INVESTIGATIONS INTO THE GASTROINTESTINAL CONTROL OF APPETITE AND NUTRITIONAL FRAILTY

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Statement of originality

This thesis 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, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Kamilia Tai

March 2008

Dedication

I dedicate this thesis to my dearest husband Payman, and to my dear parents Faezeh and Manouchehr Tai, for their unfailing support, love, and encouragement.

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Tai, K, Need, AG, Horowitz, M & Chapman, IM 2008, 'Glucose tolerance and vitamin D: effects of vitamin D deficiency', *Nutrition*. *In Press.*

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Thesis Summary

The research presented in this thesis relates to the gastrointestinal control of appetite and some of the consequences of nutritional frailty, namely postprandial hypotension and vitamin D insufficiency. Undernutrition and its consequences are increasingly common problems in an ageing population, and improved management is dependent on an understanding of the factors which are involved in the control of appetite, and the physiological decline of appetite with increasing age termed 'the anorexia of ageing'. The role of the gastrointestinal hormone ghrelin was specifically evaluated, in relation to the effects of age and nutrient digestion on circulating ghrelin concentrations (Chapters 6 and 7). The effect of fat digestion on the postprandial blood pressure response in healthy older subjects was evaluated in the study reported in Chapter 8. In addition, the results of some intervention studies are described in Chapters 9 and 10, the former study relating to nutritional supplementation as a strategy to increase energy intake, and the latter study to the effects of vitamin D replacement therapy on glucose and insulin metabolism.

Whilst plasma ghrelin concentrations are less in older than young rodents, the consequences of healthy ageing on circulating plasma ghrelin concentrations in humans are unclear. The variations in fasting ghrelin concentrations over a sixty year age range were evaluated in healthy young and older subjects (Chapter 6). Plasma ghrelin concentrations were higher in females than males, but did not correlate with age, and were inversely related to body mass index. Ghrelin was independently, and inversely, related to total body skeletal muscle mass, but not to any other body composition

variable. Strategies for increasing muscle mass, through resistance exercises, may, accordingly, aid in abolishing the compensatory rise in ghrelin concentrations seen with undernutrition and weight loss.

Plasma ghrelin concentrations increase before, and decrease to trough levels within one hour of ingestion of a meal. Macronutrients differ in their ability to suppress ghrelin, being earlier and more pronounced after carbohydrate, and relatively delayed after fat or protein, ingestion. The role of carbohydrate and fat digestion in the suppression of plasma ghrelin concentrations was investigated in healthy young adults (Chapter 7). The suppression of ghrelin concentrations following a sucrose drink was attenuated by acarbose, which slows small intestinal carbohydrate absorption. Ghrelin concentrations were also suppressed after consumption of a fat-enriched drink, however addition of orlistat, which reduces fat digestion and absorption, attenuated the fall in plasma ghrelin. Thus, nutrient digestion is required, in addition to exposure of the small intestine to nutrients, for suppression of ghrelin.

Postprandial hypotension describes a significant fall in blood pressure occurring up to two hours after a meal. The magnitude of the fall in postprandial blood pressure depends, in part, on the macronutrient composition of a meal, and the effects are particularly discernable in older adults. Although carbohydrates are particularly potent in reducing postprandial blood pressure in older adults, fat ingestion appears to have comparable, but delayed effects. The role of fat digestion in modifying the blood pressure responses was evaluated in healthy older adults (Chapter 8). There was a fall in blood pressure after ingestion of a high-fat drink. Orlistat, a lipase inhibitor which

reduces intestinal fat absorption, potentiated the fall in postprandial blood pressure after a fat-enriched drink.

Gastrointestinal function and appetite can be modulated by dietary manipulation of the macronutrient composition of an individual's diet. The intervention study described in Chapter 9 evaluated the effects of two weeks of dietary fat supplementation on the sensitivity to the satiating effects of intravenous cholecystokinin-8 in healthy older subjects. No differences were observed in fasting, or postprandial plasma cholecystokinin concentrations after the dietary supplementation period compared to regular diet. There were also no differences in spontaneous energy intake at a buffet meal in response to exogenously administered cholecystokinin between the two diet periods.

Vitamin D deficiency is common, as is type 2 diabetes, and the two conditions may be linked. There is mounting evidence linking vitamin D deficiency with abnormalities of glucose and insulin metabolism. The effects of vitamin D therapy in healthy young and older adults with low vitamin D concentrations in the setting of normal or impaired glucose tolerance were evaluated (Chapter 10). Vitamin D therapy, which normalised serum 25-hydroxyvitamin D concentrations in these individuals, did not alter glucose or insulin concentrations or insulin sensitivity during an oral glucose tolerance test.