



**An Investigation of the
'Anorexia of Ageing'**

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For The Degree Of
Doctor Of Philosophy

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December, 2000

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SUMMARY

Ageing is associated with a progressive decline in appetite and energy intake. Because the latter is often greater than the decrease in energy expenditure that also occurs with normal ageing, involuntary weight loss frequently occurs. This 'physiological' reduction in appetite and energy intake, termed the "anorexia of ageing", may also predispose individuals to pathological weight loss and malnutrition, which represent major causes of morbidity and mortality in the elderly. The cause(s) of this physiological anorexia are poorly defined.

The studies presented in this thesis address some of the mechanisms which may potentially contribute to the physiological anorexia of ageing, as suggested by previous animal and human studies. The studies reported in Chapters 8-11 are a logical progression from a study conducted during the authors' Honours Degree. In that initial study, which is described in Appendix A, the effects of intraduodenal (ID) infusion of lipid and glucose on appetite, pyloric motility and subsequent energy intake were evaluated in young and older, healthy, men. In the young, ID lipid suppressed hunger to a greater extent than ID glucose; in contrast ID lipid did not appear to reduce hunger in the older subjects. The stimulation of phasic, but not tonic, pyloric pressure waves by intraduodenal lipid infusion was greater in older than young men. There was a greater suppression of energy intake by fat than glucose in the young men, but no difference in the effects of the two nutrients in older men. These observations suggested that effects of ID nutrients on appetite are impaired in the healthy elderly. The enhanced pyloric response to ID lipid may potentially lead to slower gastric emptying.

There is some evidence that ageing is associated with an enhanced endogenous release of gastrointestinal satiety hormones, specifically cholecystokinin (CCK). The effects of ageing on endogenous release of CCK, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY) in response to intraduodenal lipid and glucose infusion were evaluated using blood samples collected during the initial study described above. Plasma CCK concentrations were higher in older than young subjects at both baseline, and in response to the ID lipid infusion. There was no difference in plasma GLP-1 or PYY concentrations between the age groups. The decrease in hunger during ID lipid was inversely related to the increase in CCK, GLP-1 and PYY in young, but not older, subjects. During ID lipid infusion the increase in isolated pyloric pressure waves (IPPW) frequency was positively related to plasma GLP-1 and PYY and the increase in

IPPW amplitude was positively related to CCK in the older, but not young, subjects while the increase in IPPW amplitude and pyloric tone was inversely related to GLP-1 and PYY in the young subjects. These observations indicate for the first time that human ageing is associated with an increase in circulating CCK concentrations which may potentially contribute to slowing of gastric emptying, increased pyloric motility and reduction in appetite

As stated previously, in the initial Honours study, there was a greater suppression of energy intake by ID fat than glucose in the young men, but no difference between the effects of the two nutrients in older men. Due to the absence of a control (saline) infusion in that study, however, it was not known whether this age-related difference was due to an increased satiating effect of ID glucose, or a reduction in the satiating effect of fat, in older compared to young men ie potential differences in the effects of ID glucose and lipid between the two groups could not be evaluated. A second study was therefore conducted, to investigate the effects of intraduodenal (ID) infusion of saline, glucose and lipid on appetite, blood glucose and gastrointestinal hormone release, gastric myoelectrical activity and energy intake in young and older healthy men. ID lipid suppressed energy intake in both the young and older men, whereas ID glucose suppressed energy intake only in the older men. The blood glucose and insulin responses to ID glucose were greater in older, than young men, with no difference in GLP-1 or GIP responses to any of the infusions. There was a greater increase in the EGG power ratio, both during and following, ID glucose in young than older subjects, and an attenuation of the EGG frequency by ID nutrients in older, but not young, men. These observations suggest that ageing is associated with nutrient-specific changes in appetite, hormonal and gastric myoelectrical responses to ID nutrients. An enhanced satiating effects of ID carbohydrate may contribute to the anorexia of ageing.

Studies in rodents have shown that the suppressive effects of exogenous CCK on appetite are enhanced in older compared to young animals. The effects of intravenous infusion of two doses of CCK-8 on appetite and energy intake were evaluated in healthy older and young humans. Older subjects ate less of a test meal during all treatment infusions than young subjects, and the suppression of energy intake by intravenous CCK-8 infusions was greater in older than young subjects. Plasma concentrations of endogenous CCK (greater than 12 amino acids) were suppressed by CCK-8 infusion in both the older and young subjects, indicative of an autocrine negative feedback mechanism that is involved in the regulation of endogenous CCK

secretion. Plasma CCK-8 concentrations rose more during the infusions in the older than young subjects, possibly explaining the greater suppression of energy intake by the CCK-8 infusions in older subjects. Nevertheless, when corrected for the higher CCK levels, there was no significant difference in the magnitude of the suppression of energy intake for a given change in plasma CCK-8 concentration from baseline immediately before the meal between the two age groups. These results indicate that the sensitivity to the suppressive effects of exogenous CCK-8 is retained in the healthy elderly. Given that healthy ageing is associated with increased fasting and lipid-induced plasma CCK concentrations, increased CCK activity may play a role in the “anorexia of ageing”.

Impaired gastric relaxation and accommodation to a meal may be associated with gastrointestinal symptoms and early satiation in patients with functional dyspepsia and diabetes mellitus. The effect of ageing on proximal gastric sensory and motor function has not been evaluated previously. A study was conducted to investigate the effects of ageing on fasting gastric compliance, the perception of gastric distension, and gastric accommodation to a meal. During both isobaric and isovolumetric distensions the pressure-volume relationship did not differ significantly between older and young subjects. During gastric distensions perceptions of fullness, abdominal discomfort and bloating were less in older than young subjects, whereas the perception of hunger was less in the young compared to older subjects. While there was no effect of age on energy intake and the size of a non-standardised test meal on the “barostat day”, the “tube-only” day and the “control day” (no nasogastric tube), young subjects ate less at the meal on the “barostat day” compared to the “tube-only day” and the “control day” and less on the “tube-only day” compared to the “control day”. In contrast, there was no effect of the different study conditions on energy intake in the older subjects and they ate similar amounts on the “tube-only day” and the “control day”. Following the meal on the “barostat day”, the maximum intrabag volume occurred later in the older compared with the young subjects. These observations indicate that healthy ageing is associated with decreased perception of gastric distension without any change in fasting gastric compliance, suggest that gastric tone late in the postprandial period may be less when compared to the young. The observation that the presence of a nasogastric tube inhibited food intake in young, but not older subjects, suggests that the control of energy intake is less sensitive to external stimuli in older than young subjects.

Studies in animals indicate the stimulation of feeding by endogenous opioids may be attenuated by “ageing”. The effects of intravenous infusion of two doses of the opioid antagonist, naloxone, on appetite and energy intake were evaluated in young and older healthy subjects. In both age groups naloxone had no significant effect on perceptions of hunger, fullness or nausea, but increased drowsiness compared to the control infusion. Naloxone infusion reduced energy intake at an ad libitum meal compared to control, with no difference between the doses in both young and older subjects. The magnitude of this suppression was slightly, but not significantly, greater in the young than older subjects, reflecting a trend to reduced suppression in older women. These observations suggest that healthy older adults retain their sensitivity to the suppressive effects of naloxone on energy intake, although possible gender differences in this sensitivity warrant further investigation. A decline in opioid activity is unlikely to contribute substantially to the physiological “anorexia of ageing”.

Ageing is associated with slight, but significant slowing of gastric emptying (GE) and impaired postprandial glucose homeostasis. In young healthy subjects dietary glucose supplementation increases the rate of gastric emptying of a glucose meal and enhances the postprandial plasma insulin and GIP response. The effects of dietary glucose supplementation on gastric emptying, postprandial blood glucose homeostasis, and appetite after a glucose/oil “preload” were evaluated in healthy older volunteers. Glucose supplementation accelerated GE of glucose, but not oil; there was a trend for an increase in GIP, no change in GLP-1, an earlier insulin peak and a subsequent reduction in blood glucose. Glucose supplementation had no effect on energy intake so that energy intake was greater during the glucose supplemented diet. Appetite ratings and energy intake at the buffet meal were also not affected by glucose supplementation. This study indicates that in the healthy elderly, glucose supplementation accelerates GE of glucose, but not fat, modifies postprandial blood glucose homeostasis and increases total energy intake.

Postprandial hypotension represents a major cause of falls and increased morbidity in the elderly. A study was conducted to determine whether slowing of gastric emptying and glucose absorption with guar gum would reduce the fall in blood pressure after an oral glucose load in healthy older subjects. The magnitude of the falls in systolic, diastolic and mean arterial blood pressure were less, and gastric emptying slower after guar gum. Blood glucose, insulin and 3-O-methyl-D-glucose (3-OMG; a non-absorbable glucose analogue) concentrations were reduced by guar gum. 3-OMG

concentrations were inversely related to the intragastric retention of glucose and blood pressure was inversely related to 3-OMG after the drink without guar. The blood glucose concentration was related to 3-OMG. The results establish that guar gum reduces the magnitude of the fall in blood pressure after oral glucose in older subjects. Slowing of gastric emptying and glucose absorption may represent a novel approach to the treatment of postprandial hypotension in the elderly.

Malnutrition is a common clinical problem in the elderly, but it remains largely unrecognised in community-dwelling persons. The prevalence of malnutrition, and relationships between nutritional status [assessed using the Mini-Nutritional Assessment (MNA)] and scores on the SF-36 Health Survey® (SF-36), Standardised Mini-Mental State Examination, Geriatric Depression Scale were evaluated in 250 Domiciliary Care 'functionally dependent' recipients. Risk factors including living status (ie alone/spouse or other), the amount of domiciliary care/ formal care (hr/month) received, medical history, number of medications, and recent hospital admissions (number of days within the last 12 months) were also recorded. In total, 59.6% were well-nourished 37.2% were 'at risk' of malnutrition and 4.4% were malnourished according to the MNA. The independent predictors of poor nutritional status were (i) a history of respiratory disease; (ii) receipt of 'Meals on Wheels'; (iii) an increased number of days spent in hospital in the past 12 months; and according to the SF-36 (iv) role limitation due to emotional problems; (v) physical functioning; (vi) general health perception and (vii) mental health. The prevalence of being 'at risk' of malnutrition was high in this population, therefore the 'functionally dependent' community-dwelling elderly may represent a subset of the elderly population who may benefit from routine screening for prevention or treatment of malnutrition.