Effects of intraduodenal protein on appetite, energy intake, and antropyloroduodenal motility in healthy older compared with young men in a randomized trial[1–3]

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ABSTRACT

Background: Protein-rich supplements are used widely for the prevention and management of undernutrition in older people. The use of protein supplements in older people could, however, be counterproductive by reducing appetite and overall energy intake.

Objective: The objective was to determine whether aging influences the effects of protein loads, administered directly into the small intestine, on energy intake, antropyloroduodenal motility, and appetite.

Design: Intraduodenal infusions (240 mL, 60 min) of saline (0 kcal, control) and protein (hydrolyzed whey) loads of 30, 90, and 180 kcal were followed by an ad libitum buffet meal in 10 young (19–29 y) and 10 healthy older (68–81 y) men. Suppression of energy intake (kcal) at the meal by protein infusion compared with control was calculated.

Results: In young subjects, a dose-responsive suppression (±SEM) of energy intake was found at the buffet meal by protein (suppression at 30 kcal: 7 ± 8%, $P = 0.189$; 90 kcal: 17 ± 8%, $P = 0.054$; 180 kcal: 33 ± 7%, $P = 0.002$), whereas suppression was observed only after the 180-kcal load in older subjects (30 kcal: 7 ± 4% increase, $P = 0.126$; 90 kcal: 6 ± 7% increase, $P = 0.291$; 180 kcal: 17 ± 6% suppression, $P = 0.016$). Suppression of energy intake by protein was less in older than in young subjects ($P < 0.005$). In young subjects, total energy intake (meal + infusion) on the 180-kcal protein-infusion day was lower than that on the control day ($P = 0.041$), whereas in older subjects it was greater on the 30-kcal ($P = 0.033$) and 90-kcal ($P = 0.016$) infusion days. Energy intake was inversely related to isolated pyloric pressure waves ($r = -0.32$, $P = 0.013$) and positively related to antral ($r = 0.30$, $P = 0.021$) and duodenal ($r = 0.35$, $P = 0.006$) pressure waves. Suppression of energy intake by protein was inversely related to the change in isolated pyloric pressure waves ($r = -0.35$, $P = 0.027$) and positively related to duodenal pressure waves ($r = 0.32$, $P = 0.044$).

Conclusions: Intraduodenal protein suppresses appetite and energy intake less in healthy older than in young adults. In older subjects, intraduodenal protein at low doses increased overall energy intake, which supports the use of protein supplements in undernourished older people. This trial was registered at www.anzctr.org.au as 12612000906853. *Am J Clin Nutr* 2014;100:1108–15.

INTRODUCTION

As for young people, the number of older people who are overweight or obese increased substantially over recent decades (1). However, healthy aging is associated with a reduction in appetite and energy, including protein intake—the "anorexia of aging" (2, 3). These changes predispose older people to weight loss (particularly loss of skeletal muscle), reduced functional capacity, and the development of pathological undernutrition, sarcopenia cachexia, and frailty (2, 4–7). The causes of anorexia of aging are poorly defined, but are likely to be many. Potential mechanisms include central and/or peripheral reductions in feeding drives and increased activity of central and/or peripheral satiety signals (8). Peripheral mechanisms, notably those related to the gastrointestinal tract, are important in regulating appetite and energy intake, particularly in the short-term after nutrient ingestion. They include interrelated intragastric mechanisms, such as variations in the rate of gastric emptying and gastric distension (9–12), and small intestinal mechanisms, such as changes in antropyloroduodenal motility and the release of appetite-regulating hormones (11, 13–17). Changes in antropyloric motility in response to nutrient ingestion are independently related to subsequent energy intake in young subjects (18) and may therefore have a causative role. Compared with young adults, older people have a reduced perception of proximal gastric distension and greater distension of the distal stomach (ie, antral) and slightly slower gastric emptying (9, 10, 12, 19)—differences that favor reductions in energy intake.

A common strategy to increase energy intake and body weight in undernourished older people is the use of protein-enriched supplements—usually high-energy drinks rich in carbohydrates and whey protein (a major protein source in dairy). Despite the

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widespread use of such supplements by older people, evidence of their efficacy is limited, and their optimal composition is unknown (20–22). The high satiating effects of dietary protein in younger adults have been extensively studied, driven primarily by attempts by overweight younger adults to lose weight (23). The effects of dietary protein on energy intake and underlying gastrointestinal mechanisms in older people are, however, largely unknown, which is surprising given the potential for protein-enriched supplements given to older people—to increase body weight and muscle mass—to reduce subsequent energy intake, which could counteract any associated protein-induced beneficial effects on muscle mass (24, 25).

In this study we aimed to characterize the effect of aging on powerful subgastric small intestinal mechanisms by infusing hydrolyzed (resembling partially digested protein) whey protein directly into the duodenum, thereby bypassing orosensory and gastric factors. We hypothesized that small intestinal administration of protein at loads lower than (0.5 kcal/min), similar to (1.5 kcal/min), and at the upper end (3 kcal/min) of normal gastric emptying rates [1–4 kcal/min (26)] would reduce energy intake, antropyloroduodenal motility, and perceptions of appetite in a load-related fashion and that the acute suppression of energy intake at a buffet meal would be less in healthy older persons than in young adults.

SUBJECTS AND METHODS

Subjects

The study included 10 healthy young men [age (mean ± SD): 23 ± 4 y (range: 19–29 y); body weight: 73 ± 7 kg (62–87 kg); height: 1.82 ± 0.02 m; BMI (in kg/m^2): 22 ± 2] and 10 healthy older men [age: 74 ± 4 y (68–81 y); body weight: 79 ± 7 kg (66–92 kg); height: 1.74 ± 0.05 m; BMI: 26 ± 2]. The body weight of the 2 groups did not differ significantly. The older subjects had a lower height and, accordingly, a higher BMI than did the young subjects ($P < 0.05$). Subjects were recruited by advertisement. On the basis of our previous work (15), we calculated that 10 subjects per group would allow us to detect a minimum suppression in energy intake after the higher protein preload (180 kcal over 60 min) compared with the control infusion of 397 kcal with $\alpha = 0.05$ and a power of 80%. Exclusion criteria were smoking, alcohol abuse, diabetes, gastrointestinal surgery (apart from uncomplicated appendectomy), significant gastrointestinal symptoms (pain, reflux, diarrhea, or constipation), or use of medications known to potentially affect energy intake, appetite, or gastrointestinal motor function. For older people, the exclusion criteria were impaired cognitive function [score <25 on the Mini-Mental State (27)], depression [score >11 on the Geriatric Depression Questionnaire (28)], and undernutrition [score <24 on the Mini Nutritional Assessment (29)]. The Royal Adelaide Hospital Research Ethics Committee approved the study protocol, and the study was registered as a clinical trial with the Australia and New Zealand Clinical Trial Registry. All subjects provided written informed consent before their inclusion in the study.

Protocol

Subjects were studied on 4 occasions, separated by ≥3 d, to determine the effects of 3 intraduodenal protein loads and a saline control (each infused for 60 min) on energy intake, antropyloroduodenal motility, perceptions of appetite, and gastrointestinal symptoms in a randomized (by using the method of randomly permuted blocks; www.randomization.com), double-blind, crossover design.

Protein solutions were prepared by dissolving whey protein hydrolysate powder (18.1% Hydrolyzed Whey Protein 821; Fonterra Co-Operative Group Ltd) in varying amounts of saline and water to achieve the desired loads [ie, 0.5, 1.5, and 3 kcal/min, which equated to 30, 90, and 180 kcal or 8, 24, and 48 g protein or 0.11 ± 0.01 (range: 0.09–0.13), 0.32 ± 0.03 (0.26–0.39), and 0.63 ± 0.06 (0.52–0.78) g protein/kg body wt] and to ensure that they were iso-osmotic (680 mOsmol/L). Infusions were prepared on the morning of each study by a research officer who was not involved in the data analysis. The infusion apparatus was covered at all times, so both the investigator and the subject were blind to the treatment. The infusions were administered at a rate of 4 mL/min (240 mL over 60 min).

Subjects were provided with a standardized evening meal [beef lasagna (McCain Foods), ~591 kcal] to consume on the night before each study, and were instructed to fast overnight from solids and liquids and to refrain from strenuous physical activity until they attended the laboratory at the University of Adelaide Discipline of Medicine, Royal Adelaide Hospital, at ~0830. On arrival, a small-diameter (3.5 mm), 16-channel [side holes spaced at 1.5-cm intervals with channels 1–6 (in the antrum), channel 7 (a 4.5-cm sleeve sensor, including channels 8 and 9 on the back of the sleeve, across the pylorus), and channels 10–16 (in the duodenum)] manometric catheter (total length: 100 cm; Dentsleeve International, Mui Scientific) was inserted into the stomach through an anesthetized nostril and allowed to pass into the duodenum by peristalsis. The correct positioning of the catheter, with the sleeve sensor straddling the pylorus, was maintained by continuous measurement of the transmucosal potential difference between the most distal antral channel (channel 6, ~−40 mV) and the most proximal duodenal channel (channel 10, ~0 mV) and a reference electrode attached to an intravenous cannula filled with sterile saline positioned subcutaneously in the left forearm. The infusion port of the catheter was located in the proximal small intestine 14.5 cm from the pylorus. All manometric channels were perfused with degassed, distilled water, except for the 2 transmucosal-potential-difference channels, which were perfused with degassed 0.9% saline at a rate of 0.15 mL/min.

Once the catheter was positioned, fasting motility was observed until phase 3 of the interdigestive migrating motor complex occurred. Immediately after cessation of phase 3 activity, during motor quiescence (phase 1 of the migrating motor complex), a visual analog scale (VAS) questionnaire to assess perceptions of appetite and gastrointestinal symptoms was completed, and baseline antropyloroduodenal motility was measured for 15 min on which the intraduodenal infusion commenced. During the infusion, antropyloroduodenal motility was measured continuously, and VAS ratings were obtained at 15-min intervals. After 60 min, the infusion was terminated and both the intraduodenal catheter and subcutaneous cannula were removed. Subjects were then presented with a standard, cold, buffet-style meal in excess of what they were expected to consume and instructed to eat freely for up to 30 min until comfortably full. Immediately after completion of the meal (90 min), the final

VAS was completed and the subjects were allowed to leave the laboratory.

Measurements

Energy intake

The amount eaten (g) was quantified by weighing the buffet meal before and after consumption. Energy intake (kcal) at the buffet meal and proportions of intake of protein, carbohydrate, and fat were calculated by using commercially available software (Foodworks; Xyris Software). Energy intake was calculated both as the intake at the buffet meal and as the total energy intake, defined as the sum of energy intake at the buffet meal and energy content of the intraduodenal infusion. Absolute and percentage suppression of energy intake (kcal) at the buffet meal by a given protein infusion compared with control was calculated.

Perceptions of appetite and gastrointestinal symptoms

Perceptions of hunger, desire to eat, prospective consumption, and fullness and nausea and bloating were rated by using validated VAS questionnaires. These questionnaires consisted of 100-mm horizontal lines, where 0 represented that the sensation was "not felt at all" and 100 represented that the sensation was "felt the greatest." Subjects placed a vertical mark on each horizontal line to indicate the strength of each sensation felt at the specified time points. Baseline fasting ratings were calculated as the mean of the 4 study days. Overall ratings for protein were calculated as the mean of the 3 protein-infusion study days.

Antropyloroduodenal motility

Antropyloroduodenal pressure waves were recorded continuously and digitized by using a computer-based system that ran commercially available software (Flexisoft v3; Oakfield Instruments) and were stored for subsequent analysis. Data were analyzed for basal pyloric pressures and number and amplitude of isolated pyloric pressure waves (IPPWs) and antral and duodenal pressure waves. Basal pyloric pressure was calculated by subtracting the mean basal pressure (with phasic pressures excluded) recorded at the most distal antral channel from the mean basal pressure recorded at the sleeve with custom-written software modified to our requirements (30). Pressure waves were defined by an amplitude >10 mm Hg with a minimum time interval of 15 s between peaks for IPPWs and antral pressure waves and 3 s for duodenal pressure waves. Baseline fasting values were calculated from 10 min before to the start of intraduodenal infusion as the mean of the 4 study days.

Data and statistical analyses

Statistical analyses were performed by using SPSS software (version 21; IBM). Between-subject effects were determined by using ANOVA. Within-subject and interaction effects were determined by using repeated-measures ANOVA. Post hoc comparisons, adjusted for multiple comparisons by using Bonferroni's correction, were performed when ANOVAs showed significant effects. Relations of energy intake with AUCs (which were calculated by using the trapezoidal rule) for antropyloroduodenal pressures and appetite were evaluated by between- and within-subject correlations (31, 32). Statistical significance was accepted at $P < 0.05$. All data are presented as means ± SEMs.

RESULTS

The study protocol was well tolerated by all subjects.

Energy intake at the buffet meal

Energy intake at the buffet meal after the intraduodenal infusions of saline (0 kcal, control) and protein loads of 30, 90, and 180 kcal were 1270 ± 150, 1123 ± 151, 1028 ± 163, and 851 ± 161 kcal, respectively, in young subjects and 1068 ± 93, 1129 ± 91, 1123 ± 98, and 899 ± 103 kcal, respectively, in older subjects. The lower (~16%) energy intake at the buffet meal during the control day in older than in young subjects was not statistically significant ($P = 0.268$). The interaction effect of age × protein load for energy intake at the buffet meal was significant ($P = 0.039$). Energy intake was dose responsively suppressed by protein in the young subjects (suppression at 30 kcal: 7 ± 8%, $P = 0.189$; 90 kcal: 17 ± 8%, $P = 0.054$; and 180 kcal: 33 ± 8%; $P = 0.002$; **Figure 1**), whereas suppression was observed in the older subjects only with the 180-kcal infusion (30 kcal: 7 ± 4% increase in intake, $P = 0.126$; 90 kcal: 6 ± 7% increase in intake, $P = 0.291$; 180 kcal: 17 ± 6% suppression, $P = 0.016$). Suppression of energy intake at the buffet meal by the protein loads was less in older than in young subjects ($P < 0.05$; **Figure 2**).

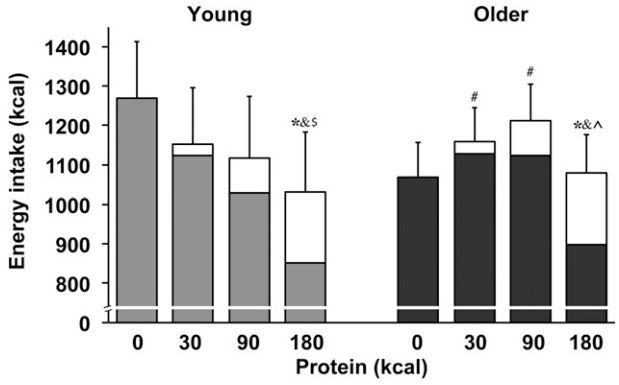

FIGURE 1. Mean (±SEM) energy intake in young (gray shading; $n = 10$) and older (black shading; $n = 10$) subjects after intraduodenal infusions of saline (open bars; 0 kcal, control) and whey protein loads of 30, 90, and 180 kcal for 60 min at 4 mL/min. In young subjects, a dose-responsive suppression of energy intake was observed at the buffet meal by protein compared with control, whereas suppression was observed only with the 180-kcal infusion in older subjects. Between-subject effects were determined by using ANOVA. Within-subject and interaction effects were determined by using repeated-measures ANOVA. A significant ($P = 0.039$) age × protein-load interaction for energy intake at a buffet meal ($P = 0.039$) and total energy intake (buffet meal + infusion) was found. $^{*}P < 0.05$ (within age group, lower energy intake at a buffet meal after protein-load infusion of 180 kcal compared with control in young and in older subjects). $^{\&}P < 0.05$ (within age group, lower energy intake at a buffet meal after protein infusion of 180 kcal compared with a 30-kcal load in young and in older subjects). $^{\wedge}P < 0.05$ (within age group, lower energy intake at a buffet meal after protein infusion of a 180-kcal compared with a 90-kcal load in older subjects). $^{\$}P < 0.05$ [within age group, lower total energy intake (energy intake at the buffet meal plus energy content of the infusion) during the 180-kcal protein-load infusion day compared with the control day in young subjects]. $^{\#}P < 0.05$ (within age group, higher total energy intake during the 30- and 90-kcal protein-load infusion day compared with the control day in older subjects).

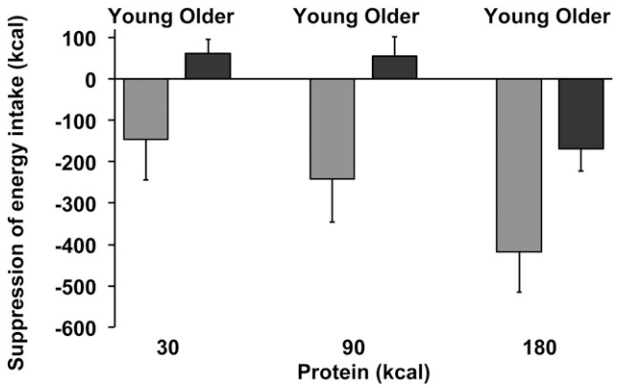

FIGURE 2. Mean (±SEM) suppression of energy intake at the buffet meal in young (gray shading; $n = 10$) and older (black shading; n = 10) subjects after intraduodenal infusions of whey protein loads of 30, 90, and 180 kcal compared with after intraduodenal infusion of saline (0 kcal, control) for 60 min at 4 mL/min. Suppression of energy intake at the buffet meal by protein was less in older than in young subjects. Main age and protein-load effects and interaction effects were determined by using repeated-measures ANOVA. The interaction age × protein load was not significant ($P = 0.569$). The main effects of age ($P < 0.05$) and protein load ($P < 0.001$) were significant.

Macronutrient intake

Proportions of intakes of protein, carbohydrate, and fat at the buffet meal during the control day were not significantly different ($P > 0.05$) between young and older subjects (**Table 1**). The young subjects increased their proportion of carbohydrates and decreased their proportion of fat intake after the intraduodenal protein infusions, which reached a level of significance after the 180-kcal load when compared with the control ($P = 0.006$ and $P = 0.036$). The interaction effect of age × protein load for proportions of intake of protein ($P = 0.228$), carbohydrate ($P = 0.074$), and fat ($P = 0.072$) was not significant.

Total energy intake

In young subjects total energy intake (ie, energy intake at the buffet meal plus energy content of the infusion) on the 30-kcal (1153 ± 151 kcal, decrease ~9%; $P = 0.288$) and 90-kcal (1118 ± 163 kcal, decrease ~12%; $P = 0.197$) protein-infusion days was nonsignificantly less than total energy intake on the control day (1270 ± 150 kcal) and was significantly less on the 180-kcal day (1031 ± 153 kcal, decrease ~19%; $P = 0.041$, Figure 1). In contrast, in older subjects total energy intake was significantly greater on the 30-kcal (1159 ± 91 kcal, increase ~9%; $P = 0.033$) and 90-kcal (1213 ± 98 kcal, increase ~14%; $P = 0.016$) protein-infusion days than on the control day (1068 ± 88 kcal) and not significantly different on the 180-kcal day compared with the control day (1079 ± 103 kcal, increase ~1%; $P = 0.861$). The interaction effect of age × protein load for total energy intake was significant ($P = 0.039$).

Antropyloroduodenal motility

Baseline IPPW number (2 ± 1 compared with 6 ± 1 per 60 min; $P = 0.024$) and amplitude (7 ± 2 compared with 21 ± 3 mm Hg; $P = 0.001$) were higher in older than in young subjects, whereas fasting basal pyloric pressures, number and amplitude of IPPWs, and antral and duodenal pressure waves were not significantly different between study days in either age group ($P > 0.05$).

In young and older subjects, IPPW number increased and antral and duodenal pressure wave numbers decreased with the 180-kcal protein load compared with the control ($P < 0.05$). Basal pyloric pressures of the protein loads were not different from control in either age group ($P > 0.05$). Antral pressure wave amplitude was higher during the 30-kcal infusion in the older than in the young subjects ($P < 0.05$; **Table 2**). Duodenal pressure wave amplitude was lower during the 180-kcal infusion in the older than in the young subjects ($P < 0.05$).

Perceptions of appetite and gastrointestinal symptoms

Appetite

Baseline ratings of hunger (67 ± 5 compared with 45 ± 9 mm; $P = 0.042$), desire to eat (69 ± 4 compared with 37 ± 8 mm; $P < 0.002$), and prospective food consumption (70 ± 4 compared with 47 ± 6 mm; $P = 0.005$) were lower in older than in young subjects; fullness was not significantly different between the young and old subjects, respectively (11 ± 3 compared with 6 ± 2 mm; $P = 0.201$). Ratings of hunger, desire to eat, prospective food consumption, and fullness were not different from baseline during the infusions (0–60 min) in both age groups ($P > 0.05$), except that ratings of prospective food consumption ($P = 0.020$) were decreased by the 30-kcal infusion in young subjects (**Figure 3**).

The age × protein-load interaction for hunger ($P = 0.379$), desire to eat ($P = 0.508$), prospective food consumption ($P = 0.065$), and fullness ($P = 0.914$) was not significant. Ratings of hunger, desire to eat, and fullness during the intraduodenal infusions were not significantly different between age groups or protein loads ($P > 0.05$).

TABLE 1
Proportions of intake of protein, carbohydrate, and fat at a buffet meal after intraduodenal protein infusions in young and older men[1]

	Young men ($n = 10$)				Older men ($n = 10$)			
	0 kcal	30 kcal	90 kcal	180 kcal	0 kcal	30 kcal	90 kcal	180 kcal
Protein (%)	20 ± 1	21 ± 1	20 ± 1	18 ± 1	21 ± 1	20 ± 1	20 ± 1	20 ± 1
Carbohydrate (%)	44 ± 3	47 ± 2	49 ± 3	53 ± 3[2]	49 ± 3	49 ± 3	49 ± 3	48 ± 3
Fat (%)	36 ± 4	32 ± 2	31 ± 2	29 ± 3[2]	30 ± 2	31 ± 2	31 ± 2	32 ± 2

[1] All values are means ± SEMs. Intake of protein was not significantly different between protein loads ($P > 0.05$). Proportions of intake of protein, carbohydrate, and fat at the buffet meal during the control day were not significantly different between age groups ($P > 0.05$). The interaction effect of age × protein load for proportions of intake of protein ($P = 0.228$), carbohydrate ($P = 0.074$), and fat ($P = 0.072$) was not significant.

[2] Significantly different from control, $P < 0.05$.

TABLE 2
Number and amplitude of IPPWs and antral and duodenal pressure waves and basal pyloric pressures during 60-min intraduodenal protein infusions in young and older men[1]

	Young men (n = 10)				Older men (n = 10)				
Protein	0 kcal	30 kcal	90 kcal	180 kcal	0 kcal	30 kcal	90 kcal	180 kcal	P^2
IPPWs									
n/60 min	41 ± 10	42 ± 9	65 ± 12	76 ± 12[3]	44 ± 11	50 ± 18	75 ± 8	85 ± 14[3]	0.980
Amplitude (mm Hg)	30 ± 5	32 ± 4	38 ± 5	39 ± 3	34 ± 7	38 ± 6	38 ± 4	47 ± 8	0.884
BPP (mm Hg)	1 ± 2	1 ± 2	−1 ± 2	3 ± 2	1 ± 5	1 ± 2	−1 ± 1	−1 ± 1	0.640
Antral pressure waves									
n/60 min	93 ± 17	102 ± 41	67 ± 21	35 ± 15[3]	73 ± 26	112 ± 40	18 ± 6	17 ± 6[3]	0.604
Amplitude	11 ± 8	12 ± 7[4]	8 ± 3	0 ± 6	28 ± 6	76 ± 16[3,4]	28 ± 12[5]	11 ± 2[3,5]	0.003
Duodenal pressure waves									
n/60 min	641 ± 81	565 ± 125	461 ± 62	380 ± 75[3]	467 ± 85	546 ± 72	376 ± 72	223 ± 46[3]	0.708
Amplitude (mm Hg)	25 ± 2[4]	28 ± 1	26 ± 1	25 ± 2[4]	38 ± 6[4]	31 ± 3	27 ± 2	16 ± 2[3–6]	0.005

[1] All values are means ± SEMs. Intraduodenal infusions consisted of saline (0 kcal, control) and whey protein loads of 30, 90, and 180 kcal for 60 min at 4 mL/min. Between-subject effects were determined by using ANOVA. Within-subject and interaction effects were determined by using repeated-measures ANOVA. BPP, basal pyloric pressure; IPPW, isolated pyloric pressure wave.
[2] Age × protein-load interaction.
[3] Significantly different from control, $P < 0.05$.
[4] Significant difference between young men and older men, $P < 0.05$.
[5] Significantly different from 30-kcal protein load, $P < 0.05$.
[6] Significantly different from 90-kcal protein load, $P < 0.05$.

Ratings of prospective food consumption (change in AUC from baseline to 60 min) for the 30-kcal protein load (372 ± 192 compared with 19 ± 189 mm; $P = 0.017$) were significantly higher than for the control in older subjects, whereas ratings of prospective food consumption for the 30-kcal protein load were significantly lower than for the control in the young subjects (−503 ± 238 compared with −59 ± 201 mm; $P = 0.007$). Furthermore, in the older subjects, mean prospective food consumption (change in AUC from baseline to 60 min of the 3 protein loads compared with control: 230 ± 215 compared with 19 ± 189 mm; $P = 0.019$) was increased by the protein loads compared with the control. However, in the young, mean prospective food consumption decreased more with the protein loads than with the control (−326 ± 213 compared with −59 ± 201 mm; $P = 0.020$).

Ratings of prospective food consumption (change in AUC from baseline to 60 min) of the 30-kcal protein load were significantly higher in older than in young subjects (−503 ± 238 mm compared with 372 ± 192 mm; $P = 0.010$). The change in mean ratings of prospective food consumption by the protein loads when compared with the control was significantly less in older than in young subject (−267 ± 94 compared with 211 ± 74 mm; $P = 0.001$).

Nausea and bloating

Ratings of nausea and bloating during the intraduodenal infusions were not significantly different between age groups or protein loads ($P > 0.05$; **Table 3**). The interaction effect of age × protein load for ratings of nausea ($P = 0.648$) and bloating ($P = 0.327$) was not significant. Ratings of nausea and bloating were not different from baseline in either age group ($P > 0.05$).

Relations between antropyloroduodenal motility and perceptions of appetite with energy intake

Within subjects, energy intake at the buffet meal was inversely related to IPPW number ($r = -0.32$, $P = 0.013$) and positively related to antral pressure wave number ($r = 0.30$, $P = 0.021$) and duodenal pressure wave number ($r = 0.35$, $P = 0.006$); between subjects, it was positively related to ratings of desire to eat ($r = 0.47$, $P = 0.037$) and prospective food consumption ($r = 0.57$, $P = 0.008$). Suppression of energy intake at the buffet meal by protein compared with control was, within subjects, inversely related to the change in IPPW number ($r = -0.35$, $P = 0.027$) and positively related to change in duodenal pressure wave number ($r = 0.32$, $P = 0.044$) and amplitude ($r = 0.48$, $P = 0.002$) by protein compared with control.

DISCUSSION

This study examined the influence of aging on the effects of intraduodenal protein administration on appetite and subsequent ad libitum energy intake. The protein infusion rates (0.5, 1.5, and 3 kcal/min) were lower than, similar to, and at the upper end of normal gastric emptying rates, ie, 1–4 kcal/min (26). Consistent with previous studies, older subjects were less hungry at baseline and ate less, 201 kcal or ~16%, on the control day than did the younger subjects (2). The major finding of our study was that protein-induced suppression of energy intake was significantly less in older than in young subjects. In particular, whereas total energy intake (at the buffet meal plus infusion) was suppressed by the intraduodenal protein infusions in young subjects, there was no suppression at any dose in older subjects, who actually had increased total energy intake.

These results are consistent with previous results indicating a reduced responsiveness in older people to the suppressive effects of nutrients on appetite and energy intake (33, 34). In the fasting state, healthy older people have lower hunger and higher fullness ratings than do young adults (12, 34–43). As in younger people, those hunger ratings are related positively and fullness ratings negatively to subsequent ad libitum energy intake (39). In response to oral or gastric nutrient administration, the reductions in hunger ratings and subsequent energy intake are less

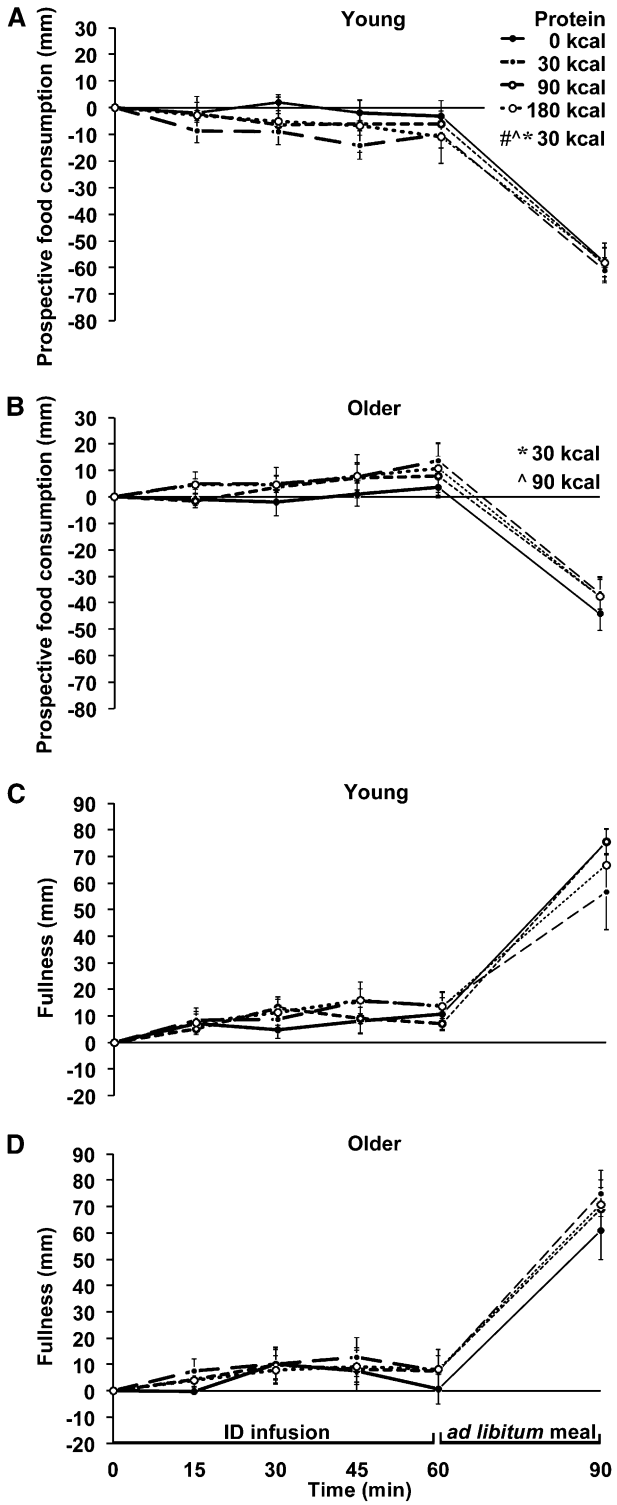

FIGURE 3. Mean (±SEM) change from fasting, baseline (0 min) visual analog scale scores of prospective food consumption (A and B) and fullness (C and D) in young ($n = 10$) and older ($n = 10$) subjects during intraduodenal infusions of saline (0 kcal, control) and whey protein loads of 30, 90, and 180 kcal for 60 min and after the ad libitum buffet meal (90 min). Between-subject effects were determined by using ANOVA. Within-subject, main age and protein-load effects and interaction effects were determined by using repeated-measures ANOVA. The age × protein-load interaction for prospective food consumption ($P = 0.065$) and fullness ($P = 0.914$) was not significant. Fullness was not significantly different between age groups ($P = 0.629$) or protein loads ($P = 0.423$). $^{\#}P < 0.05$ [time effect (0–60 min) for prospective food consumption]. $^{\wedge}P < 0.05$ (protein-load effect compared with control for prospective food consumption). $^{*}P < 0.05$ [age effect (AUC at 0–60 min) for prospective food consumption]. ID, intraduodenal.

in older than in young adults (34, 44). We have shown that the suppression of hunger ratings by intraduodenal infusions of fat and carbohydrate is less in older people than in young adults (35), and the current results—which showed less suppression of hunger ratings and subsequent energy intake by protein infusions—are, accordingly, not surprising. As in previous studies, appetite ratings were positively related to subsequent energy intake and, consistent with the effect of protein on energy intake, decreased less during the protein infusions in older than in young subjects. Thus, whereas older people are less hungry and eat less than younger adults, they appear to be less susceptible to further suppression of appetite and eating behavior by ingestion of energy and nutrients, including protein. This is consistent with the attenuated homeostatic mechanisms in older people, as evidenced by an impaired ability to compensate for modifications in diet (33).

The finding of an age-related reduction in the satiating effects of protein is important. Protein is the most satiating macronutrient in young adults when orally ingested (45) and at least as satiating as fat when infused intraduodenally (17). Furthermore, there is good evidence that high-protein diets promote satiety and aid deliberate weight loss in overweight younger adults (46). Whereas beneficial in those circumstances, protein-enriched nutritional supplements given to older people for management of undernutrition could have unintended adverse effects if satiating effects are undiminished (or increased) by age, by increasing satiety and reducing ad libitum energy intake. The use of high-protein supplements by older people for this purpose is widespread and increasing in response to greater awareness of the prevalence of undernutrition and sarcopenia in older people and evidence that protein supplementation may increase muscle mass and function (24, 25).

The reduction in suppression of appetite and feeding responses to protein in older people seen in the current study may, therefore, point to a beneficial effect of aging. If timing and preparation are optimized, it may be possible to give enough protein to older people to preserve or increase muscle mass and function without suppressing energy intake. Indeed, our observations suggest that optimal protein administration may increase overall energy intake in older people. All protein doses had a suppressive effect on total energy intake during the study (total of energy in the infusion plus that in the buffet meal) in young subjects, with a substantial 19% suppression at the highest dose. In contrast, total energy intake was not suppressed by any protein dose in the older subjects and increased significantly with the 30-kcal (9%) and 90-kcal (14%) protein doses; 90 kcal protein (22.5 g) increased total energy intake by ~145 kcal, and similar amounts of protein could reasonably be given as protein supplements several times during the day. This raises the intriguing possibility that appropriately designed protein supplements administered in divided doses might act to increase energy intake in undernourished people by meaningful amounts (>200–300 kcal/d), without the need to encourage and supervise additional energy intake.

TABLE 3
Ratings (under the curve) of nausea and bloating during 60-min intraduodenal protein infusions in young and older men[1]

	Young men (n = 10)				Older men (n = 10)			
	0 kcal	30 kcal	90 kcal	180 kcal	0 kcal	30 kcal	90 kcal	180 kcal
Nausea (mm)	657 ± 227	773 ± 300	559 ± 178	922 ± 329	196 ± 61	184 ± 61	151 ± 45	244 ± 71
Bloating (mm)	626 ± 187	803 ± 203	726 ± 203	546 ± 214	457 ± 168	470 ± 166	786 ± 292	641 ± 317

[1] Ratings of nausea (P = 0.059) and bloating (P = 0.787) were not significantly different between age groups. Ratings of nausea (P = 0.329) and bloating (P = 0.555) were not significantly different between protein loads. The interaction effect of age × protein load for ratings of nausea (P = 0.648) and bloating (P = 0.327) was not significant.

We assessed antropyloroduodenal motility to examine potential mechanisms responsible for protein-induced suppression of feeding behavior and potential age-related differences in that suppression. Gastrointestinal mechanisms involved in satiation are numerous and include variations in gastric distension (11), gastric emptying (47) (neither a factor in this intraduodenal infusion study), gut hormone secretion (eg, cholecystokinin, glucagon-like peptide 1, peptide tyrosine tyrosine and gastric inhibitory peptide, ghrelin) (15), pancreatic signals (eg, insulin) (48), plasma amino acid concentrations (eg, branched-chain amino acids) (49), diet-induced thermogenesis (50), and gluconeogenesis (51). Our group has shown that pyloric motility, particularly as reflected in the number of IPPWs, is an independent negative predictor of subsequent energy intake in young subjects (18). In the current study, pyloric motility (IPPWs) was modestly greater, in the short time period of the fasting state, in the older than in the young subjects. In both age groups, IPPW number increased and antral and duodenal pressure number decreased by the highest (180 kcal) protein load when compared with the control. Furthermore, in the combined subject group, there was an inverse relation between IPPW and energy intake and a positive relation between antral and duodenal pressures and energy intake, which further supports a relation between antropyloroduodenal motor activity and feeding behavior.

This study had several limitations, which reduced our ability to draw stronger conclusions. The subject numbers were relatively small. Nevertheless, the findings were clear cut. In the current study, protein was infused directly into the duodenum to allow exploration of small intestinal effects by bypassing higher neural, oral, and gastric mechanisms that may affect energy intake, including variations in nutrient taste, gastric distension, and gastric emptying rate. It seems that the older men had a somewhat better tolerance to the intraduodenal protein infusion than did the young men, ie, lower ratings of nausea and bloating; however, the difference was not statistically significant. We studied only men, because they appear to have the greatest ability to regulate energy intake in response to energy manipulation (34); in women, the menstrual cycle may have a confounding effect on appetite and energy intake. The results do not, therefore, necessarily apply to the effects of aging in women. Further studies are needed to determine whether this age-related reduction in protein's satiating effect is also present in women, and when the protein is administered orally and as part of a mixed-macronutrient supplement, with the ultimate aim of developing the most effective form of protein/nutritional supplement for older people, which combines the greatest anabolic effect on muscle with the least suppression of appetite and energy intake. Nevertheless, our findings provide support for the use of protein supplements in undernourished and/or sarcopenic older people, because they provide no evidence that they suppress feeding behavior and counteract attempts to increase body weight.

In summary, older men had less suppression of appetite and subsequent ad libitum energy intake by intraduodenal protein infusions than did young men, associated with antropyloroduodenal motility. At lower doses, protein administration to older people even increased overall energy intake. Future studies are needed to characterize the effects of different oral protein loads in direct comparison with saline and carbohydrate controls in older healthy and malnourished men and women compared with young subjects, which would provide comprehensive insights into the underlying mechanisms. This should lead to improved, evidence-based strategies for the use (ie, type, dose, and timing) of pure oral protein supplements to increase energy intake in older undernourished individuals or to decrease energy intake as part of a weight-loss diet strategy in older obese people.

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The authors' responsibilities were as follows—SS, MH, IC, and NDL-M: designed the research; CG, ATH, NDL-M, and SS: conducted the research; SS: generated the random allocation sequence; CG and ATH: enrolled and assigned the participants to the interventions; SS and CG: analyzed the data and performed the statistical analysis; SS, MH, IC, and NDL-M: contributed to the data interpretation; SS, CG, ATH, MH, IC, and NDL-M: contributed to the writing of the manuscript; and SS: had primary responsibility for the final content. None of the authors had any conflicts of interest to declare. Neither Fonterra nor the Royal Adelaide Hospital Research Foundation had any input in the design, implementation, analysis, or interpretation of the data.

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