INVESTIGATIONS INTO THE GASTROINTESTINAL
CONTROL OF APPETITE AND FOOD INTAKE

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THESIS SUMMARY

This thesis presents studies relating to the gastrointestinal regulation of appetite and food intake. The two broad areas that have been investigated in these studies are 1) the specific effects mediated by different nutrients present in the gastrointestinal tract and 2) the involvement of nitric oxide mechanisms in the peripheral regulation of appetite and food intake. These topics were primarily evaluated in healthy young adult humans, but also in patients with type 2 diabetes.

Obesity is an increasingly prevalent disease the causes of which relate in part to the constant and readily available supply of high fat, energy dense foods. Common dietary approaches to its treatment include a low energy, low-fat, high-carbohydrate diet; however diets with increased protein are becoming increasingly popular. The ability of high protein, rather than carbohydrate and fat pre-loads to produce greater satiety and reduced food intake after a fixed time interval and under spontaneous feeding conditions was investigated in healthy humans. Hunger decreased and fullness increased after both high carbohydrate and high protein pre-loads, relative to no pre-load. Although all nutrient pre-loads delayed the first food request, there was no effect of varying macronutrient ratios on this delay, or on the daily eating frequency. Compensation for over consumption was accurate following high protein but not following high fat or high carbohydrate pre-load, hence total daily food intake was greater after high carbohydrate and high fat pre-loads. These results indicate that the effect of increasing the protein content of the diet is probably to increase satiety and to induce a relative suppression of energy intake at subsequent meals.

Included in the many treatments for overweight and obesity are modifications to specific eating patterns. An inverse relationship has been demonstrated between the number of meals consumed per day and the general state of health. The effects of increased meal frequency on suppression of appetite and food intake were evaluated in healthy humans. Mixed-nutrient meals ingested or infused intragastrically in different frequencies had no significant effect on blood glucose concentrations, on hunger, desire to eat, fullness and satiation, or on ad libitum food intake. These findings do not support the promotion of increased meal frequency as a means of reducing food intake.
The interaction between nutrients and mucosal chemoreceptors in the small intestine plays a major role in the regulation of both gastric emptying and appetite. The contribution of the pulsatile nature of gastric emptying to small intestinal feedback mechanisms modulating antropyloroduodenal motility, gastrointestinal hormone release and food intake is unknown. The effects of intraduodenal infusions of a triglyceride mixture either continuously or in a pulsatile fashion on antropyloroduodenal motility, cholecystokinin release and appetite and food intake were evaluated in healthy humans. The two modes of lipid infusion had similar effects on antropyloroduodenal pressures, plasma cholecystokinin concentrations, hunger and fullness ratings and energy intake. These results indicate that the acute effects of intraduodenal lipid on antropyloroduodenal pressures, plasma cholecystokinin concentrations and appetite are not modified by a pulsatile mode of lipid delivery into the duodenum. The pulsatile nature of gastric emptying is therefore unlikely to contribute to any major extent to the nutrient-induced changes in antropyloroduodenal motility, but hormone release, appetite and food intake.

It is predicted that by 2010 approximately 1.5 million Australians will be affected by non-insulin dependent (type 2) diabetes mellitus. The primary aim of treatment is to reduce blood glucose concentrations, and in the case of many people with type 2 diabetes, who are overweight, to reduce body weight. Fructose has been proposed as an alternative sweetener to glucose in the diet of type 2 diabetics. The relative effects of fructose and glucose on blood glucose, plasma insulin and incretin (glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP)) concentrations, and acute food intake were investigated in patients with diet controlled type 2 diabetes and in non-diabetic, control subjects. Fructose produced smaller post-ingestion blood glucose concentrations than glucose and higher insulin concentrations in diabetics than in non-diabetics. The differences in insulin concentrations were not accounted for by increased incretin (GLP-1 and GIP) concentrations. There was no difference between the effects of fructose and glucose on suppression of food intake in either diabetics or non-diabetics. These results indicate that on the basis of initiating efficiency alone, fructose is unlikely to be useful as a replacement for glucose in the diet of obese patients with type 2 diabetes.

Complex peripheral and central pathways exist, in which a variety of neurotransmitters integrate multiple factors that regulate appetite and food intake. The inhibitory neurotransmitter, nitric oxide (NO) has emerged as a potential regulator of numerous
processes which affect feeding behaviour, including gastrointestinal transit and motility, as well as central and peripheral neural pathways implicated in the control of food intake. Nitric oxide synthase inhibitors reduce food intake in rodents and chickens. The involvement of NO in regulating appetite and food intake pre- and post-prandially was assessed in healthy humans and in an animal model of feeding regulation.

No previous studies have evaluated the possibility that NO regulates appetite and feeding behaviour in humans. NG-nitro-L-nonomethyl arginine (L-NMMA) and NG-nitro-L-arginine methyl ester (L-NAME), non-selective inhibitors of NO synthase (NOS), were administered intravenously in two separate studies, to evaluate the role of NO in the short-term regulation of appetite in healthy subjects. Neither drug had any effect on energy intake or sensation of hunger or fullness. Consistent with a systemic effect both L-NMMA and L-NAME decreased heart rate and blood pressure. It is unlikely that peripheral NO has a role in the regulation of normal human appetite and food intake.

To evaluate the role of NO mechanisms in mediating the effects of small intestinal nutrients on antropylooduodenal motility and appetite in healthy humans, intravenous L-NAME was administered prior to and concurrent with intraduodenal lipid infusion. NG-nitro-L-arginine methyl ester (L-NAME) increased diastolic blood pressure, decreased heart rate and had no effect on antropylooduodenal pressures or food intake. Intravenous administration of the systemic NO synthase inhibitor L-NAME, in a dose that affects cardiovascular function in humans, does not modify the antropylooduodenal motor and appetite responses to intraduodenal lipid infusion. Despite having significant effects on cardiovascular function in the doses used, neither L-NMMA nor L-NAME, had any effect on feeding or appetite and antropylooduodenal motor responses to intraduodenal lipid. These results suggest that NO does not affect short-term appetite, food intake or antropylooduodenal motor function in humans.

The studies reported in this thesis provide new information on the regulation of appetite food intake by gastrointestinal mechanisms in healthy and type 2 diabetics humans. These observations will contribute to advances in basic appetite physiology and clinically to dietary interventions in the treatment of obesity and type 2 diabetes mellitus.