of obesity and associated diseases, including type-2 diabetes mellitus, continues to increase at an alarming rate. The available therapies have largely ignored the key role of the gastrointestinal tract in determining appetite and blood glucose regulation in responses to ingested nutrients. A detailed understanding of these gastrointestinal mechanisms is critical in aiding development of new and effective interventions for obesity.

The research presented in this thesis focuses on the complex gastrointestinal mechanisms involved in the regulation of glycaemia, appetite and energy intake in response to protein in lean and obese individuals. In particular, this research explores the gastrointestinal motor and hormonal responses to nutrients involved in energy intake regulation and blood glucose control in both healthy lean and obese individuals. Using the novel, non-invasive technique of 3-dimensional ultrasound, the study described in chapter 5 reports that, in lean individuals, the rate of gastric emptying of drinks containing 30g and 70g of protein was comparable (kcal/min; 30g: 2.6±0.2, 70g: 2.9±0.3), and within the ranges previously observed for fat and carbohydrate (1-4 kcal/min). This was reflected by similar releases of cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), glucose-dependent inhibitory polypeptide (GIP), insulin and glucagon, for ~45 min following the drinks. Beyond 45 min, the 70g load resulted in more sustained hormone release, reflecting greater total calories and thus prolonged delivery of nutrient to the small intestine. Energy intake was comparable between the two loads, suggesting that a threshold amount of protein may exist, beyond which no additional appetite-suppressive benefit occurs.

In the studies described in chapters 6-8, intraduodenal infusions, combined with high-resolution manometry, were used to evaluate the effects of nutrients in the small intestine on

antropyloroduodenal motility and gastrointestinal hormone release. Nutrients were infused directly into the duodenum at standardised rates, reflecting the normal range of gastric emptying; intraduodenal infusion bypasses orosensory and gastric influences, isolating the effects of nutrient to the small intestine.

The first of these studies reported that intraduodenal protein has load-dependent effects on antropyloroduodenal motility, ghrelin, CCK, GLP-1, peptide tyrosine tyrosine (PYY), insulin and glucagon, glycaemia, and energy intake at a subsequent meal in lean individuals. The second study reported that load-dependent effects of protein on antropyloroduodenal motility and CCK, GLP-1, GIP, insulin and glucagon release are also apparent in obese individuals, suggesting that small intestinal sensitivity to protein remains intact in obesity. The final study demonstrated, in lean individuals, that intraduodenal lipid modulates gastrointestinal motor responses and CCK and GLP-1 concentrations more potently than an equicaloric protein load. In contrast, protein had more pronounced effects on insulin and glucagon release. Despite these differences, protein and lipid suppressed energy intake comparably, suggesting that different mechanisms may underlie the suppression of energy intake by these nutrients.

These data provide novel insights into the roles that gastrointestinal motor and hormone responses to dietary protein play in the regulation of blood glucose, appetite and energy intake in lean and obese individuals. These observations provide potential mechanistic explanations for the effects of high-protein diets on glycaemic control, and appetite. Importantly, they provide a basis for future development of nutrition-based interventions for the treatment of obesity.

Declaration of Originality

I, Amy Hutchison, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Amy Hutchison

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Publications Arising From This Thesis

The data presented in this thesis have formed the basis of the publications listed below:

Ryan AT, Feinle-Bisset C, Kallas A, Wishart JM, Clifton PM, Horowitz M, Luscombe Marsh ND. Intraduodenal protein modulates antropyloroduodenal motility, hormone release, glycemia, appetite, and energy intake in lean men. Am J Clin Nutr 2012;96:474-82. DOI:10.3945/ajcn.112.038133

Ryan AT, Luscombe-Marsh ND, Saies AA, Little TJ, Standfield S, Horowitz M, Feinle-Bisset C. Effects of intraduodenal lipid and protein on gut motility and hormone release, glycemia, appetite, and energy intake in lean men. Am J Clin Nutr 2013;98:300-11. DOI:10.3945/ajcn.113.061333

Hutchison AT, Piscitelli D, Horowitz M, Jones KL, Clifton PM, Standfield S, Hausken T, Feinle-Bisset C, Luscombe Marsh ND. Acute load-dependent effects of oral whey protein on gastric emptying, gut hormone release, glycemia, appetite and energy intake in healthy males. Am J Clin Nutr 2015; DOI: 10.3945/ajcn.115.117556

Hutchison AT, Feinle-Bisset C,Fitzgerald PCE, Standfield S, Horowitz M, Clifton PM, Luscombe Marsh ND. Comparative effects of intraduodenal protein on antropyloroduodenal motility, gut hormones, glycemia, appetite and energy intake in lean and obese men. Am J Clin Nutr 2015; DOI:10.3945/ajcn.115.114538

Other Publications

Soenen S, Giezenaar C, **Hutchison AT,** Horowitz M, Chapman I, Luscombe-Marsh ND. Effects of intraduodenal protein on appetite, energy intake, and antropyloroduodenal motility in healthy older compared with young men in a randomized trial. Am J Clin Nutr 2014; 100:1108-15. DOI:10.3945/ajcn.114.087981

Giezenaar C, Trahair LG, Rigda RS, **Hutchison AT,** Feinle-Bisset C, Luscombe-Marsh ND, Hausken T, Jones KL, Horowitz M, Chapman IM, et al. Lesser suppression of energy intake by orally ingested whey protein in healthy older men compared with young controls. Am J Physiol Regul Integr Comp Physiol 2015;309:R845-54.. DOI: 10.1152/ajpregu.00213.2015

Ullrich SS, Otto B, **Hutchison AT,** Luscombe-Marsh ND, Horowitz M, Feinle-Bisset C. Comparative effects of intraduodenal protein and lipid on ghrelin, peptide YY, and leptin release in healthy men. Am J Physiol Regul Integr Comp Physiol 2015; 308:R300-4. DOI:10.1152/ajpregu.00504.2014

Luscombe-Marsh, ND, **Hutchison AT,** Soenen S, Steinert RE, Clifton P, Horowitz M, Feinle-Bisset C. Plasma free amino acid responses to intraduodenal whey protein and relationships with insulin, glucagon-like peptide-1 and energy intake in lean healthy men. Nutrients; submitted 23 October 2015.

Dedication

Ko te manu e kai ana i te miro, nōna te ngahere.
Ko te manu e kai ana i te mātauranga, nōna te ao.

The bird that partakes of the miro berry reigns in the forest.
The bird that partakes of the power of knowledge has access to the world.

This thesis is dedicated to
my husband, Rob,
for always inspiring and challenging me,
and my whānau,
for your unwavering love and support.

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List of abbreviations

APD	Antropyloroduodenal motility
ANOVA	Analysis of Variance
ARC	Arcuate nucleus
AUC	Area under the curve
BMI	Body Mass Index
CCK	Cholecystokinin
CHO	Carbohydrate
CV	Coefficients of Variance
DPP-IV	Dipeptidyl peptidase-IV
EDTA	ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbance assay
FFM	Fat free mass
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic peptide
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HOMA-IR	Homeostatic model assessment of insulin resistance
ID	Intraduodenal
IPPW	Isolated pyloric pressure wave
LCD	Low calorie diet
MI	Motility index
MMC	Migrating motor complex
mV	Millivolt
NIDDM	Non-insulin dependent Diabetes Mellitus
NS	Not significant

PWs	Pressure waves
PYY	Peptide tyrosine tyrosine
RIA	Radioimmunoassay
TAA	Total Free Amino Acids
TFEQ	Three Factor Eating Questionnaire
TMPD	Transmucosal potential difference
T2DM	Type 2 Diabetes Mellitus
VAS	Visual Analog Scale Questionnaire