Postdoctoral Fellowship at the University of Adelaide, Discipline of Medicine, Adelaide, Australia

Project: 459

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Project Summary

The generous financial support by the SFEFS enabled me to broaden my scientific knowledge and expertise in state-of-art gastrointestinal physiology medical research, but also to further strengthen my skills in molecular and basic science. This postdoctoral fellowship provided by the SFEFS, undoubtedly, has been an excellent opportunity to promote my academic career as a nutritional scientist.

Under the excellent supervision of Professor Christine Feinle-Bisset, who leads the clinical laboratory of 'Gastrointestinal Physiology and Nutrition' at the University of Adelaide, I could study the effects of intragastric (IG) amino acids (L-Leucin and L-Isoleucin) infusions on gastric emptying, gut hormone release, blood glucose response as well as energy intake in healthy, normal-weight subjects (Co-Author of manuscript 1; Abstract see below, manuscript in preparation).

In addition to the nutritional studies, I performed extensive statistical analyses of pooled data from selected studies, performed in the 'Gastrointestinal Physiology and Nutrition' laboratory over several years, to evaluate the relative contribution of gut hormones and motility to the energy intake-suppressant effects of lipid and protein in healthy, lean men (First-Author of manuscript 2; Abstract see below, manuscript in preparation). Both manuscripts will soon be submitted to 'The American Journal of Clinical Nutrition'.

Furthermore, Professor Amanda Page, the group leader of the 'Gastrointestinal Vagal Afferent Research Group', which is part of the University of Adelaide's new Centre for Nutrition and Gastrointestinal Diseases located within the South Australian Health and Medical Research Institute (SAHMRI), gave me the opportunity to work in her group and to establish and test the Ussing chamber technology, an ex vivo tissue model. The Ussing chamber is a suitable physiological model to measure peptide release and transport across ex vivo epithelial tissue, like the stomach or intestine, which bears more relevance to the physiological in vivo situation than in vitro cell studies. I was the person in charge to set up the model and in future it will be used to study nutrient-stimulated gastric peptide release from enteroendocrine cells in the stomach of healthy, lean mice.

During my research with Professor Amanda Page, Richard L. Young, who is the head of the 'Intestinal Nutrient Sensing Group' at the Centre for Nutrition & Gastrointestinal Diseases (The

University of Adelaide), offered me a 2-year full-time postdoc position in his group which I happily accepted. This postdoc position will give me the unique opportunity to perform state-of-art research at the SAHMRI, the new flagship facility for nutrition and metabolism research in human and animal cells in Australia, and to combine my newly acquired skills in medical research and my profound knowledge in molecular and basic research in animals.

Therefore I am very grateful to the SFEFS for providing the funding for the postdoctoral fellowship which was a critical step in the pursuit of my scientific and academic career, as it allowed me to further consolidate and continue my research at a highly competitive level.

Furthermore, I want to thank my former PhD supervisor and mentor, Professor Wolfgang Langhans, who strongly supported me throughout my scientific career and encouraging me to apply for the SFEFS fellowship for Australia. A big thank you goes to Professor Christine Feinle-Bisset and Professor Amanda Page, who gave me the great opportunity to work in their laboratories and for their outstanding supervision.

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ABSTRACT (Manuscript 1; In preparation, subject to change):

Effects of intragastric administration of L-leucine or L-isoleucine on gastric emptying of, and gut hormones and blood glucose responses to, a liquid mixed-nutrient meal, and on subsequent energy intake, in healthy, normal-weight humans.

Ullrich S [1,2], **Schober G [1,2]**, Nkamba I [1,2], Fitzgerald P [1,2], Steinert RE [3], Horowitz M [1,2], Feinle-Bisset C [1,2].

[1] University of Adelaide Discipline of Medicine, Adelaide, Australia; [2] NHMRC National Health and Medical Research Council of Australia Centre of Research Excellence in Translating Nutritional Science to Good Health, Adelaide, Australia; [3] DSM Nutritional Products, R & D Human Nutrition and Health, Kaiseraugst, Switzerland

Background and Objective: The branched-chain amino acids, leucine and isoleucine, have been shown to lower blood glucose (BG). Moreover, in our recent study, intraduodenal (ID) infusion of leucine decreased energy intake in healthy, lean men. We have now investigated the effects of intragastric (IG) administration of leucine and isoleucine on gastric emptying of, and the blood glucose responses to, a mixed-nutrient drink, and subsequent energy intake. *Methods:* In two separate studies, healthy, normal-weight subjects (each n=12) received, on three separate occasions, IG infusions of either leucine or isoleucine (5 g or 10 g) or control (C, t=-15 min). 15 min later, subjects consumed a mixed-nutrient drink (400 kcal, 56 g carbohydrates), and gastric emptying (^{13}C-acetate breath test) and BG and insulin, C-peptide and glucose-dependent insulinotropic polypeptide (GIP) were measured for 60 min (t=0-60 min). Immediately afterwards, ad-libitum energy intake was assessed. *Results:* For leucine, there was no significant difference between treatments for peak BG (t=15 min, mmol/l; C: 7.2±0.3, 5 g: 6.6±0.2, 10 g: 6.4±0.2). There was a trend for an effect of treatment on BG AUC (P=0.076). Leucine stimulated the release of insulin and C-peptide compared with C in response to the mixed-nutrient drink (t=0-60 min; P<0.05 for both) and the release of GIP after the infusion (t=0 min; P<0.01), but not in response to the drink. Leucine had no significant effects on gastric emptying or energy intake. For isoleucine, both loads reduced peak BG (mmol/l; C: 7.3±0.2, 5 g: 6.7±0.2, 10 g: 6.2±0.3; P<0.05 for both) and 10 g significantly reduced BG AUC compared with C (P<0.01). Isoleucine had no effect on insulin, C-peptide and GIP secretion. Gastric emptying was slower after 10 g isoleucine compared with C (P<0.05). Isoleucine did not affect energy intake. *Conclusion:* Our data suggest that despite their structural similarity, leucine and isoleucine differentially affect BG and gastric emptying. Although the effects on BG were small in this group of healthy, lean subjects, the effects of both amino acids on BG warrant further evaluation in patients with type 2 diabetes. Due to the elevated BG levels in those patients, a greater BG-lowering effect, compared with the healthy subjects in our current study, is likely. Further studies also need to investigate underlying mechanisms, why ID, but not IG infusiond of leucine reduced energy intake.

ABSTRACT (Manuscript 2; In preparation, subject to change):

Relative contributions of upper gut hormones and motility to the energy intake-suppressant effects of lipid and protein in healthy, lean men.

Schober G [1,2], Lange K **[1,2]**, Steinert RE [3], Ryan AT **[1,4]**, Luscombe-Marsh ND [2,5], Horowitz M [1,2], Landrock MF [1], Seimon RV [6], Feinle-Bisset C [1,2].

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Background and Objective: The presence of nutrients in the small intestine modulates gastrointestinal (GI) motility, stimulates the release of gut hormones, and supresses appetite and energy intake (EI). In this study we have determined which, if any, of these parameters are independent predictors of EI supressent effects of lipids and proteins. *Methods:* Data from nine published studies, involving a total of 117 healthy, normal-weight men, in which antropyloroduodenal (APD) pressures, GI hormones and perceptions were measured during intraduodenal (ID) lipid, protein or amino acids infusions, were pooled. In all studies ad-libitum EI at a buffet lunch was quantified immediately after the infusions. To select specific motor, hormone or perception variables for inclusion in a multi-variable mixed-effects model for determination of independent predictors of EI, all variables were assessed for collinearity and, using bivariate analyses adjusted for repeated measures. Within-subject correlations between EI and these variables were determined. *Results:* While correlations between EI and APD pressures, plasma hormone concentrations and gastrointestinal perceptions were found only the mean amplitude of antral pressure waves (APWs), peak basal pyloric pressures (BPP), plasma GLP-1 premeal concentrations, and nausea were identified as independent determinants of acute EI (all $P<0.05$); thus an

increase in APW of 1mm.Hg was associated with an increase in EI by ~2.5 kJ , while an increase in peak BPP of 1 mm.Hg, GLP-1 premeal concentration of 1 pmol/L and nausea of 1 mm.min, respectively, were associated with reductions in EI by ~48 kJ, ~19.2 kJ and ~0.15 kJ, respectively. *Conclusion:* We have identified specific changes in GI motor and hormone function, i.e. stimulation of BPP, plasma GLP-1, and nausea that are associated with a nutrient-dependent acute suppression of EI.