Effects of varying combinations of intraduodenal lipid and carbohydrate on antropyloroduodenal motility, hormone release, and appetite in healthy males

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Submitted 18 November 2008; accepted in final form 3 February 2009

AFTER INGESTION OF A MEAL, the interaction of nutrients with small intestinal receptors modulates gastrointestinal function and energy intake (2, 7, 17). For example, intraduodenal infusion of lipid stimulates isolated pyloric pressure waves (IPPWs) and suppresses antral and duodenal pressure waves (2, 8, 17), resulting in a slowing of gastric emptying (16), which is energy intake (2, 7, 8, 17). For example, intraduodenal infusion of lipid and glucose modulate antropyloroduodenal motility, hormone release, and appetite in healthy males. Am J Physiol Regul Integr Comp Physiol 296: R912–R920, 2009. First published February 11, 2009; doi:10.1152/ajpregu.90934.2008.—Intraduodenal infusions of both lipid and glucose modulate antropyloroduodenal motility and stimulate plasma CCK, with lipid being more potent than glucose. Both stimulate glucagon-like peptide-1, but only lipid stimulates peptide YY (PYY), while only glucose raises blood glucose and stimulates insulin. When administered in combination, lipid and carbohydrate may, thus, have additive effects on energy intake. However, elevated blood glucose levels do not suppress energy intake, and the effect of insulin is controversial. We hypothesized that increasing the ratio of maltodextrin, a complex carbohydrate, relative to lipid would be associated with a reduction in effects on antropy-loroduodenal pressures, gut hormones, appetite, and energy intake, when compared with lipid alone. Ten healthy males were studied on three occasions in double-blind, randomized order. Antropyloroduodenal pressures, plasma CCK, PYY and insulin, blood glucose, and appetite were measured during 90-min intraduodenal infusions of 1) 3 kcal/min lipid (L3), 2) 2 kcal/min lipid and 1 kcal/min maltodextrin (L2/CHO1), or 3) 1 kcal/min lipid and 2 kcal/min maltodextrin (L1/CHO2). Energy intake at a buffet lunch consumed immediately after the infusion was quantified. Reducing the lipid (thus, increasing the carbohydrate) content of the infusion was associated with reduced stimulation of basal pyloric pressures (r = 0.76, P < 0.01), plasma CCK (r = 0.66, P < 0.01), and PYY (r = 0.98, P < 0.001), and reduced suppression of antral (r = −0.64, P < 0.05) and duodenal (r = −0.69, P < 0.05) pressure waves, desire-to-eat (r = −0.8, P < 0.001), and energy intake (r = 0.74, P < 0.01), with no differences in phasic (isolated) pyloric pressures. In conclusion, in healthy males, intraduodenal lipid is a more potent modulator of gut function, associated with greater suppression of energy intake, when compared with isocaloric combinations of lipid and maltodextrin.

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plasma CCK concentrations was much greater with the higher fat infusion (26), but neither gastrointestinal motor function nor energy intake was evaluated.

The aim of this study was, therefore, to evaluate the effects of different combinations of intraduodenal lipid and carbohydrate, delivered at the same caloric load (3 kcal/min), on antropyloroduodenal (APD) motility, hormone release, appetite, and energy intake in healthy males. Intraduodenal, as opposed to intragastric, infusion of nutrients was used to bypass gastric emptying, and the infusion rate was selected to be within the range of average gastric emptying in humans (9, 23). We hypothesized that increasing the ratio of maltodextrin, a polysaccharide, relative to lipid would be associated with a reduction in effects on APD motility, stimulation of plasma CCK and PYY, and a reduced suppression of appetite and energy intake, despite greater rises in blood glucose and plasma insulin concentrations, when compared with lipid alone.

MATERIALS AND METHODS

Subjects

Ten healthy males [age 25 ± 3 (range 19 - 47) years, body mass index: 22.8 ± 0.7 (range 19.7–25.6) kg/m²] participated in the study, which conformed to the guidelines set out in the Declaration of Helsinki, as well as to Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, revised November 13, 2001, effective December 13, 2001. All subjects were unrestrained eaters, as determined by a score of <12 on the eating restraint component of the three-factor eating questionnaire (36). Each subject was questioned prior to the study to exclude significant gastrointestinal symptoms or disease, current use of medication known to affect gastrointestinal function or appetite, cigarette smoking, or intake of >20 g alcohol/day. The Royal Adelaide Hospital Research Ethics Committee approved the study protocol, and all subjects provided informed, written, consent prior to their inclusion.

Study Outline

The study compared the effects of two different combinations of intraduodenal lipid and maltodextrin at 1) 4.18 kJ/min (1 kcal/min) lipid and 8.36 kJ/min (2 kcal/min) maltodextrin (L1/CHO2) and 2) 8.36 kJ/min (2 kcal/min) lipid and 4.18 kJ/min (1 kcal/min) maltodextrin (L2/CHO1), with 3) lipid alone at 12.54 kJ/min (3 kcal/min) (L3), for 90 min on APD motility, gastrointestinal hormone release, appetite, and energy intake.

Intraduodenal Nutrient Infusions

Intralipid (20%, 350 mOsmol/kg, 8.36 kJ/ml, Fresenius Medical Care Australia Pty Ltd, Smithfield, NSW, Australia), a lipid emulsion consisting of long-chain triglycerides, was used as the fat source, and maltodextrin (Kingfood Australia Pty Ltd, Kings Park, NSW, Australia), a lipid emulsion consisting of long-chain triglycerides, was used as the fat source, and maltodextrin stock solution (417 mOsmol/kg) was prepared by dissolving 150 g of maltodextrin powder in distilled water to make up a 1,000 ml solution. The composition of 1 ml of each nutrient solution was as follows: L1/CHO2: 0.12 ml Intralipid, 0.84 ml maltodextrin solution, 0.04 ml distilled water; L2/CHO1: 0.25 ml Intralipid, 0.42 ml maltodextrin solution, 0.33 ml 392 mOsmol/l saline; and L3: 0.38 ml Intralipid, 0.62 ml 417 mOsmol/l saline. All three infusions had an osmolality of 392 mOsml/l and were administered at a rate of 4 ml/min, so that a total volume of 360 ml, containing 1,129 kJ, was infused on each study day. Both the investigator who performed the studies and analyzed the data (Seimon) and the subject were blinded to the treatment on each study day; infusions were prepared by another investigator, who was not involved in primary data analysis, on the morning of each study.

Protocol

Each subject was studied on three occasions, separated by 3–14 days, in double-blind, randomized order. Subjects were provided with a standardized evening meal [Beef lasagna (McCain Foods, Wendouree, Victoria, Australia) or spinach and ricotta ravioli (Lean Cuisine, Rhodes, NSW, Australia)] for the night prior to each study at 2000 and then fasted overnight from solids and liquids before attending the laboratory at 0830.

A 16-channel manometric catheter (Dentsleeve International, Mississauga, Ontario, Canada) (13, 30) was inserted through an anesthetized nostril into the stomach, allowed to pass into the duodenum by peristalsis and positioned across the pylorus as described previously (13, 30). After correct positioning of the catheter, fasting motility was monitored until the occurrence of a phase III of the migrating motor complex (8). After a phase III, an intravenous cannula was inserted into a forearm vein for blood sample collection. At t = −10 min, a baseline blood sample was taken and a visual analog scale questionnaire (VAS), assessing perceptions of appetite, completed (27). At t = 0 min duodenal infusion of either L1, L3, 2) L2/CHO1, or 3) L1/CHO2 commenced and continued for 90 min. During the infusions, 10-ml blood samples were obtained and VAS completed every 10 min at t = 0–30 min and then every 15 min at t = 30–90 min. At t = 90 min, the infusion was discontinued, and subjects were extubated and offered a cold, buffet-style, meal (14) to consume freely until comfortably full for up to 30 min (t = 90–120 min). After ingestion of the meal, at t = 120 min, a final blood sample was taken, and VAS was completed before the subject was allowed to leave the laboratory.

Measurements

Antropyloroduodenal pressures. Manometric pressures were digitized and recorded on a computer-based system, running commercially available software (HAD, A/Prof GS Hebbard, Melbourne, Australia), and stored for subsequent analysis. APD pressures were analyzed for J number and amplitude of antral pressure waves (PWs), 2) basal pyloric pressure and number and amplitude of IPPWs, and 3) the number and amplitude of duodenal PWs. PWs in the antrum, pylorus, and duodenum were defined by an amplitude ≥10 mmHg, with a minimum interval of 15 s between peaks for antral and pyloric waves, and 3 s for duodenal waves (34). Basal pyloric pressure was calculated for each minute by subtracting the mean basal pressure (excluding phasic pressures) recorded at the most distal antral channel from the mean basal pressure recorded at the sleeve (18), using custom-written software (Prof. A. Smout, Gastrointestinal Motility Unit, University Hospital, Utrecht, Netherlands), modified to our requirements.

Plasma CCK, PYY, insulin, and blood glucose concentrations. Ten-milliliter venous blood samples were collected in ice-chilled EDTA-treated tubes containing 400 kIU aprotinin (Trasylol; Bayer Australia, Pymble, Australia) per liter blood.

Venous blood glucose concentrations (mmol/l) were determined immediately by the glucose oxidase method using a portable glucometer (Medisense Precision QID; Abbott Laboratories, Bedford, MA).

Plasma was obtained by centrifugation of blood samples at 3,200 rpm for 15 min at 4°C. The plasma samples were frozen at −70°C for later analysis of CCK, PYY, and insulin.

Plasma CCK concentrations (pmol/l) were determined by radioimmunoassay after ethanol extraction, using a previously described radioimmunoassay (35). A commercially available antibody (C2581, Lot 105H4852, Sigma-Aldrich, St. Louis, MO), raised in rabbits against the synthetic sulfated CCK-8, was employed. This antibody binds to all CCK peptides containing the sulfated tyrosine residue in position 7, shows a cross-reactivity of 26% with unsulfated CCK-8, <2% cross-reactivity with human gastrin (0.2% with gastrin 1 and 1%...
with Big gastrin), and does not bind to structurally unrelated peptides. The intra-assay coefficient of variation (CV) was 6.2%, the inter-assay CV 14.8% and the detection limit 2.5 pmol/l.

Plasma PYY concentrations (pmol/l) were analyzed by radioimmunoassay using an adaptation of a previously described method (29). An antisera (kindly donated by Dr. B. Otto, Medizinische Klinik, Klinikum Innenstadt, University of Munich, Munich, Germany), raised in rabbits against human PYY(1-36) (Sigma-Aldrich), was employed, that is, the assay does not distinguish between PYY(1-36) and PYY(3-36). The antisera showed <0.001% cross-reactivity with human pancreatic polypeptide and sulfated CCK-8 and 0.0025% cross-reactivity with human neuropeptide Y. The intra-assay CV was 12.3%, the inter-assay CV was 16.6%, and the detection limit was 1.5 pmol/l.

Plasma insulin concentrations (mU/l) were measured by ELISA (Diagnostik Systems Laboratories, Webster, TX) (28). The intra-assay CV was 2.6%, the inter-assay CV was 6.2%, and the sensitivity was 2.6 mU/l.

**Appetite**. Appetite perceptions (desire-to-eat and fullness) were measured using validated VAS questionnaires (27). Nausea was also assessed. Each VAS consisted of a 100-mm horizontal line, where 0 represented “sensation not felt at all” and 100 represented “sensation felt the greatest”. The subject placed a vertical mark along the horizontal line to indicate the strength of the sensation felt at that particular time point.

**Energy intake**. The buffet meal was weighed before and after consumption to quantify the amount eaten (g). Energy intake (kJ) and macronutrient distribution (% energy from fat, carbohydrate, and protein) were evaluated using the software program Foodworks (Xyris Software, ver. 3.01, Highgate Hill, QLD, Australia) (14).

**Data and statistical analysis**. “Baseline” values for plasma hormone concentrations, blood glucose, and VAS were calculated as the means of values obtained at t = −10 min and t = 0 min, and for the number and amplitude of antral and duodenal PWs and IPPWs and basal pyloric pressure as the means of values obtained between t = −15 and 0 min. During the 90-min infusion period, antral and duodenal PWs were expressed as total numbers and mean amplitudes over 90 min. Basal pyloric pressures and the number and amplitude of IPPWs were expressed as means over 15-min intervals between 0 and 90 min. Mean values for plasma hormone and blood glucose concentrations and VAS scores were calculated at each time point between 0 and 120 min. All motility and VAS data were expressed as changes from baseline, and plasma hormone and blood glucose concentrations were expressed as absolute values. Plasma hormone and blood glucose concentrations, basal pyloric pressures, IPPWs, and VAS scores were analyzed by repeated-measures ANOVA, with time and treatment as factors. The number and amplitude of antral and duodenal PWs and energy intake (amount and energy consumed, as well as macronutrient distribution) were analyzed by one-way ANOVA. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni’s correction, were performed if ANOVAs revealed significant effects.

Relationships between antral and duodenal PWs, energy intake, areas under the curve (AUCs; calculated using the trapezoidal rule) for basal pyloric pressures, IPPWs, plasma hormone and blood glucose concentrations, and VAS scores with increasing lipid loads were evaluated using a linear correlation (r) for each subject. Only r values >0.5 were considered physiologically relevant. The sample of correlation coefficients for each parameter was tested against 0 in a one-sample t-test.

Maximum likelihood models, corrected for repeated measures, were used to calculate the strength and slope of the relationships (which we assumed as linear) between energy intake with motility parameters, plasma hormones, and blood glucose, using either AUCs or total values of the parameters.

Statistical significance was accepted at P < 0.05.

**RESULTS**

All subjects tolerated the experimental conditions well, and none spontaneously reported nausea. Duodenal infusions of L3, L2/CHO1, and L1/CHO2 commenced 119 ± 19, 95 ± 8, and 100 ± 11 min, respectively, after intubation; i.e., there was no difference between study conditions.

**Antropyloroduodenal Pressures**

**Antral pressures**. There was no significant effect of treatment on the number or amplitude (Table 1) of antral PWs, although the mean number was greater during L1/CHO2 compared with L2/CHO1 and L3. There was an inverse relationship between the number (r = −0.64, P = 0.05), but not the amplitude, of antral PWs with the load of lipid administered, such that increasing the load of lipid was associated with fewer antral PWs.

**Pyloric pressures**. **Basal pyloric pressure**. Data from only n = 9 subjects could be included into the analysis due to technical problems. There were differences in baseline pyloric pressures between study days (P < 0.05). Basal pyloric pressures were lower for L2/CHO1 (P < 0.05) and L1/CHO2 (P < 0.001) compared with L3, with no difference between L1/CHO2 and L2/CHO1 (L3: 2.6 ± 2.2 mmHg, L2/CHO1: −0.4 ± 1.1 mmHg, L1/CHO2: −2.4 ± 1.4 mmHg). The negative baseline values during L1/CHO2 most likely reflect the positioning of the subject relative to the calibration level, while those during L2/CHO1 were within the limits of measurement. There was an effect of time (P < 0.001) and a treatment by time interaction between 0 and 30 min (P < 0.01), for basal pyloric pressure (Fig. 1A). Basal pyloric pressure was greater during L3 between 15 and 45 min (P < 0.05), and during L2/CHO1 between 0 and 60 min (P < 0.05) compared with baseline, while there was no change from baseline during L1/CHO2. Basal pyloric pressures were lower during L2/CHO1 (P < 0.01) and L1/CHO2 (P < 0.01) between 15 and 30 min compared with L3, with no difference between L2/CHO1 and L1/CHO2. Surprisingly, there was no relationship between basal pyloric pressure and the load of lipid administered, possibly due to relatively large variations between subjects and treatments.

**Isolated pyloric pressure waves**. There were no differences in the number of isolated pyloric pressures between study days at baseline (L3: 0.2 ± 0.1, L2/CHO1: 0.2 ± 0.1, L1/CHO2: 0). There was an effect of time, but not treatment, on isolated pyloric pressures (P < 0.001). All three infusions increased the number (P < 0.001) (Fig. 1B) and amplitude.

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<th>Table 1. Total number and amplitude of antral and duodenal pressure waves during 90 min duodenal infusions of L3, L2/CHO1, and L1/CHO2</th>
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<td><strong>Total Number</strong></td>
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<td>Antral PWs</td>
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<td>Duodenal PWs</td>
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Data are expressed as means ± SE (n = 10) and expressed as total numbers and mean amplitudes over 90 min. PWs, pressure waves; L3, 12.54 kJ/min lipid; L2/CHO1, 8.36 kJ/min lipid and 4.18 kJ/min maltodextrin; and L1/CHO2, 4.18 kJ/min lipid and 8.36 kJ/min maltodextrin.* Significant difference vs. L3; P < 0.01.
(P < 0.001) (data not shown) of IPPWs throughout the entire infusion period compared with baseline, with no difference between treatments. There was no relationship between the number, or amplitude, of IPPWs with the load of lipid administered.

**Duodenal pressure waves.** There was a significant effect of treatment on the number (P < 0.05), but not the amplitude, of duodenal PWs (Table 1). The number of duodenal PWs was greater during L1/CHO2 compared with L3 (P < 0.01), and tended to be greater compared with L2/CHO1 (P = 0.08), with no difference between L3 and L2/CHO1. There was an inverse relationship between the number (r = -0.69, P < 0.01), but not the amplitude, of duodenal PWs with the load of lipid administered, such that increasing the load of lipid was associated with fewer duodenal PWs.

**Plasma CCK, PYY, and insulin and blood glucose concentrations.** **Plasma CCK.** There were no differences in baseline plasma CCK concentrations between study days (L3: 2.5 ± 0.4 pmol/l, L2/CHO1: 2.7 ± 0.2 pmol/l, L1/CHO2: 2.9 ± 0.5 pmol/l). There was a treatment by time interaction for plasma CCK concentrations (Fig. 2A). There was a significant effect of treatment on the number (P < 0.05), but not the amplitude, of duodenal PWs (Table 1). The number of duodenal PWs was greater during L1/CHO2 compared with L3 (P < 0.01), and tended to be greater compared with L2/CHO1 (P = 0.08), with no difference between L3 and L2/CHO1. There was an inverse relationship between the number (r = -0.69, P < 0.01), but not the amplitude, of duodenal PWs with the load of lipid administered, such that increasing the load of lipid was associated with fewer duodenal PWs.

**Plasma CCK, PYY, and insulin and blood glucose concentrations.** **Plasma CCK.** There were no differences in baseline plasma CCK concentrations between study days (L3: 2.5 ± 0.4 pmol/l, L2/CHO1: 2.7 ± 0.2 pmol/l, L1/CHO2: 2.9 ± 0.5 pmol/l). There was a treatment by time interaction for plasma CCK concentrations (Fig. 2A).
concentrations \((P < 0.01)\) (Fig. 2A). Plasma CCK increased within 10 min of the start of all infusions, reaching a peak at \(t = 20\) min, after which time concentrations plateaued. At \(t = 90\) min, plasma CCK concentrations were still significantly greater for all three treatments compared with baseline \((P < 0.001)\). Plasma CCK concentrations were lower during L2/CHO1 between 0 and 90 min \((P < 0.05)\), and during L1/CHO2 between 20 and 75 min \((P < 0.05)\), compared with L3, with no difference between L2/CHO1 and L1/CHO2. There was a direct relationship between plasma CCK concentrations with the load of lipid administered \((r = 0.66, P < 0.05)\), such that increasing the load of lipid was associated with greater plasma CCK concentrations.

There was an effect of treatment on plasma CCK at \(t = 120\) min, i.e., immediately following the buffet meal \((P < 0.05)\). Plasma CCK was greater after L1/CHO2 compared with L3 and L2/CHO1 \((P < 0.05\) for both), with no difference between L3 and L2/CHO1.

**Plasma PYY.** There were no differences in baseline plasma PYY concentrations between study days \((L3: 28.3 \pm 3.7\) pmol/l, L2/CHO1: 32.7 \pm 4.6 pmol/l, L1/CHO2 27.9 \pm 3.9 pmol/l). There was a treatment by time interaction for plasma PYY concentrations \((P < 0.001)\) (Fig. 2B). Plasma PYY increased within 20 min of the start of L3 and L2/CHO1 infusion and continued to increase with L3 throughout the 90-min infusion. PYY concentrations plateaued after 30 min of the start of L2/CHO1 infusion, but concentrations were still significantly greater at \(t = 90\) min compared with baseline \((P < 0.05)\), while concentrations did not change from baseline during L1/CHO2. Plasma PYY concentrations were lower during L2/CHO1 between 30 and 90 min \((P < 0.01)\), and during L1/CHO2 between 20 and 90 min \((P < 0.01)\), compared with L3, and lower during L1/CHO2 between 20 and 90 min compared with L2/CHO1 \((P < 0.01)\). There was a direct relationship between plasma PYY concentrations with the load of lipid administered \((r = 0.98, P < 0.0001)\), such that increasing the load of lipid was associated with greater plasma PYY concentrations.

There was an effect of treatment on plasma PYY at \(t = 120\) min \((P < 0.001)\). Plasma PYY was greater after L3 compared with L2/CHO1 \((P < 0.05)\) and L1/CHO2 \((P < 0.001)\) and greater after L2/CHO1 compared with L1/CHO2 \((P < 0.01)\).

**Blood Glucose.** There were no differences in baseline blood glucose concentrations between study days \((5.6 \pm 0.2\) mmol/l for all infusions). There was a treatment by time interaction for blood glucose concentrations \((P < 0.001)\) (Fig. 2D). Blood glucose increased within 20 min of the start of L2/CHO1 and L1/CHO2 infusions and after \(t = 30\) min concentrations fell gradually, while concentrations decreased slightly throughout the L3 infusion. At \(t = 90\) min, blood glucose concentrations were lower for L3 \((P < 0.05)\), and greater for L1/CHO2 \((P < 0.001)\), compared with baseline. Blood glucose concentrations were greater during L2/CHO1 between 20 and 90 min \((P < 0.05)\) and during L1/CHO2 between 10 and 90 min \((P < 0.001)\), compared with L3, and greater during L1/CHO2 between 10 and 90 min compared with L2/CHO1 \((P < 0.01)\). There was an inverse relationship between blood glucose concentration with the load of lipid administered \((r = -0.99, P < 0.001)\), such that increasing the load of lipid was associated with lower blood glucose concentrations.

There was no effect of treatment on blood glucose at \(t = 120\) min.

**Plasma Insulin.** There were no differences in baseline plasma insulin concentrations between study days \((L3: 16.8 \pm 4.7\) mU/l, L2/CHO1: 16.9 \pm 5.0 mU/l, L1/CHO2 17.6 \pm 4.9 mU/l). There was a treatment by time interaction for plasma insulin concentrations \((P < 0.001)\) (Fig. 2C). Plasma insulin increased within 20 min of the start of L2/CHO1 and L1/CHO2 infusions. Plasma insulin continued to rise until \(t = 75\) min during L1/CHO2, reaching a peak at \(t = 30\) min during L2/CHO1, after which time concentrations gradually fell, while there was no change from baseline during L3. At \(t = 90\), min plasma insulin concentrations were still significantly greater for L1/CHO2 \((P < 0.001)\) and slightly greater for L2/CHO1 \((P < 0.01)\), compared with baseline. Plasma insulin concentrations were greater during L1/CHO2 \((P < 0.001)\) and L2/CHO1 \((P < 0.05)\) between 20 and 90 min, compared with L3, and greater during L1/CHO2 between 30 and 90 min compared with L2/CHO1 \((P < 0.01)\). There was an inverse relationship between plasma insulin concentration with the load of lipid administered \((r = -0.98, P < 0.001)\), such that increasing the load of lipid was associated with lower plasma insulin concentrations.

There was no effect of treatment on plasma insulin at \(t = 120\) min.

**Appetite perceptions and nausea.** Desire-to-eat. There were differences in baseline scores for desire-to-eat between study days \((P < 0.01)\). Desire-to-eat was lower during L1/CHO2 compared with L2/CHO1 and L3 \((P < 0.001\) for both), with no difference between L2/CHO1 and L3 \((L3: 65 \pm 8, L2/CHO1: 67 \pm 6, L1/CHO2: 51 \pm 9)\). There was a treatment by time interaction for desire-to-eat \((P < 0.001)\) (Fig. 3A). Desire-to-eat decreased within 20 min of the start of L3 and L2/CHO1, while there was no change from baseline during L1/CHO2. At \(t = 90\) min, desire-to-eat was lower for L3 \((P < 0.001)\) and L2/CHO1 \((P < 0.05)\), and greater for L1/CHO2 \((P < 0.05)\), compared with baseline. Desire-to-eat was greater during L1/CHO2 \((P < 0.05)\) at \(t = 20, 45, 75,\) and 90 min, and during L1/CHO2 between 20 and 90 min \((P < 0.001)\), compared with L3, and greater during L1/CHO2 at \(t = 20\) min and between 45 and 90 min compared with L2/CHO1 \((P < 0.05)\). There was an inverse relationship between desire-to-eat with the load of lipid administered \((r = -0.80, P < 0.05)\), such that increasing the load of lipid was associated with reduced desire-to-eat.

**Fullness.** There were no differences in baseline scores for fullness between study days \((L3: 11 \pm 5, L2/CHO1: 15 \pm 6,\) and L1/CHO2: 17 \pm 7)\). There was no effect of treatment on scores for fullness \((P < 0.001)\) (Fig. 3B) and, while scores appeared to increase during the infusions, scores at \(t = 90\) min did not differ from those at baseline for any of the three treatments.

**Nausea.** There were no differences in baseline scores for nausea between study days \((L3: 5 \pm 2, L2/CHO1: 5 \pm 2,\) and L1/CHO2: 7 \pm 4)\). There was a significant effect of time, but not treatment, for nausea \((P < 0.001)\) (Fig. 3C). Although scores were overall very low, L3 increased nausea between 45 and 90 min compared with baseline \((P < 0.01)\), while L2/CHO1 or L1/CHO2 had no effect. There was a direct relationship between nausea with the load of lipid administered \((r = 0.74, P < 0.05)\), such that increasing the load of lipid was associated with greater nausea.
There was an effect of treatment on energy intake (kJ) \((P < 0.01)\), but not the amount eaten \((g)\) (Table 2). Energy intake was greater for both \(L2/CHO1\) \((P < 0.01)\) and \(L1/CHO2\) \((P < 0.01)\) compared with L3, with no difference between \(L2/CHO1\) and \(L1/CHO2\), and \% fat consumed tended to be less after L3.

**Relationships Between APD Motility, Plasma CCK, PYY, and Insulin, Blood Glucose, Appetite Perceptions, and Energy Intake**

There were direct relationships between nausea with AUC of plasma PYY \((P < 0.001)\), and between desire-to-eat and antral number \((P < 0.05)\), and inverse relationships between fullness with both the total number \((P < 0.001)\) and amplitude \((P < 0.05)\) of antral waves, and the number of duodenal waves \((P < 0.001)\) and between desire-to-eat and AUC of plasma PYY \((P < 0.01)\).

There were direct relationships between energy intake with AUC for plasma insulin \((P < 0.05)\), blood glucose \((P < 0.05)\), desire to eat \((P < 0.05)\), and prospective consumption \((P < 0.01)\), and also a trend for the total number of duodenal PWs \((P = 0.07)\), and inverse relationships between energy intake with AUC for plasma PYY \((P < 0.01)\) and nausea \((P < 0.001)\). There were no significant relationships between energy intake with antral PWs, or AUCs for basal pyloric pressures, IPPWs and plasma CCK.

**DISCUSSION**

Our study establishes that there are major differences in the effects of isocaloric, intraduodenal combinations of lipid and maltodextrin, and lipid alone, on APD motility, gastrointestinal hormone release, appetite, and energy intake in healthy lean males. During infusion of both \(L2/CHO1\) and \(L1/CHO2\), stimulation of pyloric pressures, suppression of antral and duodenal PWs, stimulation of CCK and PYY, and suppression of appetite and energy intake were less, while blood glucose and insulin were greater, when compared with lipid alone, and these responses were related to the lipid load. There were also significant relationships between appetite and energy intake with parameters of gut motor and hormone function.

To assist in the interpretation of our observations, the following points, relating to the experimental design, should be considered. Intralipid was selected as it has been used in previous studies that evaluated the effects of fat on gastrointestinal function and appetite \((7, 11, 17)\). Maltodextrin was selected, rather than glucose, because of its low osmolarity \((12)\) and because, as a lipid, it requires digestion. Our study did not

**Energy Intake**

There was a trend for the percentage of energy from fat \((P = 0.07)\), but not protein, consumed at the buffet meal (Table 2). The \% carbohydrate consumed was lower after both \(L2/CHO1\) \((P < 0.05)\) and \(L1/CHO2\) \((P < 0.01)\) compared with L3, with no difference between \(L2/CHO1\) and \(L1/CHO2\), and \% fat consumed tended to be less after L3.

**Table 2. Energy intake, amount eaten, and macronutrient distribution in response to 90-min duodenal infusions of L3, L2/CHO1, and L1/CHO2**

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<th></th>
<th>L3</th>
<th>L2/CHO1</th>
<th>L1/CHO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake, kJ</td>
<td>4240±451</td>
<td>5290±461*</td>
<td>5459±330*</td>
</tr>
<tr>
<td>Amount eaten, g</td>
<td>1125±97</td>
<td>1188±153</td>
<td>1277±76</td>
</tr>
<tr>
<td>% fat</td>
<td>29±2</td>
<td>32±1</td>
<td>33±2</td>
</tr>
<tr>
<td>% carbohydrate</td>
<td>49±3</td>
<td>45±2*</td>
<td>44±2*</td>
</tr>
<tr>
<td>% protein</td>
<td>22±1</td>
<td>22±1</td>
<td>23±1</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SE \((n = 10)\). *Significant difference vs. L3; \(P < 0.05\).
include any control infusions, either a nutrient/energy free control, one containing pure carbohydrate, or diluted lipid emulsions, reflecting the lipid loads in the combined infusions, as the number of intubations required would have represented an excessive burden for subjects; therefore, we are unable to comment on the magnitude of effects of the infusions used. Further studies are warranted to address these questions. However, the primary focus of the study was to evaluate the effects of a combination of nutrients relative to lipid on gut function and energy intake, having evaluated the effects of lipid and glucose in isolation previously (2, 7, 8, 28–30). We only included males, as they have been reported to be more sensitive to dietary manipulation than females (33); hence, we cannot extend our findings to female subjects.

Previous studies have established that isocaloric, intraduodenal infusions of long-chain triglycerides (Intralipid) and glucose suppress antral and duodenal pressures and stimulate pyloric pressures, with lipid being more potent (2, 8, 28, 30). Our data demonstrate that when the two nutrients are administered in combination, their effects on most aspects of gastrointestinal motor function can be related to the increasing lipid content of the infusions, consistent with previous observations that the stimulation of pyloric pressures and suppression of antral and duodenal PWs is related to the load of lipid administered (30) and that lipid is more potent than carbohydrate (2, 8, 24). Hence, even when lipid and carbohydrate are administered in combination, the more potent effect of lipid is maintained and fat and carbohydrate do not apparently have synergistic or additive effects. Interestingly, our results demonstrated no difference in the effect isolated pyloric pressures between the three treatments, suggesting that energy load was the predominant factor or that a maximum number of isolated pyloric pressure was reached with all three treatments. Taken together, the data may suggest that the mechanisms that regulate antral and duodenal pressures differ from those that regulate isolated pyloric contractions.

The more potent effect of lipid, compared with maltodextrin, on motility also applies to the release of CCK and PYY. It has been reported that lipid, whether ingested orally or administered directly into the small intestine, causes much greater release of CCK and PYY than carbohydrate (1, 26, 28, 30). For example, although a load of 4 kcal/min for both lipid and glucose stimulated plasma CCK release, plasma CCK concentrations were twice as high during lipid compared with glucose (28, 30). It is important to recognize though that comparisons across studies may be difficult, as they relate to unpaired data sets. Another study in humans, comparing the effects of orally ingested fat (as cream), carbohydrate (glucose), and protein (fish) on plasma PYY, demonstrated that fat markedly stimulated PYY release, while glucose caused only a slight increase that was not sustained (1). Our previous studies have also established a load-dependent stimulation of PYY in response to increasing loads of Intralipid, with a load of >1 kcal/min of lipid required to elicit this response (30). In the current study, all three infusions increased plasma CCK within 10 min, with the infusion containing lipid alone having the greatest effect. In contrast to CCK, only L3 and L2/CHO1 stimulated plasma PYY, with the response delayed compared with CCK, and concentrations did not plateau during L3. The rapid hydrolysis and absorption of carbohydrate limits the presence of carbohydrate in the distal small intestine, whereas digestion of fat takes longer, associated with slower absorption, allowing undigested fat to move downstream (22, 25). This is a likely explanation for the highest load of lipid (L3) reaching the distal part of the small intestine, where PYY is predominantly released (1), stimulating a greater release of PYY with increasing loads of lipid, while the lowest load of lipid (L1/CHO2) had no effect on plasma PYY concentrations, as much of it would have been absorbed proximally. Not surprisingly, increasing the maltodextrin content of the infusion was associated with increasingly greater blood glucose and plasma insulin concentrations. There has been some controversy over the effect of insulin on energy intake (21, 32, 37), while modest hyperglycemia does not appear to affect energy intake (21, 32). Accordingly, our data support the notion that increases in blood glucose and plasma insulin do not contribute to the suppression of energy intake in our experimental paradigm.

Previous studies have demonstrated that lipid, when administered intraduodenally, is a more potent suppressant of appetite and energy intake compared with carbohydrate (7, 8). In our study, appetite perceptions were greatly suppressed, as the amount of lipid administered increased, and the infusion with the highest lipid content suppressed energy intake compared with the infusions containing carbohydrate. The infusion containing lipid alone (L3) consisted of 180 kcal more fat than L1/CHO2, and this resulted in a mean 289-kcal reduction in energy intake at the buffet meal; that is, the “reduction ratio”, i.e., the potency of a given amount of energy administered to cause a suppression of subsequent energy intake, from the additional amount of fat infused was 1.6. In contrast, in previous studies, either oral ingestion or intragastric infusion of fat resulted in a reduction ratio of only 0.25 (6). These differences most likely reflect the inefficient gastric delivery of fat to the duodenum, an inefficiency that increases over time, as residual fat is proportionally distributed further and further away from the antropyloric outflow tract and layered on top of remaining intragastric contents (5, 9). This is a conceivable explanation for the discrepancy in the effects of oral vs. small intestinal fat on energy intake. There was also a significant difference in the macronutrient distribution between treatments. The percentage energy from carbohydrate consumed at the buffet meal was greatest, and the percentage from fat was lowest, after infusion of lipid alone (L3), compared with the infusions containing carbohydrate. The reason(s) for this is (are) unclear, and analysis of the foods eaten did not indicate major differences in the overall choice of the foods eaten on the different study days, which could have explained the differences. Further studies are required to substantiate, or refute, this finding.

While it is well established that excessive oral fat ingestion leads to caloric overconsumption (15), the data from our study, administering nutrients directly into the small intestine, suggest that the nutrient that most potently modulated various aspects of gastrointestinal motor and hormonal function, that is, lipid, caused the greatest suppression of appetite and energy intake, indicating that acute appetite regulation may be related to specific modifications in these functions. This hypothesis is supported by data from our recent study (4), in which the greater the number of IPPWs, stimulated by intravenous infusion of CCK-8, the greater was the suppression of energy intake. Although such relationships do not establish causal links, the possibility that changes in gut function may deter-
mine acute energy intake would not be surprising and warrants further evaluation. This is particularly relevant, as effective therapies for the management of obesity are still scarce, and those that are available have, for the main part, not focused on the gastrointestinal tract as a target.

**Perspectives and Significance**

Our observations indicate that, when administered directly into the small intestine, lipid is the most potent macronutrient in modulating gastrointestinal motility, gut hormone release, and appetite, so that when combined with carbohydrate, additive effects are not evident. Our data are consistent with the concept that nutrient-induced modulation of gastrointestinal motility and hormone release are important contributors to the regulation of acute energy intake in healthy males. Further studies are required to explore and define the relationship between gastrointestinal function and the acute regulation of energy intake, as well as the concept that targeted manipulation of gastrointestinal function (e.g., by intestinal administration of small amounts of nutrients) could be utilized to suppress appetite, given the substantial implications for novel approaches to the prevention and management of obesity.

**REFERENCES**

Kate Feltrin was supported by a Dawes Scholarship from the Royal Adelaide Hospital. Ixchel Brennan was supported by a Dawes Scholarship

**GRANTS**

Kate Feltrin was supported by a Dawes Scholarship from the Royal Adelaide Hospital. Ixchel Brennan was supported by a Dawes Scholarship jointly provided by the Royal Adelaide Hospital and the University of Adelaide. Christine Feinle-Bisset was supported by a Career Development Award from the National Health and Medical Research Council of Australia.

**REFERENCES**


