# Duodenal and ileal glucose infusions differentially alter gastrointestinal peptides, appetite response, and food intake: a tube feeding study

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## ABSTRACT

**Background:** Activation of the ileal brake through the delivery of nutrients into the distal small intestine to promote satiety and suppress food intake provides a new target for weight loss. Evidence is limited, with support from naso-ileal lipid infusion studies.

**Objective:** The objective of the study was to investigate whether glucose infused into the duodenum and ileum differentially alters appetite response, food intake, and secretion of satiety-related gastrointestinal peptides.

**Design:** Fourteen healthy male participants were randomly assigned to a blinded 4-treatment crossover, with each treatment of single-day duration. On the day before the intervention (day 0), a 380-cm multilumen tube (1.75-mm diameter) with independent port access to the duodenum and ileum was inserted, and position was confirmed by X-ray. Subsequently (days 1–4), a standardized breakfast meal was followed midmorning by a 90-min infusion of isotonic glucose (15 g, 235 kJ) or saline to the duodenum or ileum. Appetite ratings were assessed with the use of visual analog scales (VASs), blood samples collected, and ad libitum energy intake (EI) measured at lunch, afternoon snack, and dinner.

**Results:** Thirteen participants completed the 4 infusion days. There was a significant effect of nutrient infused and site (treatment × time, $P < 0.05$) such that glucose-to-ileum altered VAS-rated fullness, satisfaction, and thoughts of food compared with saline-to-ileum (Tukey's post hoc, $P < 0.05$); decreased ad libitum EI at lunch compared with glucose-to-duodenum [−22%, –988 ± 379 kJ (mean ± SEM), Tukey's post hoc, $P < 0.05$]; and increased glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) compared with all other treatments (Tukey's post hoc, $P < 0.05$).

**Conclusions:** Macronutrient delivery to the proximal and distal small intestine elicits different outcomes. Glucose infusion to the ileum increased GLP-1 and PYY secretion, suppressed aspects of VAS-rated appetite, and decreased ad libitum EI at a subsequent meal. Although glucose to the duodenum also suppressed appetite ratings, eating behavior was not altered. This trial was registered at www.anzctr.org.au as ACTRN12612000429853. *Am J Clin Nutr* 2017;106:725–35.

**Keywords:** glucose, appetite, food intake, brake, ileum, duodenum, GLP-1, PYY, ghrelin

## INTRODUCTION

Long-term regulation of satiety is important for control of eating behavior, energy balance, and weight management (1), with the gastrointestinal tract (GIT) playing a central role as the source of neural and humoral signals modulated by diet and promoting satiety (2, 3). The ileal brake describes a GIT feedback loop with origin in the distal small intestine that may alter events in the proximal gut, including slowing gastric emptying, inhibiting gut motility, and slowing the transit of nutrients (4). Proposed stimuli for the brake include the arrival of nutrients into the ileal lumen, lumen wall distension. and changes in the lumen pH, leading to the activation of vagal afferents or release of GIT peptides (5) to suppress food intake. A possible role of the ileal brake in the regulation of satiety, food intake, and body weight has driven an interest in foods that may activate this mechanism (4, 6).

Evidence comes primarily from lipid infusion, although few researchers have undertaken the difficult task of naso-ileal (NI) infusion. An early study of corn oil emulsion delivered to the ileum of healthy volunteers decreased both hunger and energy intake (EI) (7), and Maljaars and coworkers (8–11) have since shown enhanced satiety and decreased EI, alongside altered GIT peptides, in several NI lipid infusion studies. Interest increased

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Abbreviations used: EEC, enteroendocrine cell; EI, energy intake; GD, glucose-to-duodenum; GI, glucose-to-ileum; GIP, gastric inhibitory polypeptide; GIT, gastrointestinal tract; GLP-1, glucagon-like peptide-1; iAUC, incremental AUC; NI, naso-ileal; PYY, peptide YY; SD, saline-to-duodenum; SI, saline-to-ileum; TOF, thoughts of food; VAS, visual analog scale.

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when a commercial lipid emulsion, purported to be protected from absorption in the proximal small intestine and delivered intact into the ileum, was shown to suppress EI (12–14), although this was not a universal finding (15–17).

Although carbohydrates may evoke stronger satiety than lipids on an isoenergetic basis (18–20), whether they successfully "brake" eating if delivered distally to the small intestine is less well understood. GIT components of the ileal brake are long shown to be induced by carbohydrate infusion in both human (21–23) and animal (24–28) studies, manifested by delay in gastric emptying and small intestinal transit, decreased secretion of digestive enzymes, and changes in gut peptides. To date, to our knowledge, only 1 study investigating eating behavior has infused carbohydrate into the ileum, with low-dose sucrose (12.9 g, ~216 kJ, 90 min) shown to increase peptide YY (PYY) and decrease EI, but with no change in appetite sensations or glucagon-like peptide-1 (GLP-1) (29). Interestingly, sodium-dependent glucose transporter-1 and glucose transporter 2 are present in low abundance in the ileum (30). The site of feedback initiation may determine the severity of the brake. Several studies have infused glucose into the duodenum to activate the duodenal brake (31–35), but only some report suppression of EI (33, 35). Woltman and Reidelberger (36) were first to compare duodenal and ileal infusion of glucose in a rodent study, reporting greater decreases in meal size and frequency at the distal site.

The primary aim of our study was to determine the effect of glucose infusion into the ileum. We hypothesized that this would enhance satiety and decrease EI at a subsequent meal when compared with both saline control (0 kJ) and glucose to the duodenum. To confirm the successful delivery of glucose, the peptides GLP-1 and PYY cosecreted by enteroendocrine cells (EECs) (37, 38) located predominantly in the ileum were measured.

## METHODS

### Participants

Fourteen healthy, lean male volunteers [BMI (in kg/m$^2$): 18–25] aged 18–60 y were recruited via electronic advertisements and posters in the Auckland area. Participants were nonsmokers, had no history of cardiovascular disease, diabetes, or any other serious metabolic, endocrine, or GIT disease, and were not taking any medications that may have had an effect on appetite or weight regulation throughout the trial period. Participants with hypersensitivities or allergies to any foods or ingredients included in the study, as well as those who disliked or were unwilling to consume items listed as study foods (breakfast and ad libitum meals), unwilling or unable to comply with study protocol, or who were participating in another clinical intervention trial were excluded. Participants were ascertained healthy by self-report and blood tests during the screening visit. A fasting venous sample was collected for the measurement of biochemistry and hematology, including: full lipid profile, plasma glucose, full blood count, liver function tests, and iron studies. Human ethics approval was obtained from the Auckland Regional Health and Disabilities Ethics Committee (ref. no. NTY/11/03/034), and all participants provided written informed consent. The trial was registered at the Australian and New Zealand clinical trials registry, number ACTRN12612000429853. The trial was conducted at the Human Nutrition Unit of the University of Auckland (Auckland, New Zealand).

### NI tube

The NI tube was a 380-cm, 5-channel (3-lumen, 1-balloon inflation channel, 1 stiffener channel; 1.75-mm external diameter), rubber silicon infusion tube (Dentsleeve International, Ltd.). The functional length of the tube was 340 cm, with the initial 40 cm used as a connecting segment "octopus," which attached to the nutrient infusion bags. A single ileal channel (0.6-mm luminal diameter) terminated 300 cm distal to the connector end (≥170 cm distal from the pylorus) for ileal infusion with 3 side holes spaced at 0.5-cm intervals. Two duodenal channels (0.35-mm luminal diameter each) terminated 100 cm distal to the connector end (~15 cm from the pylorus) with 3 side holes spaced at 1-cm intervals for duodenal infusion. As the small diameter of the duodenal infusion channel greatly increased the resistance and work of the pump, having a potential impact on reducing the final flow rate and volume, the 2 duodenal channels ran in parallel. The fourth channel was filled with a guide-wire stiffener to facilitate passage of the tip to the ileum and played a role as a radiopaque marker to aid the assessment of the positioning of the tube. The tube had tungsten pellets encased in silicone attached to the distal tip to aid passage through the pylorus and a balloon (2 cm in length) that could be inflated with normal saline through the balloon channel to facilitate propulsion along the small intestine. The fifth channel provided access to inflate the balloon. The tube was fitted with radiopaque markers that enabled assessment of the location of the tube once in the gastrointestinal tract.

### Study design

This was a residential, controlled, single-blind, randomized 4-treatment crossover study to compare the effects of glucose or saline infused over 90 min into either the duodenum or ileum. Randomization was conducted by Latin square. The 4 treatment arms comprised glucose-to-ileum (GI), saline-to-ileum (SI), glucose-to-duodenum (GD), and saline-to-duodenum (SD) and each was of single-day duration. There was no washout period between the treatments due to the complexity of NI tube insertion and removal, as per previous infusion protocols (8–11, 29). Appetite and food intake were assessed during 4 d of full supervision at the Human Nutrition Unit, adhering to the recommendations of Blundell et al. (39).

#### *Ileal and duodenal infusion*

The infusions comprised 15 g glucose in isotonic solution (235 kJ, 4% glucose and 0.18% NaCl wt/vol, product no. S03W7; Baxter) or saline (0 kJ, 0.9% NaCl wt/vol, product no. S31N5; Baxter), to sustain the osmotic equilibrium along the GIT. The total volume infused was 375 mL over 90 min at a rate of 4.2 mL/min, delivering glucose to both the duodenum and ileum at a rate of 0.16 g/min (2.6 kJ/min; **Table 1**). Infusion was performed with the use of a standard Alaris GP infusion pump (Alaris; Becton Dickinson) attached to the octopus at the proximal end of the NI tube.

#### *Day 0: NI tube insertion*

On the morning before the intervention (day 0), participants attended Auckland City Hospital at 0830 for intubation, after an overnight fast from 2200. On arrival, participants were administered oral metoclopramide (10 mg) to stimulate gut motility. The distal end of the 340-cm NI tube was lubricated with 2% xylocaine gel, and the participants were offered the application of a nasal local anesthetic spray. The tube was introduced through

**TABLE 1**
Naso-ileal infusion of glucose and saline into the ileum and duodenum[1]

| | GI | SI | GD | SD |
|---|---|---|---|---|
| Infusion rate, mL/h | 250 | 250 | 250 | 250 |
| Infusion time, min | 90 | 90 | 90 | 90 |
| Total volume infused, mL | 375 | 375 | 375 | 375 |
| Total glucose infused, g | 15 | 0 | 15 | 0 |
| Total glucose infused, kJ | 235 | 0 | 235 | 0 |

[1] Glucose: 4% glucose + 0.18% NaCL wt/vol; saline: 0.9% NaCL wt/vol. GD, glucose-to-duodenum; GI, glucose-to-ileum; SD, saline-to-duodenum; SI, saline-to-ileum.

an anesthetized nostril down into the stomach. Once the tip was in the stomach, estimated as 70 cm from the distal tip by an ~270 cm marking on the tube at the nose, the tube was secured in place by taping it to the participant's face to prevent it from moving and coiling inside the stomach. This procedure took ~10–15 min. The balloon was then inflated with ~3 mL normal saline to facilitate the tube moving down into the small intestine. The participants were offered a snack comprising a savory muffin and banana to generate peristalsis and descent of the tube. After ~30 min, the tube was released and allowed to pass through the pylorus into the duodenum by peristalsis. Participants rested for 2–3 h at the hospital to allow time to get comfortable with the tube in situ and then relocated to the Human Nutrition Unit residential facility. At mid-afternoon, 6–7 h after the NI tube insertion, the position of the tube was determined by plane abdominal X-ray imaging and confirmed by a radiologist.

*Days 1–4*

On the first study day (day 1), an indwelling venous cannula was inserted into a forearm vein for the collection of repeat blood samples, after which an identical protocol was followed for days 1–4 (**Figure 1**). Following an overnight fast, at 0830 the position of the tube was again determined by abdominal X-ray imaging and confirmed by a radiologist. At 0920, a basal blood sample was collected, visual analog scales (VASs) were completed to assess subjective appetite ratings, and breakfast was given at 0930 [time ($t$) = –120 min]. Glucose or saline infusion began at 1130 ($t$ = 0 min), with the intent of mimicking the arrival of dietary components into the ileum ~2 h after ingestion of the breakfast meal.

*Standardized breakfast, ad libitum meals, and EI*

Breakfast was a standardized 2-MJ mixed-nutrient meal, and all items were consumed within 15 min. The breakfast was designed as a low phytochemical meal, as a variety of herbal and food phytochemicals have been proposed to affect appetite (40), and comprised English crumpets with butter, bacon with maple-flavored syrup, and dairy yogurt (**Table 2**). A restricted-item lunch meal was served at 1330 ($t$ = 120 min), snack at 1530 ($t$ = 240 min) and dinner at 1930 ($t$ = 480 min, Table 2), from which participants could eat ad libitum. Meal items were weighed by 2 separate observers before and after consumption of each of the meals or snacks. Energy, fat, carbohydrate, and protein intake were calculated with the use of the dietary software program FoodWorks (Professional Edition, version 5; Xyris Software). Participants were allowed 30 min to consume each meal or snack and were advised that they could eat as much or as little as they chose and should eat until they felt comfortably full. Distractions were kept to a minimum by seating participants within individual dining booths with no reading materials, mobile phone, tablet, or other electronic items. Background music was used to dampen the sound of cutlery, crockery, and the noises of eating. Participants were asked to remain in their individual booths for 30 min. Participants were supervised throughout the day, were not allowed to sleep, and were instructed to go to bed at 2230 each night.

## Appetite ratings

VASs were used to assess hunger, fullness, satisfaction, thoughts of food (TOF), and GIT symptoms, including nausea and abdominal discomfort. Participants marked responses by placing a vertical line across the 100-mm scale according to subjective feelings. VAS measurements were collected on 6 occasions before the infusion; fasted prebreakfast ($t$ = −120 min), immediately postbreakfast ($t$ = −105), at 30-min intervals over the next hour ($t$ = −90, −60, −30 min), and immediately pretreatment ($t$ = 0 min). Once the infusion commenced, VAS ratings were recorded at 15-min intervals over the following hour ($t$ = 15, 30, 45, and 60 min), then every 30 min until consumption of the snack ($t$ = 90, 120, 150, 180, 210, 240 min) and every 60 min for the remainder of the day ($t$ = 300, 360, 420, and 480 min). Immediately after breakfast, the ad libitum lunch and ad libitum dinner meal participants also rated pleasantness,

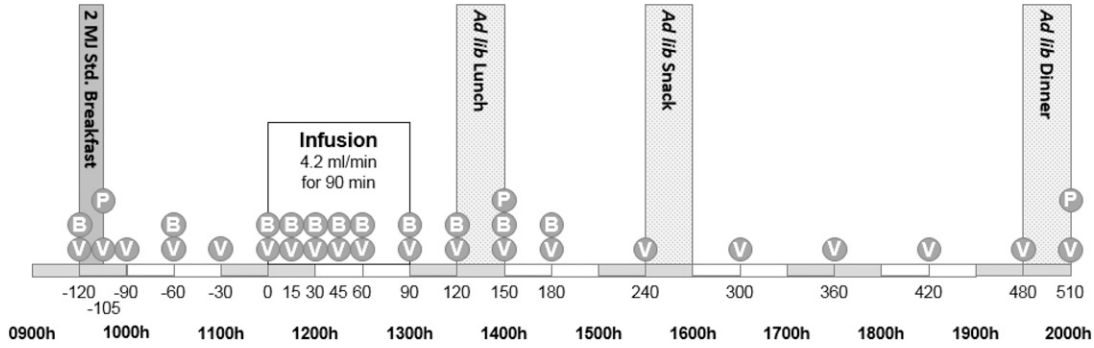


**FIGURE 1** Study protocol on days 1–4 when, after intubation and confirmation of siting of the tube by abdominal X-ray, glucose or saline was infused into the duodenum or ileum. Fifteen grams (235 kJ) isotonic glucose or saline was infused over 90 min with no adverse side effects. The $x$-axis shows single-day protocol from −120 to 510 min. The tube was well tolerated and intake from lunch, afternoon snack, and dinner was assessed throughout the 4 d of the study. *Ad lib*, ad libitum; B, blood sample; P, palatability–visual analog scale; Std., standardized; V, hunger ratings–visual analog scale.

**TABLE 2**
Composition of the standardized breakfast and ad libitum lunch, snack, and dinner meals[1]

| | Weight, g | Energy, kJ | CHO, g | CHO, en% | Fat, g | Fat, en% | Prot, g | Prot, en% |
|---|---|---|---|---|---|---|---|---|
| Breakfast, 2 MJ | | | | | | | | |
| Baked goods, crumpet | 85 | 676 | 32.3 | 80 | 0.8 | 4 | 5.1 | 12 |
| Dairy spread, butter | 10 | 303 | 0.01 | 0.1 | 8.1 | 100 | 0.01 | 0 |
| Bacon, shoulder, grilled | 50 | 239 | 2.3 | 16 | 2.7 | 42 | 6 | 42 |
| Syrup, maple flavored | 30 | 387 | 21.8 | 99 | 0 | 0 | 0 | 0 |
| Yogurt, natural | 125 | 454 | 13.8 | 51 | 3.5 | 29 | 5.4 | 19 |
| Water | 250 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 550 | 2059 | 71.2 | — | 15.1 | — | 16.5 | — |
| Ad lib lunch | | | | | | | | |
| Meat sauce, beef and tomato | 1385 | 3858 | 55.2 | 24 | 39 | 38 | 82.6 | 36 |
| Pasta, spirals, boiled | 1010 | 5770 | 277.5 | 82 | 5.6 | 4 | 45 | 13 |
| Madeira cake | 280 | 4620 | 155.1 | 56 | 44.8 | 37 | 14.6 | 5 |
| Water | 250 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 2925 | 14178 | 487.8 | — | 89.4 | — | 142.2 | — |
| Ad lib snack | | | | | | | | |
| Sponge cake, vanilla | 495 | 8102 | 183.7 | 38 | 120.6 | 56 | 32.6 | 7 |
| Water | 250 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 745 | 8102 | 183.7 | — | 120.6 | — | 32.6 | — |
| Ad lib dinner | | | | | | | | |
| Lamb casserole | 2550 | 7483 | 201.8 | 45 | 47.3 | 24 | 139.6 | 31 |
| Rice, long grain, steamed | 933 | 5880 | 314 | 90 | 4 | 3 | 25.6 | 7 |
| Pears, tinned, drained | 550 | 1584 | 99 | 96 | 1.1 | 3 | 1.1 | 1 |
| Custard, vanilla | 1000 | 5000 | 188 | 63 | 31 | 23 | 36 | 12 |
| Water | 250 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 5283 | 19947 | 802.8 | — | 83.4 | — | 202.3 | — |

[1] Ad lib, ad libitum; CHO, carbohydrate; en%, energy percent; Prot, protein.

visual appeal, smell, taste, aftertaste, and overall palatability on a separate 100-mm VAS.

### Blood samples

A total of 11 blood samples were collected throughout each study day for the measurement of glucose, insulin, GLP-1, PYY, gastric inhibitory polypeptide (GIP), and ghrelin. Plasma glucose was analyzed at LabPLUS Ltd. (International Accreditation New Zealand, accreditation number 204) with the use of Roche cobas 8000 modular analyzer (c702 module). Plasma insulin, GLP-1, GIP, PYY and ghrelin samples, collected into prechilled tubes containing EDTA with dipeptidyl-aminopeptidase IV inhibitor (25 $\mu$L of a 2 mM solution of Diprotin A; Peptides International) and protease inhibitor cocktail (182 $\mu$L of solution containing 1 tablet of Complete Mini EDTA-free protease inhibitor dissolved in 2 mL of water; Roche) were centrifuged, snap frozen, and stored at −80°C until analysis with the use of the MILLIPLEX MAP Human Metabolic Hormone Magnetic Bead Panel 96-Well Plate Assay (catalog number HMHMAG-34K; Merck-Millipore). Samples were assayed as a single batch and in duplicate, and plates were read with the use of the Bioplex 100 Analyzer System (Bio-Rad). The insulin range was 137.2–100,000 pg/mL [interassay CV: 4.2%; intra-assay CV: 5.0%]; the GLP-1 range was 14.4–7910 pg/mL (interassay CV: 7.3%, intra-assay CV: 6.3%); the PYY range was 1–6628 pg/mL (interassay CV: 13%, intra-assay CV: 9.0%); the GIP range was 2.7–2000 pg/mL (interassay CV: 4.7%, intra-assay CV: 3.5%); and the ghrelin range was 13.7–10,000 pg/mL (interassay CV: 5.2%; intra-assay CV: 4.7%).

### Statistical analyses

Participant characteristics were summarized as means ± SDs. Efficacy endpoints were means ± SEMs. VAS appetite ratings, VAS palatability ratings, and blood biomarkers were analyzed with the use of repeated measures linear mixed models, and energy and macronutrient intake at individual meals was analyzed with the use of 1-way ANOVA (SAS software, PROC MIXED function, version 9.2; SAS Institute Inc.). Participant, infusion (treatment condition), study day (visit number), and study period (time) were included in the procedure, with baseline measures as covariates where relevant, as was diet-time interaction, which addressed whether the trajectory over time after the infusion differed between infusion treatments (treatment × time). Tukey's post hoc analysis was used for pairwise comparisons between treatments where main effect ANOVA was significant. Incremental AUC (iAUC) for VAS ratings and blood markers was calculated as the AUC of the net change ($\Delta$) from baseline measured over 0–120 min ($AUC_{\Delta 0–120\ min}$) immediately after the infusion with the use of GraphPad Prism software (version 6.05; GraphPad Software). Statistical significance was set at $P < 0.05$.

## RESULTS

### Participants

Of the 14 participants randomly assigned into the trial, 13 completed all 4 treatment arms. The participants were healthy, lean males with a mean age of 22 ± 4.2 y and a mean BMI of 22.8 ± 1.5 (**Table 3**). One participant withdrew from the trial after

**TABLE 3**
Characteristics of the 13 male participants who completed 4 treatment arms[1]

| | Mean ± SD | Range |
|---|---|---|
| Age, y | 22.8 ± 4.2 | 20–32 |
| Body weight, kg | 72.3 ± 6.4 | 65.5–83.4 |
| BMI, kg/m$^2$ | 22.8 ± 1.5 | 19.9–25.3 |
| Waist circumference, cm | 78.9 ± 4.1 | 72–87 |
| SBP, mm Hg | 116 ± 10.1 | 99–130 |
| DBP, mm Hg | 59 ± 4.8 | 51–67 |

[1] All measurements recorded at screening visit. DBP, diastolic blood pressure; SBP, systolic blood pressure.

completion of 3 treatments due to excessive pulling of the tube at the nares, which appeared on X-ray examination to be caused by coiling of the NI tube within the stomach and small intestine.

## VAS ratings

### *Appetite: hunger, fullness, satisfaction, and TOF*

The mean ratings for hunger and fullness measured throughout the study day on each of the 4 treatment arms are shown in **Figure 2**A, D. Changes were predictable throughout the day, driven primarily by the timing of the meals and snacks, with no evidence that the small-diameter NI tube was adversely altering these measures of subjective reporting. Before the breakfast meal, fasting hunger and fullness were similar on each of the 4 test days ($P > 0.05$) and, as expected, there were significant postprandial changes after each eating occasion ($P < 0.05$). In both GI and GD infusions (Figure 2B), VAS-hunger ratings were below respective matched saline controls, but neither represented a statistically significant suppression of hunger. The histogram (Figure 2C) shows the change in hunger over 120 min between the start of infusion (t = 0 min) and the lunch meal ($iAUC_{\Delta 0–120\ min}$). Similar effects were seen for VAS fullness, but with a significant difference between the 4 treatment arms during infusion (main effect ANOVA, Figure 2E, $P < 0.05$). Post hoc pairwise comparisons confirmed greater fullness when glucose was infused irrespective of the site and was significant for GI compared with SI at 90 and 120 min and GD compared with SD at 90 min (Tukey's post hoc, $P < 0.05$). GI and GD did not differ. VAS-rated changes in satisfaction and TOF (**Figure 3**) were similar and consistent with those of hunger and fullness. Again, there was a significant difference in both satisfaction and TOF between the 4 treatments when analyzed during the 120 min after the infusion (Figure 3B, E, main effect ANOVA, $P < 0.05$). Post hoc pairwise comparisons also identified a significant difference in $\Delta$ satisfaction between GI and SI at 90 and 120 min, and $\Delta$ TOF between GI and SI at 90 min (Tukey's

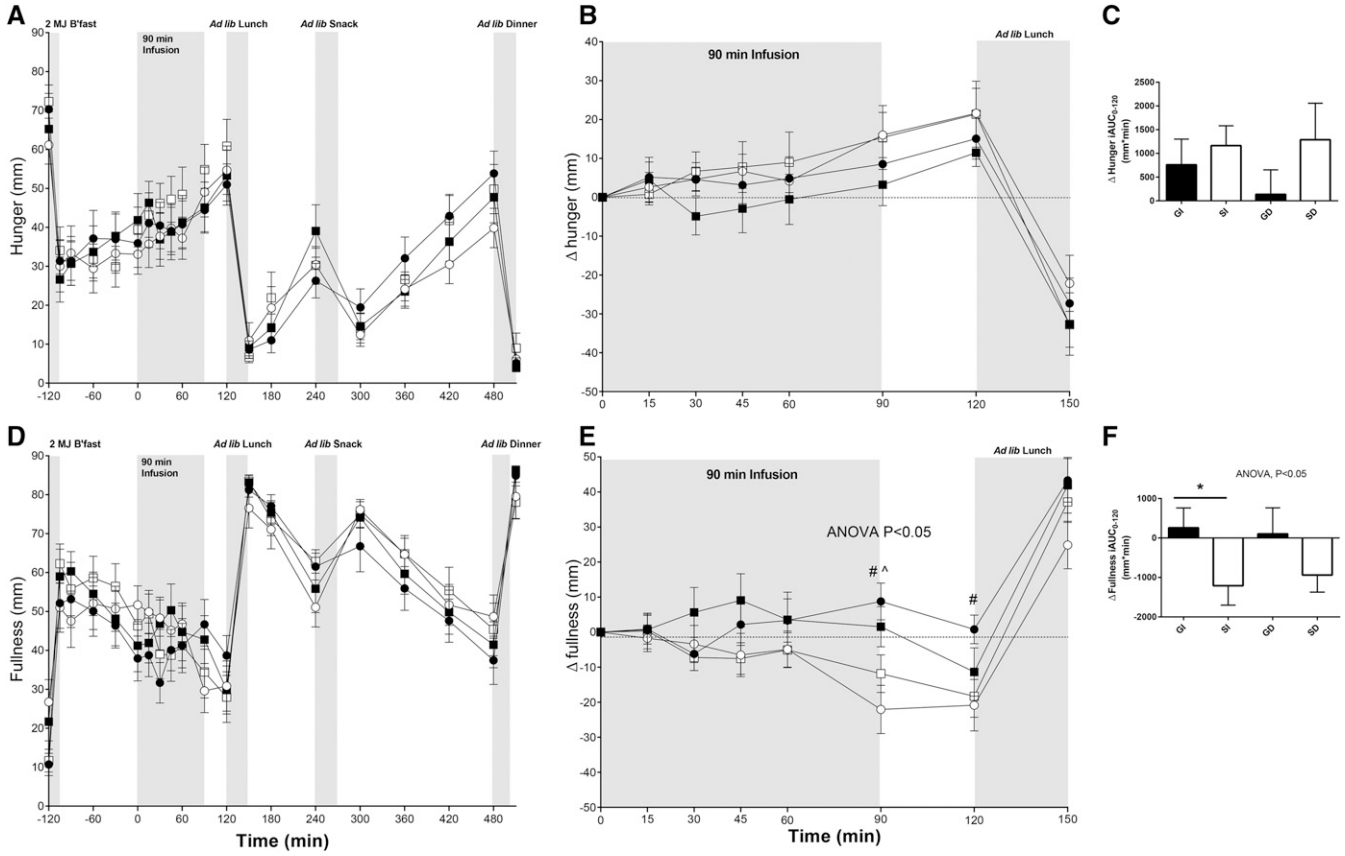


**FIGURE 2** VAS results for (A) hunger and (D) fullness throughout the day in response to the 4 infusions. Changes ($\Delta$) in the ratings of (B) hunger and (E) fullness from the start of the 90-min infusion ($t = 0$ min) are shown as $\Delta$ VASs. Histograms show $iAUC\Delta_{0–120\ min}$ for $\Delta$ with respect to (C) hunger and (F) fullness from the start of the 90-min infusion to the start of lunch. Main effect, ANOVA; Tukey's post hoc pairwise comparisons: GI > SI, $^{\#}P < 0.05$, $^{*}P < 0.05$; GD > SD, $^{\wedge}P < 0.05$. Values are means ± SEMs; $n = 13$. *Ad lib*, ad libitum; B'fast, breakfast; GD (■), glucose-to-duodenum; GI (●), glucose-to-ileum; iAUC, incremental AUC; SD (□), saline-to-duodenum; SI (○), saline-to-ileum; VAS, visual analog scale.

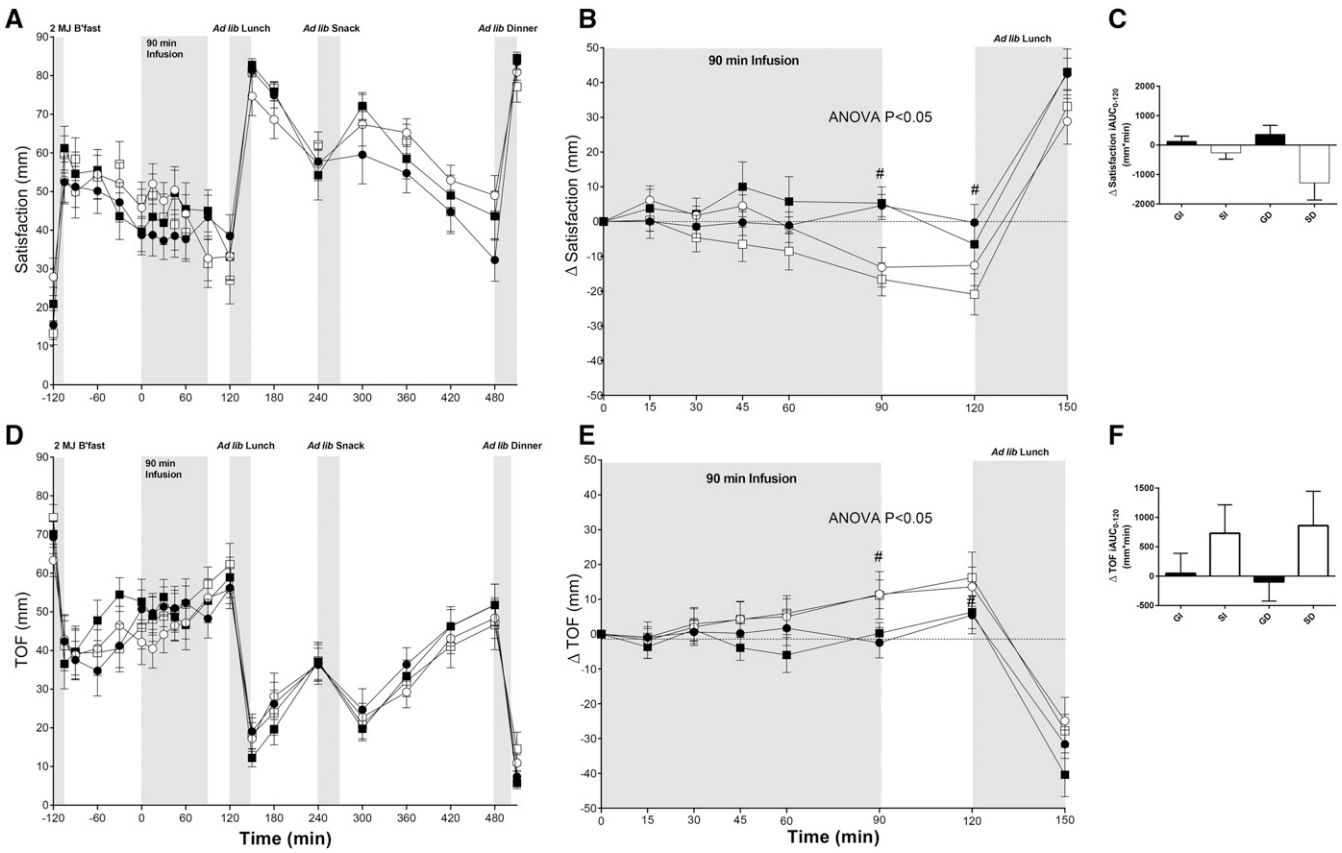


**FIGURE 3** VAS results for (A) satisfaction and (D) TOF throughout the day in response to the 4 infusions. Changes ($\Delta$) in the ratings of (B) satisfaction and (E) TOF from the start of the 90-min infusion ($t = 0$ min) are shown as $\Delta$ VASs. Histograms show $iAUC\Delta_{0–120\ min}$ for $\Delta$ with respect to (C) satisfaction and (F) TOF from the start of the 90-min infusion to the start of lunch. Main effect ANOVA; Tukey's post hoc pairwise comparisons: GI compared with SI, $^{\#}P < 0.05$. Values are means ± SEMs; $n = 13$. *Ad lib*, ad libitum; B'fast; breakfast; GD (■), glucose-to-duodenum; GI (●), glucose-to-ileum; $iAUC\Delta_{0–120\ min}$, change in incremental AUC from 0 to 120 min; SD (□), saline-to-duodenum; SI (○), saline-to-ileum; TOF, thoughts of food; VAS, visual analog scale.

post hoc, $P < 0.05$). Histograms showing iAUC satisfaction and TOF during the 120 min between the start of infusion and the lunch meal ($iAUC_{\Delta 0–120\ min}$) are shown in Figure 3C, F. Again, there was no difference between GI and GD for satisfaction or TOF throughout the intervention.

### *Palatability, nausea, and abdominal pain*

The reported palatability and sensory assessment of the breakfast, lunch, and dinner meals was high (60–80 mm) and was similar between meals ($P > 0.05$), indicating that the tube was not causing any serious discomfort during eating and that there was no detectable decrease in sensory response to meals or snacks over the 4 consecutive study days (data not shown). Throughout the trial, the ratings for nausea and abdominal pain were low (<20 mm) despite the prolonged in situ period of the tube and infusion of glucose into the distal small bowel with the possibility of overflow into the colon.

## Blood parameters

### *Glucose and insulin*

The plasma concentrations of glucose and insulin are shown in **Figure 4**. Mean fasting ($t = -120$ min) glucose and insulin concentrations did not differ between treatments ($P > 0.05$), and as expected, the breakfast and lunch meals caused an increase in both on all occasions (Figure 4A, D). Notably, circulating glucose concentrations increased only during GD infusion (main effect ANOVA, $P < 0.05$; Figure 4B) with a peak at 45 min and a subsequent return to baseline by 120 min. Conversely, GI infusion did not cause an increase in circulating glucose concentrations. Pairwise comparisons confirmed the increase in circulating glucose concentrations during GD infusion relative to all other treatments (GI, SI, and SD) at 30, 45, and 60 min (Tukey's post hoc, $P < 0.05$). The iAUC of the change in glucose concentrations during infusion (Figure 4C, $iAUC_{\Delta 0–120\ min}$) confirmed the significant increase after GD infusion. During GD infusion, the plasma concentrations of insulin also increased above baseline ($t = 0$ min) with a peak at 30 min (Figure 4E), and post hoc pairwise comparisons confirmed an increase after GD infusion relative to all other treatments (GI, SI, and SD) at 15, 45, and 90 min (Tukey's post hoc, $P < 0.05$). As was observed for glucose, GI infusion did not promote an increase in circulating insulin concentrations.

### *GLP-1, PYY, GIP, and ghrelin*

Plasma GLP-1, PYY, GIP, and ghrelin concentrations through the morning are shown in **Figure 5**. Fasting concentrations ($t = -120$ min) were well matched between treatment groups for all peptides ($P > 0.05$). As expected, GLP-1 concentrations increased after both breakfast and lunch on all 4 study days (Figure 5A). There was also an effect of infusion treatment

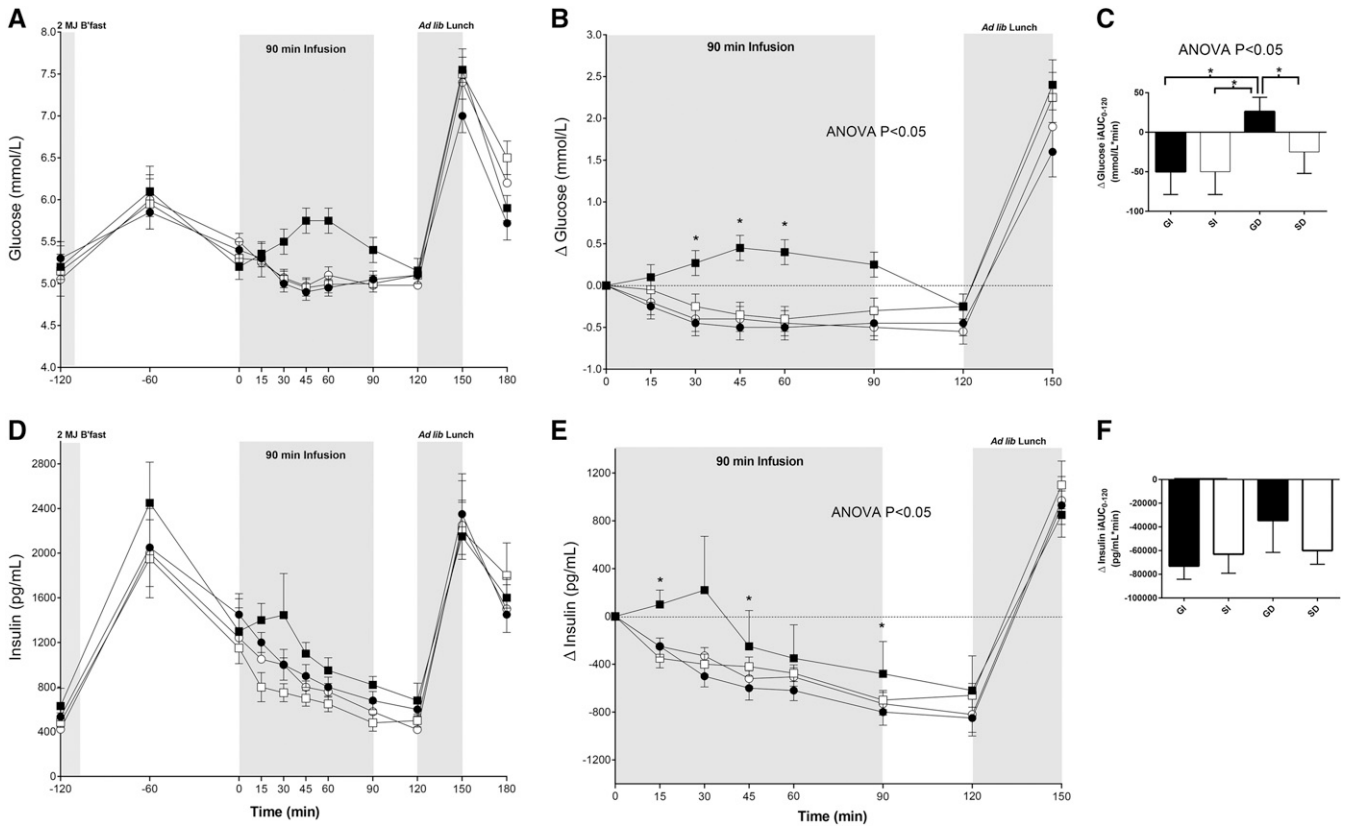


**FIGURE 4** Plasma concentrations of (A) glucose and (D) insulin in response to the 4 infusions, with changes ($\Delta$) in plasma (B) glucose and (E) insulin concentrations from the start of the 90-min infusion ($t$ = 0 min). Histograms show iAUC$\Delta_{0–120\ min}$ for $\Delta$ with respect to (C) glucose and (F) insulin from the start of the 90-min infusion to the start of lunch. Main effect ANOVA; Tukey's post hoc pairwise comparisons: GD > all other treatments, *$P < 0.05$. Values are means ± SEMs; $n$ = 13. *Ad lib*, ad libitum; B'fast; breakfast; GD (■), glucose-to-duodenum; GI (●), glucose-to-ileum; iAUC$\Delta_{0–120\ min}$, change in incremental AUC from 0 to 120 min; SD (□), saline-to-duodenum; SI (○), saline-to-ileum.

group (main effect ANOVA, $P < 0.05$), with GI significantly increasing circulating concentrations of GLP-1 relative to all other treatments (SI, GD, and SD) by 90 min (Tukey's post hoc, $P < 0.05$). This is also highlighted in the iAUC of GLP-1 during the 120 min between the start of infusion and the lunch meal (iAUC$_{\Delta 0–120\ min}$; Figure 5C, upper panel). PYY concentrations showed a similar response to infusion (main effect ANOVA, Figure 5B, $P < 0.05$), and again, pairwise comparisons identified an increase in PYY concentrations during GI infusion relative to all other treatments (SI, GD, and SD) at 45, 90, and 120 min (Tukey's post hoc, $P < 0.05$), as highlighted in the histogram of iAUC during the 120 min between the start of infusion and the lunch meal (iAUC$_{\Delta 0–120\ min}$, Figure 5C, lower panel). Both breakfast and lunch meals caused a rapid increase in GIP concentrations on all 4 study days (Figure 5D), and 2 h after the breakfast meal at infusion baseline ($t$ = 0 min) peptide concentrations remained ~3-fold higher than fasting concentrations ($t$ = –120 min). Circulating concentrations of GIP continued to drop during the 90-min infusion, and although there was a far smaller response than was seen for plasma glucose concentrations (Figure 4A), again it was GD infusion that suppressed this gradual decline in GIP concentrations relative to the other 3 treatment groups ($P < 0.05$). Pairwise analyses showed GIP concentration after GD to be higher than after SD at 15, 30, and 60 min and greater than all other infusion treatments at 90 min (Tukey's post hoc, $P < 0.05$).

Contrary to the response of the other peptides, intake at both breakfast and lunch meals suppressed circulating ghrelin concentrations, as was expected for this orexigenic peptide. There was an effect of infusion treatment group on ghrelin concentration during the 90-min infusion (main effect ANOVA, $P < 0.05$), with circulating concentrations consistently lower during the delivery of GI and GD relative to their respective saline controls. Pairwise analyses showed ghrelin concentration after GI to be significantly lower than after SI at 15, 30, 60, and 90 min (Tukey's post hoc, $P < 0.05$). This finding is highlighted in the histogram of iAUC$_{\Delta 0–120\ min}$ (Figure 5F, lower panel).

### EI at ad libitum meals

Nutrient infusions had a significant effect on ad libitum EI at the lunch meal, given 2 h after the start of the infusion (main effect ANOVA, $P < 0.05$; **Figure 6**), but not at any of snack, dinner, or total intake throughout the day (all $P > 0.05$; data not shown). Mean ± SEM intake at lunch was 4447 ± 405, 4929 ± 452, 5434 ± 414, and 5189 ± 348 kJ for GI, SI, GD, and SD respectively, such that EI after GI infusion was lowest. A pairwise comparison showed a difference in EI between GI and SI control of −481 ± 329 kJ (−10%, $P$ = 0.16), but variability between participants prevented this from reaching statistical significance, although compensating for the additional 235 kJ administered during GI infusion. Unexpectedly, EI was highest

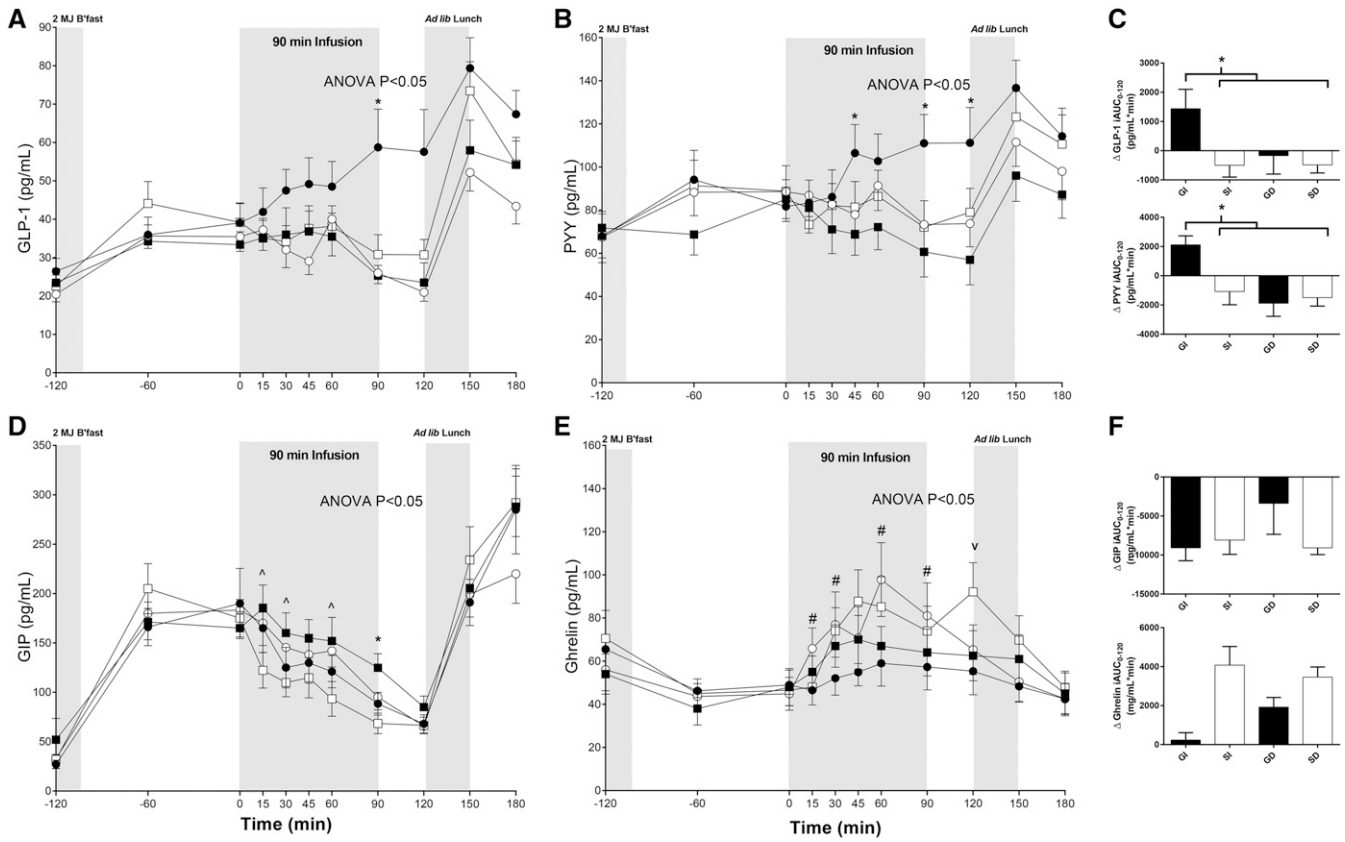


**FIGURE 5** Plasma concentrations of (A) GLP-1 and (B) PYY in response to the 4 infusions; main effect, ANOVA; Tukey's post hoc pairwise comparisons: GI > all other treatments, $^{*}P < 0.05$. Plasma concentrations of (D) GIP and (E) ghrelin in response to the 4 infusions; GD > all other treatments, $^{*}P < 0.05$; GD > SD, $^{\wedge}P < 0.05$; GD < SD, $^{\vee}P < 0.05$; GI < SI, $^{\#}P < 0.05$. Histograms show $iAUC\Delta_{0-120\ min}$ for changes ($\Delta$) in (C, upper panel) GLP-1, (C, lower panel) PYY, (F, upper panel) GIP, and (F, lower panel) ghrelin concentrations from the start of the 90-min infusion to the start of lunch. Values are means ± SEMs; $n$ = 13. *Ad libitum*, ad libitum; B'fast; breakfast; GD (■), glucose-to-duodenum; GI (●), glucose-to-ileum; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; $iAUC\Delta_{0-120\ min}$, change in incremental AUC from 0 to 120 min; PYY, peptide YY; SD (□), saline-to-duodenum; SI (○), saline-to-ileum.

after GD treatment, where pairwise comparison revealed a nonsignificant 6% greater intake than SD and a significantly greater intake than GI [987 ± 379 kJ (mean ± SEM), 22%, Tukey's post hoc, $P < 0.05$].

## DISCUSSION

This study showed that glucose delivery to proximal and distal regions of the small intestine had site-specific effects on parameters related to appetite and food intake, which may in turn be of relevance to body weight management. Infusion into the distal ileum was more successful in suppressing eating behavior than the proximal duodenum in lean young men. Although glucose infusion to both regions favorably altered reported appetite when compared with matched nonnutritive saline controls, infusion into the ileum also suppressed food intake at the next meal by close to 1 MJ compared with duodenal infusion (−987 kJ, −22%). The decrease in EI at lunch after ileal glucose infusion compared with nonnutritive saline more than compensated for the additional 235 kJ infused, despite high variance between participants in this small study. The inability of duodenal glucose to suppress food intake was in part unexpected, although some prior studies have failed (31, 34) or shown variable (35) suppression of EI or less suppression than lipid infusion (32). Delivery of glucose to the duodenum was confirmed by the rapid increase in plasma concentrations, as well as the secretion of insulin and GIP. The lack of a glucose peak during NI infusion was unexpected in light of the presence of the glucose transporters sodium-dependent glucose transporter-1 and glucose transporter 2 in this region of the GIT (30). A clear and significant increase in GLP-1 and PYY concentrations was observed, confirming the arrival of carbohydrates into the ileum where these secretory EECs are abundant (41). Notably, as expected, the glucose spike during duodenal infusion did not promote GLP-1 or PYY secretion based on the lower abundance of EECs (42).

The ability of dietary lipids to promote the ileal brake has been previously shown by Maljaars and coworkers (8, 9, 11) in clinical studies where 3 g (113 kJ), 6 g (225 kJ), and 9 g (339 kJ) lipid infused into the ileum over 45–90 min consistently altered VAS-rated hunger and fullness, although not EI. They also compared the delivery of lipid into the duodenum and ileum (10), reporting effects on food intake (−15%, 77 g) only after 6-g ileal infusion. Previous animal studies of lipid infusion into the duodenum, jejunum, and ileum have failed to provide consensus (36, 43). There are considerably fewer studies investigating the effects of carbohydrates on appetite-related aspects of the ileal brake. Recently, van Avesaat et al. (29) reported the first clinical study of a 12.8-g sucrose infusion (2.4 kJ/min, over 90 min, 217 kJ) into the ileum of 13 participants, observing increased PYY and

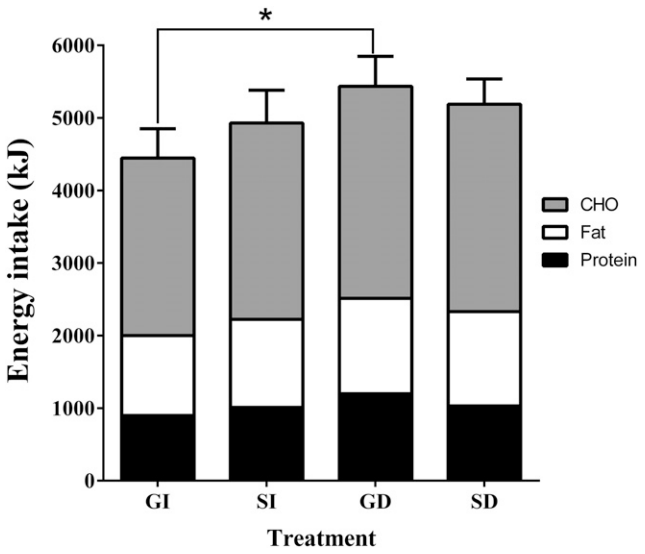


**FIGURE 6** Energy intake at the ad libitum lunch following the 4 infusions. There was a significant difference in energy intake between treatments (ANOVA, $P < 0.05$), with Tukey's pairwise post hoc significant for GI compared with GD ($P < 0.05$). *$P < 0.05$. Values are means ± SEMs; $n = 13$. CHO, carbohydrate; GD, glucose-to-duodenum; GI, glucose-to-ileum; SD, saline-to-duodenum; SI, saline-to-ileum.

cholecystokinin, 32% (785 kJ) decrease in EI at a subsequent meal, but no change in appetite sensations or increase in GLP-1 concentrations. Conversely, infusion of 15 g (235 kJ) glucose over 90 min in our current study significantly altered fullness, satisfaction, and TOF relative to a saline control, but elicited a smaller decrease in food intake (−10%, 481 kJ) despite the increase in both GLP-1 and PYY concentrations. To date, these studies show ileal infusion of 200–250 kJ as both lipids and carbohydrates induce various aspects of the brake, including evidence of 10–30% suppression of EI. Whether there are macronutrient-specific responses additional to the effect of total caloric load remains to be determined.

The release of GLP-1 and PYY through EEC-sensing intraluminal nutrients has been proposed as the primary mechanism for induction of the ileal brake. The association between the release of GLP-1 and the inhibition of gastric acid secretion, a key GIT aspect of the brake, after infusion of starch or maltose was first shown in humans by Layer et al. (23, 44), who compared ileal carbohydrate, lipid, and protein infusion. The location of GLP-1 receptor within areas of the central nervous system implicated in appetite control, including the arcuate and paraventricular nucleus of the hypothalamus and the area postrema of the brainstem (45), support its central anorectic activity. PYY also has effects on gut motility, as well as central activation of the vagus-brainstem-hypothalamic pathway, and has been shown to be elevated in the studies of Maljaars et al. (8, 11) and van Avesaat et al. (29). Cosecretion of GLP-1 and PYY by EECs located predominantly in the ileum is the likely reason for increased plasma concentrations after ileal glucose infusion in our study. Importantly, alongside daily abdominal X-ray imaging, peptide secretion confirmed the correct siting of the NI tube and successful glucose delivery. In addition, this is the first report, to our knowledge, of ghrelin suppression by ileal carbohydrates. Most abundant in gastric mucosa, ghrelin-secreting cells may be distributed throughout other regions of the gut, including at lower cell density in the ileum (46). Comparable inhibitory effects have been observed after infusion of both gastric and duodenal glucose loads (34). Our study protocol was based on that of Maljaars and coworkers (8–11). Before commencement, wider diameter tubes (4.7 and 3.0 mm) were evaluated for tolerability and maintenance. Participants reported pain in the nose and throat after intubation related to tube diameter and discomfort, which was important because it prevented consumption of solid food and hence the use of a narrow, 1.75-mm NI tube. Interestingly, the earlier clinical trials intubated participants with a 3.5-mm tube, but had few reports of pain or discomfort. Dose and rate of infusion are also important factors to consider in glucose infusion studies. The maximum glucose absorption rate in the small intestine has been proposed as ~8 kJ/min for every 30 cm of intestine, below which little glucose escapes proximal absorption to transit into the ileum (47, 48). In our study, a low glucose infusion rate of <3 kJ/min was used to ensure complete ileal absorption and prevent spillover into the colon, which may fuel resident bacteria, bloating, and discomfort. The lack of blood glucose peak after NI infusion was unexpected. GLP-1–mediated incretin effects, known to enhance insulin sensitivity, glucose disposal, and suppress hepatic glucose (49, 50), may have masked the peak. Alternately, although bacteria flourish primarily in the colon, proximal migration into the ileum inhabited by bacterial populations of $\leq 10^9$ CFU/mL (51) may limit glucose availability for uptake into venous circulation. The measurement of products of fermentation, including short-chain fatty acids, may help to unravel this issue, but the considerable length and small diameter of the NI tube prevented the withdrawal of ileal contents for analysis. The strengths of the trial included the high level of supervision, with all foods provided and EI measured over 4 d. Conversely, the study was limited by the lack of between-treatment washout, an issue that was also faced by Maljaars et al. (8–10) and van Avesaat et al. (29). Repeated intubation and extubation for 4 treatments would likely have resulted in high dropout. Although the treatment order was randomized, carry-over effects cannot be entirely excluded.

In conclusion, in this carefully controlled 4-d tube feeding study, there was evidence that ileal delivery of glucose promoted aspects of VAS-rated appetite, ileal peptides GLP-1 and PYY, as well as ghrelin and altered short-term ad libitum food intake at a subsequent lunch meal. Although ileal versus duodenal infusion did not alter VAS outcomes, gut peptides increased during ileal infusion and EI was suppressed. This is the first trial, to our knowledge, to deliver glucose to the ileum and to show greater carbohydrate-induced suppression of EI compared with duodenal infusion, supporting previous clinical studies showing site-specific effects across the proximal small intestine (47). The suppression of food intake through oral delivery of available carbohydrates into the ileum would require protection from absorption during transit through the duodenum and jejunum. Promoting carbohydrate malabsorption after a meal and in the absence of significant GI discomfort remains a major challenge, but may be an area worthy of future investigation.

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The authors' responsibilities were as follows—SDP: was responsible for the protocol design, regulatory procedures, data interpretation, and trial supervision, and was the primary author of the manuscript; HSS: was responsible for participant recruitment, trial management, and data entry and contributed to interpretation and manuscript preparation; A-TM and ML: contributed as clinical supervisors; SCB: conducted the statistical analyses; MP and KL: conducted the laboratory analyses; JD: conducted participant intubation; JRI: contributed to the protocol design, interpretation of data, manuscript preparation, and fundraising; and all authors: read and approved the final manuscript. SDP holds the Fonterra Chair in Human Nutrition at the University of Auckland. The remaining authors reported no conflicts of interest related to the study.

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