High-fat diet effects on gut motility, hormone, and appetite responses to duodenal lipid in healthy men

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Boyd, K. A., D. G. O’Donovan, S. Doran, J. Wishart, I. M. Chapman, M. Horowitz, and C. Feinle. High-fat diet effects on gut motility, hormone, and appetite responses to duodenal lipid in healthy men. Am J Physiol Gastrointest Liver Physiol 284: G188–G196, 2003. First published October 30, 2002; 10.1152/ajpgi.00375.2002.—There is evidence that gastrointestinal function adapts in response to a high-fat (HF) diet. This study investigated the hypothesis that an HF diet modifies the acute effects of duodenal lipid on appetite, antropyloroduodenal pressures, plasma CCK and plasma glucagon-like peptide-1 (GLP-1) levels in humans. Twelve healthy men were studied twice in randomized, crossover fashion. The effects of a 90-min duodenal lipid infusion (6.3 kJ/min) on the above parameters were assessed immediately following 14-day periods on either an HF or a low-fat (LF) diet. After the HF diet, pyloric tonic and phasic pressures were attenuated, and the number of antropyloroduodenal pressure-wave sequences was increased when compared with the LF diet. Plasma CCK and GLP-1 levels did not differ between the two diets. Hunger was greater during the lipid infusion following the HF diet, but there was no difference in food intake. Therefore, exposure to an HF diet for 14 days attenuates the effects of duodenal lipid on antropyloroduodenal pressures and hunger without affecting food intake or plasma hormone levels.

antropyloroduodenal pressures; cholecystokinin; glucose-like peptide-1; energy intake

There is evidence that previous patterns of macronutrient intake (2, 4, 13–15, 17, 18, 31, 43, 44, 49) or fasting (12) affect gastrointestinal function. In the context of obesity, the effects of gastrointestinal adaptation to a high-fat (HF) intake are of particular interest and relevance. However, these issues have been evaluated predominantly in animals. In rats, exposure to an HF diet for 1 (43), 2 (49) or 8 (44) wk increases intestinal villus height (44) and pancreatic lipase secretion (43, 49) and modifies the response to intraduodenal fat infusion with attenuation of the inhibition of gastric emptying (13), increased stimulation of plasma CCK (49), and attenuation of the inhibition of food intake (13–15). Furthermore, the inhibitory effects of exogenously administered CCK on food intake and gastric emptying are also decreased following an HF diet (13, 14). Whereas these observations indicate that the gastrointestinal tract has the capacity to increase its digestive and absorptive capacity for fat, the fat content of these diets was 34 or 54% (13–15); the latter may be considered unphysiologically high.

In humans, relatively few studies have investigated the responses of the gastrointestinal tract to diets high in a particular nutrient. After an HF diet for 2 wk, gastric emptying and mouth-to-cecum transit in response to an HF test meal were faster (17). Similarly, supplementation of the diet with glucose for 7 days accelerated gastric emptying of a glucose drink (18). These changes appear to be nutrient-specific, because supplementation of the diet with glucose (18) or fat (8) did not alter gastric emptying of a low-nutrient protein drink (18) or a high-carbohydrate yogurt (8), respectively. The motor mechanisms that underlie the acceleration of gastric emptying following an HF diet have not been assessed.

Only two studies have hitherto investigated the effect of a period on an HF diet on food intake; unlike animals, food intake from a test meal was unchanged following an HF diet (17, 24). In the latter study, the plasma CCK response to a test meal was increased following the HF diet (24), suggesting that the sensitivity to CCK may be reduced by an HF diet (13, 14).
However, it is also possible that the differences in CCK secretion are the result of the accelerated gastric emptying (8, 17). This possibility can be eliminated by delivering nutrients directly into the small intestine.

The potential role of GLP-1 in mediating the adaptive responses to an HF diet has not been studied. We have reported recently that plasma GLP-1 concentrations in response to duodenal glucose or lipid do not differ between healthy and obese subjects (19), suggesting that overconsumption of food does not affect GLP-1 secretion; however, another study has suggested that GLP-1 secretion is decreased in obese subjects (51).

The aim of this study was, therefore, to investigate the hypothesis that an HF diet attenuates the effects of duodenal lipid on appetite, antropyloroduodenal (APD) motility, and plasma CCK and GLP-1 levels.

METHODS

Subjects

Twelve healthy male Caucasian subjects (mean age: 26.7 ± 1.7 yr, range 20–40 yr) with normal body weight and height [body mass index (BMI): 24.2 ± 0.5 kg/m², range 21.9–27.7 kg/m²] were studied. All subjects were unrestrained eaters [scoring <12 on the restrained eating part of the three-factor eating questionnaire (50)] without a history of gastrointestinal surgery or disease or any clinically significant abnormality in the prestudy screening [complete blood exam including erythrocyte sedimentation rate, liver function tests (liver enzymes), thyroid function test (for TSH), plasma urea, and electrolytes]. Only one subject smoked (maximum 10 cigarettes/day), and no subject habitually consumed >20 g alcohol/day. The protocol, which conformed to the standards set by the Declaration of Helsinki, was approved by the Royal Adelaide Hospital Human Ethics Committee, and all subjects gave their informed, written consent before inclusion.

Experimental Protocol

Study outline. The subjects maintained a 5-day food diary (including 3 weekdays and a weekend) before inclusion in the study to ensure their usual energy and fat intake were within the normal range (25–35% energy from fat) before completing two 14-day dietary periods [HF and low-fat (LF)] in a single-blind, randomized, crossover fashion. The two diet periods were separated by a 14-day period during which subjects consumed their regular diet. Immediately after each diet, the effects of a 90-min duodenal lipid infusion on APD pressures, plasma CCK, and GLP-1, perceptions of appetite-related sensations and food intake were assessed. Subjects were asked to refrain from alcohol and record any daily exercise. Body weight was measured before and after each diet.

Diets. The HF diet was designed to provide a net excess of ~190 g fat/day (40–43% of total daily energy intake) compared with the LF “control” diet. The protein content (in grams) was matched for both diets, whereas the carbohydrate content differed, i.e., during the LF diet, additional energy was derived from carbohydrate instead of fat. The diets were not designed to be isocaloric, because an HF diet tends to be associated with a higher total energy intake (34). The planned daily intake of macronutrients and total energy is shown in Table 1.

Table 1. Planned energy and macronutrient intake per day (average of 14 days)

<table>
<thead>
<tr>
<th>Diet</th>
<th>Energy, kJ</th>
<th>Fat</th>
<th>Protein</th>
<th>Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-fat</td>
<td>20,123</td>
<td>224</td>
<td>120</td>
<td>545</td>
</tr>
<tr>
<td>%Energy</td>
<td>42</td>
<td>10</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Low-fat</td>
<td>11,191</td>
<td>33</td>
<td>120</td>
<td>457</td>
</tr>
<tr>
<td>%Energy</td>
<td>11</td>
<td>18</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

Six daily meal plans (including breakfast, lunch, dinner, and snacks adapted to suit the taste of each subject and repeated randomly over the 2-wk period) were designed for both the HF and LF diets to increase variety and to facilitate subject compliance. Both diets incorporated similar foods (e.g., HF or LF varieties) to disguise the focus of the study from the subjects (subjects were informed that the aim of the study was to evaluate the effect of different foods on gastrointestinal motility and hormone release, and our interest in the effects on appetite were not mentioned). Commercially available foods were weighed and repackaged in neutral containers in the Department of Medicine before being supplied to the subjects at 3- to 4-day intervals during each 14-day period. A diary with instructions on what and when to eat was provided with the food, and subjects were requested to document what they had consumed. These diaries were reviewed on four occasions during each diet period to ascertain compliance.

Gastrointestinal and appetite responses to a duodenal lipid infusion. On the day immediately following each of the two diet periods, subjects arrived at the laboratory at 8:30 AM following an overnight fast from 10 PM the previous evening. A 16-channel manometric assembly (Dentsleeve, Adelaide, Australia) was inserted through an anaesthetised nostril and allowed to pass through the stomach and into the duodenum by peristalsis. The manometric assembly consisted of six antral channels, a 4.5-cm pyloric sleeve sensor with two equally spaced channels situated on the back, and seven duodenal channels, with all side holes positioned at 1.5-cm intervals. An additional channel, ~11.75 cm distal to the pylorus, was used to administer the lipid infusion. The positioning of the sleeve across the pylorus was verified by measurement of the antroduodenal transmucosal potential difference (TMPD). TMPD was monitored continuously through the most distal antral channel and the most proximal duodenal channel using a 20-gauge saline-filled cannula placed subcutaneously in the left forearm as a reference (2). All manometric channels were perfused at a rate of 0.08 ml/min with degassed, distilled water, except for the TMPD channels, which were perfused with degassed normal saline.

Once the catheter was in position, fasting motility was observed until the occurrence of phase III of the migrating motor complex (MMC) (2). An intravenous cannula was inserted into the right arm for blood sampling, and a blood sample was taken immediately (t = −15 min). At t = 0 min, an intraduodenal infusion of a lipid emulsion [Intralipid 10%; 300 mosmol/kgH₂O, 10% triglyceride, 2.5% glycerol, 1.2% phospholipid, 2,300 kJ/500 ml; Kabi Pharmacia, Sweden] was administered for 90 min at a rate of 1.36 ml/min, equivalent to 6.28 kJ/min (565 kJ/90 min). APD pressures were recorded continuously throughout the study, visual analog scales (VAS) assessing appetite-related sensations were administered, and blood samples were taken every 15 min from t = −15 min until t = 90 min (Fig. 1), when the infusion was stopped and the catheter, removed. Fifteen minutes later (t = 105 min), after a further blood sample and VAS, subjects...
were presented with a buffet-style meal (11) providing foods in quantities in excess of which subjects were expected to eat. Subjects were allowed 30 min to consume the meal (i.e., t = 105–135 min) and instructed to eat until they were comfortably full. At t = 135 and 165 min, further blood samples were collected and VAS was administered; then the intravenous cannula was removed, and subjects were allowed to leave the laboratory.

Analysis of APD pressures. Manometric pressures were digitized using an NBM1016H data-acquisition board and recorded on a computer-based system (PowerMac 7100/75; Apple Computer, Cupertino, CA) running commercially available software [MAD; written by C. Malbert (Unité de Flux Digestifs, Institut National de la Recherche Agronomique, Saint Gilles, France) in Labview 3.0.1 (National Instruments)] and then stored for later analysis. APD pressures were analyzed using commercially available software [Trace 1.1; written by G. S. Hebbard (Royal Melbourne Hospital, Melbourne, Australia)]. This allowed the data to be visualized as a color-contour plot, with different pressures represented as different colors and with time and space representation. Antral and pyloric waves with an amplitude 10 mmHg and duodenal waves 6 mmHg were analyzed (1). Waves were characterised as either isolated (occurring in only 1 channel) or part of a pressure sequence (occurring in at least 2 channels). A pressure-wave sequence was defined as two or more temporally related pressure waves. Pressure waves in adjacent channels were regarded as temporally related if they had onsets within 3 s (in the duodenum) or 5 s (in the antrum) of each other (1). For all waves, site of occurrence and onset time were recorded. In addition, isolated waves were characterized by their amplitudes, and pressure-wave sequences were characterized by the distance traveled. Data were analyzed in 15-min segments, including the baseline period (t = −15 to 0 min) and the first 45 min of the lipid infusion (t = 0–45 min); we have found previously that the major effects of lipid occur during this time (2). Basal pyloric pressure ("tone") was calculated for each minute by subtracting the mean basal pressure (excluding phasic pressures) recorded at the most distal antral side hole from the mean basal pressure recorded at the sleeve (29) and averaged over 15-min periods. All pressure analyses were jointly performed by two blinded observers, i.e., both were unaware of the study conditions.

Appetite-related sensations and food intake. Perceptions of hunger, fullness, desire to eat, and nausea were assessed using previously validated VAS (46). Each VAS consisted of a 100-mm line, with 0 mm representing “sensation not felt” and 100 mm representing “sensation extremely strong.” Food intake during the 14-day diet periods and from the buffet-style meal was analyzed using commercially available software [Foodworks version 2.10; Xyris software (Australia), Highgate Hill, QLD, Australia] (11). The amount eaten (g), total energy intake (kJ), and macronutrient distributions (% energy and g) were analyzed. Compliance with the prescribed diets was quantified by calculating ratios (expressed in %) between actual and intended intakes for energy and all three macronutrients.

Plasma CCK and GLP-1 concentrations. For the determination of plasma CCK and GLP-1, 10-ml samples of venous blood were collected in ice-chilled EDTA-treated tubes containing 400 KIU aprotinin (Trasylol; Bayer Australia, Pymple, Australia) per milliliter of blood. Plasma was separated by centrifugation (3,200 rpm for 15 min at 4°C) within 30 min of collection and stored at −70°C until assayed.

Plasma CCK (pmol/l) was determined after ethanol extraction by radioimmunoassay (37). A commercially available antibody (C2581, Lot 105H4852, Sigma, St. Louis, MO) raised in rabbits against synthetic sulphated CCK-8 was employed. This antibody binds to all CCK peptides containing the sulphated tyrosine residue in position 7, shows a 26% cross-reactivity with unsulphated CCK-8, <2% cross-reactivity with human gastrin, and does not bind to structurally unrelated peptides. The intra-assay coefficient of variation was 9%, and the interassay coefficient of variation was 27%, with a sensitivity of 1 pmol/l.

Plasma GLP-1-7–36 (pmol/l) was determined by radioimmunoassay after ethanol extraction of plasma samples (53) with 125I-labeled GLP-1 as a tracer. The antibody was provided by S. R. Bloom (Hammersmith Hospital, London, UK) and had been raised in rabbits immunized with GLP-1-7–36 conjugated to bovine serum albumin by carbodiimide. The antibody had 100% cross-reactivity with synthetic GLP-1-7–36 amide (Peninsula Laboratories, Belmont, CA) but did not cross-react with GLP-1-7–37 amide, glucagon, gastric inhibitory polypeptide, or other gut or pancreatic peptides. The minimal detectable limit was 2 pmol/l. The interassay coefficient of variation was 18%.

Statistical analysis. For pressure parameters, baseline values were calculated as the mean of values obtained between t = −15 min and t = 0 min, for VAS scores and plasma hormone concentrations, baseline values were calculated as the mean of values obtained at t = −15 and 0 min, and the remaining data were expressed as changes from baseline. VAS profiles were also characterized by their slopes (between t = 15 and 90 min).

Data were analyzed using repeated-measures ANOVA, with time and treatments as factors. A paired t-test was used...
to compare food intake data (amount and energy consumed and macronutrient distribution) and the slopes of the VAS profiles between the 2 days. Data are presented as means ± SE, and P < 0.05 is regarded as statistically significant.

RESULTS

Study procedures (including placement of the nasoduodenal catheter, the lipid infusion, and blood sampling) were well tolerated by all but one subject. This subject experienced severe nausea during the lipid infusion following both diets (LF, at 40 min; HF, at 85 min), necessitating premature removal of the nasoduodenal tube on both occasions. Therefore, data from this subject were not included in the analysis.

The diets were well tolerated by all subjects, with 98% compliance. There were no significant changes in body weight between the diets in any of the subjects (HF diet, before: 81.4 ± 2.7 kg, after: 82.7 ± 2.7 kg; P = 0.06; LF diet, before: 81.8 ± 2.5 kg, after: 81.7 ± 2.5 kg; P = 0.89). Although three of the subjects were slightly overweight (25 kg/m² < BMI < 27.7 kg/m²), the observed effects of the diets were not related to body weight or BMI.

APD Pressures

Isolated antral waves. Antral activity was consistently low throughout the lipid infusion following both HF and LF diets, and neither number nor amplitude of waves differed from baseline values (data not shown).

Pyloric tone. Basal pyloric pressure increased during the lipid infusion, with a maximum response between t = 15 and 30 min on both days; the magnitude of this response was less after the HF diet when compared with the LF diet (treatment effect: P = 0.013; Fig. 2A).

IPPWs. The amplitude of IPPWs increased within 15 min of commencing the duodenal lipid infusion (P < 0.001 vs. baseline; Fig. 2B) and was significantly less following the HF diet when compared with the LF diet (treatment effect: P = 0.018). An increase in the number of IPPWs was evident after 15 min of the infusion (P < 0.001 vs. baseline; Fig. 2C), and there was no difference between the two diets.

Isolated duodenal waves. The amplitude of isolated duodenal waves was less between t = 15 and 30 min of the infusion following the HF diet when compared with the LF diet (P = 0.006; Fig. 3A). The number of isolated duodenal waves increased from baseline in the first 15 min of the infusion following the LF diet (P = 0.604; Fig. 3B), and there was no difference between the two diets.

Pressure-wave sequences. The total number of APD pressure-wave sequences, commencing in the antrum, pylorus, or duodenum, was greater between t = 30 and 45 min following the HF diet when compared with the LF diet (P = 0.039; Fig. 4).

Appetite-Related Sensations and Food Intake

Baseline ratings for hunger and desire to eat were higher, and the rating for fullness was lower after the LF diet (Table 2). The initial increase in these ratings following the LF diet was followed by a decrease from t = 15 to 30 min (Fig. 5, A and B). In contrast, after the HF diet, ratings of hunger (Fig. 5A) and desire to eat (Fig. 5B) increased steadily throughout the infusion. The slopes of the profiles for hunger and desire to eat were markedly different between the two diets [hunger, LF-diet: −0.18 ± 0.01 mm/min, HF-diet: 0.14 ± 0.09 mm/min (P = 0.009; Fig. 5A); desire to eat, LF-
After both diets, fullness ratings increased during the lipid infusion (time effect: \( P < 0.004 \)), with no difference in the slopes between the two conditions [LF diet: \(0.05 \pm 0.02\) min/mm, HF-diet: \(0.08 \pm 0.09\) min/mm \( P = 0.35\); Fig. 5C)]. Ratings for nausea and anxiety were consistently low during all studies (data not shown).

### Table 2. Baseline VAS ratings

<table>
<thead>
<tr>
<th>Sensation</th>
<th>High-Fat Diet</th>
<th>Low-Fat Diet</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunger</td>
<td>31 \pm 8</td>
<td>49 \pm 9</td>
<td>0.014</td>
</tr>
<tr>
<td>Desire to eat</td>
<td>35 \pm 9</td>
<td>51 \pm 9</td>
<td>0.016</td>
</tr>
<tr>
<td>Fullness</td>
<td>17 \pm 7</td>
<td>11 \pm 4</td>
<td>0.053</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 \pm 2</td>
<td>5 \pm 2</td>
<td>0.240</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 \pm 8</td>
<td>7 \pm 3</td>
<td>0.263</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>28 \pm 6</td>
<td>35 \pm 8</td>
<td>0.069</td>
</tr>
</tbody>
</table>

Data are means \( \pm \) SE; \( n = 11 \). VAS, visual analog scale.

diet: \(-0.05 \pm 0.06\) min/mm, HF-diet: \(0.06 \pm 0.06\) min/mm \( P = 0.049\); Fig. 5B). After both diets, fullness ratings increased during the lipid infusion (time effect: \( P = 0.004\)), with no difference in the slopes between the

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Fig. 3. Duodenal motility in response to intraduodenal lipid infusion. Amplitude (A) and number (B) of isolated duodenal pressure waves in response to intraduodenal lipid infusion following LF and HF diets. Data are means \( \pm \) SE for 15-min periods \( n = 11 \). Significant differences from LF: \(* P = 0.006\).

Fig. 4. Total number of pressure-wave sequences in response to intraduodenal lipid infusion following LF and HF diets. Data are means \( \pm \) SE for 15-min periods \( n = 11 \). Significant differences from LF: \(* P = 0.039\).

Fig. 5. Subjective sensations of hunger (A), desire to eat (B), and fullness (C) during intraduodenal lipid infusion following LF and HF diets. Data are means \( \pm \) SE and expressed as changes from baseline. Baseline values were established as the average of ratings at \( t = -15\) min and \( t = 0\) min \( n = 11 \). Significant differences from LF: \(* P = 0.009\); \#P = 0.049.
There were no significant differences in the total energy intake from the buffet meal or the macronutrient distribution between the two conditions (Table 3).

**Plasma CCK and GLP-1 concentrations.** After both the HF and LF diets, plasma CCK peaked 15 min into the lipid infusion before reaching a plateau for the remainder of the infusion (time effect: $P = 0.001$; Fig. 6A). A second rise in plasma CCK concentrations occurred in response to meal ingestion on both days (data not shown). No differences were found between the two study days (treatment effect: $P = 0.81$). Plasma GLP-1 rose steadily throughout the lipid infusion (time effect: $P = 0.001$), and a peak was observed in response to meal ingestion on both days (data not shown), but there were no differences between the two conditions (treatment effect: $P = 0.89$; Fig. 6B).

**DISCUSSION**

Our study has evaluated the effects of varying dietary fat and energy content (HF diet) on the APD pressure, appetite, and plasma CCK and GLP-1 responses to an intraduodenal lipid infusion in healthy male subjects. Ingestion of an HF compared with an LF diet (that was also lower in energy) for 14 days 1) attenuated pyloric tone and isolated pyloric and duodenal phasic pressure activity and increased the occurrence of pressure-wave sequences in response to intraduodenal lipid and 2) increased perceptions of hunger and desire to eat, without affecting plasma CCK and GLP-1 concentrations or food intake.

Administration of lipid into the small intestine slows gastric emptying by decreasing antral contractions (28) and increasing pyloric tonic and phasic pressure activity (2, 28). Pyloric activity is probably the most important mechanism for the slowing of gastric emptying, because it regulates the rate of transpyloric flow (28). It has been established that gastric emptying of fat is accelerated following a diet high in fat (8, 17), but the motor changes that may be associated with ingestion of a diet high in fat and energy have not been investigated. Our data show that gastrointestinal adaptation to an HF diet is associated with a decrease in both pyloric tone and the amplitude but not the number of IPPWs in response to duodenal lipid, suggesting a decrease in pyloric contractile force or resistance that is likely to, at least in part, contribute to the acceleration of gastric emptying observed after a period on an HF diet. Future studies need to assess antropyloroduodenal motility and gastric emptying concurrently to fully establish the relationship.

The presence of nutrients in the duodenum converts "propulsive" contractile activity into a pattern of predominantly isolated "stationary" contractions, which are thought to increase the resistance to flow (6), promote the mixing of chyme, and result in slowed transit (1, 6). The observed reduction in the number and amplitude of isolated duodenal waves, as well as the increase in the number and length of pressure-wave sequences following the HF diet may account for the previously described increase in mouth-to-cecum transit following an HF diet (17). Acceleration of gastric emptying and intestinal transit may, in turn, explain the necessity for increased digestive and absorptive capacity in the intestine, as has been observed in rats (44, 49), to compensate for the increased nutrient delivery to the small intestine.

The observed lack of change in the CCK response to lipid following the HF diet is in contrast with previous work both in animals (49) and humans (24), in which increases in plasma CCK were found after periods on HF diets. These apparent discrepancies may be attrib-

Table 3. Energy and macronutrient intake at the buffet meal

<table>
<thead>
<tr>
<th></th>
<th>High-Fat Diet</th>
<th>Low-Fat Diet</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kJ</td>
<td>5,633±329</td>
<td>5,550±373</td>
<td>0.402</td>
</tr>
<tr>
<td>Weight, g</td>
<td>1,400±89</td>
<td>1,429±93</td>
<td>0.313</td>
</tr>
<tr>
<td>Fat, g</td>
<td>21.8±6.6</td>
<td>13.5±4.1</td>
<td>0.197</td>
</tr>
<tr>
<td>%</td>
<td>54±2</td>
<td>31±2</td>
<td>0.112</td>
</tr>
<tr>
<td>Protein, g</td>
<td>59.5±2.4</td>
<td>60.7±4.9</td>
<td>0.383</td>
</tr>
<tr>
<td>%</td>
<td>18±1</td>
<td>20±2</td>
<td>0.168</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>160.2±9.2</td>
<td>166.2±10.3</td>
<td>0.178</td>
</tr>
<tr>
<td>%</td>
<td>46±2</td>
<td>49±2</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Data are means ± SE; $n = 11$. 

Fig. 6. Plasma CCK (A) and glucagon-like peptide-1 (GLP-1; B) concentrations in response to intraduodenal lipid infusion following LF and HF diets. Data are means ± SE $(n = 11)$. Baseline values were established as the average of concentrations at $t = -15$ min and $t = 0$ min.
unable to differences in methodology. Spannagel et al. (49) only assessed CCK 15 min after the start of a lipid infusion, and a separate group of rats was used for the control condition (i.e., LF diet). In humans, the increases in plasma CCK following an HF diet were observed in response to an oral mixed-nutrient test meal (24). Hence, in this latter study, the reported differences in plasma CCK could reflect changes in the rate of gastric emptying (8, 17), in that acceleration of gastric emptying would allow an increased rate of nutrient delivery to the small intestine, thereby increasing CCK secretion. Our results would support this possibility, because plasma CCK in response to the duodenal lipid infusion, which eliminated the influence of gastric emptying, did not differ between the two study conditions, suggesting that an HF diet does not result in changes in CCK secretion when gastric emptying is taken into account.

Although our data may suggest that changes in pyloric activity following the HF diet are independent of the actions of CCK, it should be recognized that CCK receptors are present in the region of the pylorus (48), and it has been suggested that CCK controls gastric emptying through its actions on the pylorus (22, 48). Accordingly, it remains possible that the observed decrease in pyloric activity (despite similar levels of circulating CCK) may reflect a decrease in the sensitivity of pyloric CCK receptors following exposure to high levels of dietary fat. This hypothesis is, in turn, supported by studies in experimental animals in which the inhibitory effects of exogenous CCK on food intake and gastric emptying were diminished following an HF diet (13, 14). Such studies would be of interest in humans.

Plasma GLP-1 levels were characterized by a gradual increase during the first 45 min of the lipid infusion, followed by a plateau evident during the remainder of the infusion period. The lack of a difference in plasma GLP-1 following the HF diet is consistent with our plasma CCK data, and, as has already been discussed for CCK, the possibility of a reduced sensitivity to the action of GLP-1 cannot be discounted and warrants exploration. Moreover, the possibility of an involvement of other peptides implicated in the regulation of appetite, including ghrelin, peptide YY, orexins, and gastric inhibitory peptide needs to be considered.

The observed differences in the baseline ratings following the two diets (subjects were less hungry following the HF diet) are likely to reflect the greater energy intake during this diet, when compared with their habitual or the LF diet. The ratings of hunger and desire to eat in response to the lipid infusion were greater following the HF diet, when compared with the LF diet, and increased even further during the infusion, indicating that the inhibitory effects of intraduodenal fat on appetite are attenuated. In contrast, ratings of fullness did not differ after the two diets. A possible explanation for this apparent discrepancy between hunger and fullness ratings may be that the sensation of “fullness” is related to gastric distension (33), whereas “hunger” may reflect small intestinal nutrient exposure (32). Actual food intake was also not altered. The reason for this is unclear, but there are a number of possible explanations. It is possible that the assessment of subjective sensations is a more sensitive measure of appetite in a laboratory setting than the amount of food ingested; humans are very sensitive to the environmental stimuli of the laboratory (5). The differences in baseline ratings, combined with the increases in ratings in response to the infusion following the HF diet or the decreases following the LF diet, resulted in similar ratings by the time the buffet meal was served and may account for the lack of difference in food intake. Another possibility is that the 2-wk period of altered fat intake was insufficient to achieve a change in food intake despite the effects on gastric emptying and intestinal transit (17). Indeed, a previous study also failed to achieve changes in food intake after 2 wk on an HF diet (24). Studies assessing the effect of longer diet periods are required to define the time course of the gastrointestinal adaptation process.

Our methodological approach warrants some discussion. We acknowledge that the subject number was relatively small, and an increase may have allowed us to detect differences in energy or macronutrient intakes. However, the subject number was clearly sufficient to detect differences in APD pressures in response to the two diets. We included only healthy young male subjects, because these appear to be most sensitive to dietary manipulation (42, 47). However, future studies need to address gastrointestinal responses to dietary adaptation in obese subjects. Our diets were designed to resemble realistic diets that were consumed by free-living subjects, hence the HF diet contained ~40% fat, whereas the LF diet contained ~10% fat. We did not attempt to match the total energy content of the two diets, because an HF diet also tends to be higher in energy (24, 34). Therefore, it remains to be determined whether our effects are due to the fat or the energy content of the diets, and this needs to be kept in mind when interpreting the data from our study. By manipulating the fat content of the diet, the content of the other macronutrients, protein and carbohydrate, inevitably changed also, leading to a slight increase in the relative (%) contribution to the total energy content by these nutrients. However, the absolute amounts (g) of carbohydrate and protein ingested did not differ between the HF and the LF diets. Having said this, our study design does not allow us to conclude whether the observed changes are due to an increase in fat or a relative decrease in carbohydrate in the diets. Our study did not address whether the observed effects on appetite and APD motility are specific for fat, as has been demonstrated for the acceleration of gastric emptying following an HF diet (8). The dose of the lipid infusion was chosen because it approximates the “average rate” at which nutrients are emptied from the stomach into the small intestine (16). The duodenal lipid infusion consisted predominantly of long-chain triglycerides derived from soybean oil. Both the chain length and saturation of fatty acids has been demonstrated to affect perceptions of appetite, plasma CCK concentrations, and gastric motility differentially (20,
23, 40), hence, the effects of our infusion should, perhaps, not be generalized to all fats. Administering the lipid load directly into the duodenum enabled us to standardize the amount of lipid delivered by excluding any confounding factors due to the previously reported changes in gastric emptying. It is, however, important to recognize that duodenal administration of nutrients excludes any orosensory or gastric influences that also contribute to gastric emptying and appetite regulation (9). The absence of these influences may also, in part, explain the lack of an effect of an HF diet on some of the parameters evaluated in our study.

In conclusion, our study demonstrates that gastrointestinal function is modulated by the ingestion of a diet high in both fat and energy for 14 days, resulting in a decrease in tonic and phasic pyloric activity and an increase in APD contractile activity, as well as increased hunger ratings in response to intraduodenal lipid. The lack of change in plasma CCK and GLP-1 suggests an altered sensitivity to the action of these peptides. Our observations may provide important insights into the changes in the gastrointestinal tract that may eventually lead to the development of obesity.

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