Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusion in humans


University of Adelaide Department of Medicine, Royal Adelaide Hospital, Adelaide, SA 5000, Australia

Submitted 2 December 2002; accepted in final form 7 January 2003

The interaction of nutrients with small intestinal receptors regulates both gastric emptying and appetite and stimulates the release of gastrointestinal hormones, including CCK and glucagon-like peptide-1 (GLP-1). In healthy subjects, intraduodenal infusion of fat slows gastric emptying (20) and reduces hunger and subsequent food intake (6, 29–31); these effects are, at least in part, mediated by CCK (16, 30). The slowing of gastric emptying by small intestinal nutrients is associated with a reduction in proximal gastric tone (10), suppression of antral pressure waves (PW) (20, 33), and stimulation of tonic and phasic pyloric pressures (13, 21). The increase in pyloric motility may be the most important of these mechanisms, because the stimulation of phasic and tonic pyloric pressures is associated with cessation of transpyloric flow (46).

Studies in animals (36, 37, 40) and humans (5, 11, 24, 32, 39) suggest that the slowing of gastric emptying, suppression of appetite, and stimulation of CCK secretion by fat are dependent on lipolysis of triglyceride to fatty acids. In particular, in animals, lipase inhibition accelerates gastric emptying of fat (34, 35). In humans, it has also been established that both pharmacological inhibition of lipase (3, 24) and pancreatic exocrine insufficiency (5) are associated with more rapid gastric emptying of fat. Recent studies (11) also suggest that fat digestion is required for the triggering of gastrointestinal sensations, such as fullness and nausea, as induced by concurrent gastric distension and duodenal infusion of a triglyceride emulsion.

Recent studies (11, 32, 39) used the lipase inhibitor tetrahydrolipstatin (THL), a specific and potent inhibitor of gastric and intestinal lipases (19). When ingested with a meal in the recommended dose of 120 mg, THL inhibits fat digestion by ~30% (48). However, the weight loss in obese subjects may be less than would be predicted by the degree of inhibition of fat absorption. Although the cause(s) of the latter is unknown, it is possible that some patients may increase their energy intake in compensation for the unabsorbed fat; this hypothesis is supported by two studies that indicate that lipase inhibition may attenuate the suppression of subsequent food intake by fat (32, 39). Immediately after a 60-min duodenal infusion of olive oil, healthy subjects ate significantly more from a test meal when the olive oil contained 120 mg THL compared with olive oil alone (32). Furthermore, when healthy subjects were given 120 mg THL orally with a high-fat yogurt preload at breakfast, their energy intake during the remainder of the day was greater compared with the yogurt alone (39). The secretion of CCK in response to a meal or intestinal fat infusion is known to be attenuated by lipase inhibition (3, 11, 32), providing a potential causal link between lipase inhibition and the...
increase in food intake. GLP-1 is also released by meal ingestion or intestinal nutrient administration (23). Moreover, there is persuasive evidence that GLP-1 plays an important role in the regulation of appetite (12, 17) and the modulation of gastrointestinal motility and gastric emptying (38, 43). The effect of lipase inhibition on GLP-1 secretion is unknown.

The motor mechanisms associated with the accelerated gastric emptying of fat induced by lipase inhibition have not been evaluated. Furthermore, no studies have assessed the impact of lipase inhibition on antropyloroduodenal (APD) motility and appetite concurrently. It is conceivable that diminished small intestinal feedback inhibition by fat will result in decreased phasic and tonic pyloric pressure activity and increased “propulsive” antroduodenal motor patterns. Such changes may potentially be associated with more rapid small intestinal transit so that the interaction of fat with small intestinal receptors is reduced, leading to gastrointestinal side effects as well as a reduction in feedback signals to slow gastric emptying and decrease appetite. The potential impact of accelerated gastric emptying on appetite is uncertain, but it has been suggested that a slowing of gastric emptying may decrease food intake by enhancing gastric distension (8).

The aims of this study were to evaluate in healthy subjects the broad hypothesis that the stimulation of tonic and phasic pyloric pressure activity, inhibition of propulsive APD motor patterns, suppression of appetite, and secretion of gastrointestinal hormones (CCK, GLP-1) by intraduodenal fat are attenuated by inhibition of lipase. We used an intraduodenal infusion to bypass gastric mechanisms (and potential effects of lipase inhibition on gastric emptying) involved in the regulation of food intake.

**METHODS**

Subjects

Sixteen healthy male subjects, aged 21–39 yr, took part in the study. Male subjects were studied because they are most sensitive to dietary manipulation (41). The subjects were of normal body weight for height [with a body mass index of 19.5–27.6 kg/m² (mean: 24.1 kg/m²)], unrestrained eaters [score of <12 on the restraint section of the 3-factor eating questionnaire (45)], were not taking medication that could affect appetite, body weight, or gastrointestinal function, and had no history of gastrointestinal disease. Subjects with a consumption of alcohol >20 g/day or who smoked were also excluded. Before entry into the study, each subject underwent a prestudy “screening,” which included a medical history, a physical examination, clinical laboratory tests, 12-lead ECG, and measurement of vital signs. The study protocol was approved by the Research Ethics Committee of the Royal Adelaide Hospital and was performed in accordance with principles laid out by the Declaration of Helsinki; each subject gave informed, written consent before inclusion. The subjects were informed of this possibility and asked to report any side effects as well as their severity.

**Intraduodenal Fat Infusion**

The preparation of the emulsions has been described in detail previously (11) and was carried out by the Royal Adelaide Hospital pharmacy to allow a double-blind study design. The infusion rate was 1.4 ml/min, corresponding to

**Experimental Protocol**

The studies were carried out in randomized order according to a double-blind, two-period crossover design (Fig. 1). On each study day, the subject arrived at the laboratory at 8:00 AM following an overnight fast. A small-diameter manometric assembly (Dentsleeve, Wayville, Australia) incorporating a pyloric sleeve sensor was inserted through an anesthetized nostril into the stomach and allowed to pass through the pylorus into the duodenum by peristalsis. The correct position of the sleeve was verified by continuously monitoring the antroduodenal transmucosal potential difference (TMPD) gradient across the pylorus (2, 31). Fasting motility was observed until phase III of the interdigestive migrating motor complex (MMC) occurred (31). Immediately after cessation of phase III activity, an intravenous cannula was placed in a left antecubital vein for blood sampling and the first “baseline” blood sample (for subsequent measurement of plasma CCK and GLP-1) was taken, and a visual analog scale (VAS) to evaluate appetite-related sensations administered (t = −30 min). Two more baseline blood samples and VAS scores were obtained at t = −15 min and at t = 0 min. At t = 0 min (during phase I or II of the MMC), infusion of a long-chain triacylglyceride emulsion, either without (FAT) or with (FAT-THL) 120 mg of the lipase inhibitor THL (F Hoffmann-La Roche, Basel, Switzerland), was commenced and continued for 120 min (i.e., until t = 120 min). Blood samples were taken, and VASs were administered at 15-min intervals throughout the infusion. APD motility was recorded continuously from t = −30 min until t = 120 min, at which time the manometric assembly was removed. Fifteen minutes later, at t = 135 min, each subject was offered a cold buffet-style lunch and allowed 30 min to eat (31). At t = 165 min, the food was removed, another blood sample was taken, and a VAS was administered. After a further 30 min (t = 195 min), a final blood sample was taken, and a VAS was completed. The intravenous cannula was then removed, and the subject was allowed to leave the laboratory.

The occurrence of lower gastrointestinal side effects was not assessed formally. However, subjects were informed of this possibility and asked to report any side effects as well as their severity.

![Study protocol](Chart.png)

Fig. 1. Study protocol. Each subject received a duodenal infusion of a fat emulsion at a rate of 2.8 kcal/min for 120 min on 1 day with and on the other day without 120 mg of the lipase inhibitor tetrahydrolipstatin (THL). Appetite-related sensations, plasma CCK and glucagon-like peptide-1 concentrations, and antropyloroduodenal pressure activity were measured during the infusion. Immediately following the infusion, food intake at a buffet meal was quantified (t = 135–165 min).
an energy delivery of 2.8 kcal/min, so that the total volume infused in 120 min was 168 ml (a total of 2.52 g soy lecithin, 1.96 g ethanol, 33.6 g soy oil, 130.2 g 0.9% saline, and 120 mg THL on 1 day). In our previous study (11), in which stool collections were performed, lipase inhibition during intraduodenal administration of this particular emulsion was shown to result in an inhibition of absorption of ~75% of the fat (unpublished data).

**Measurement of APD Pressures**

Intraluminal pressures were recorded with a perfusion manometry system and a 17-channel manometric assembly (outer diameter: 4.0 mm). Sixteen channels (lumen diameter: 0.5 mm) were used to record pressures, and one (lumen diameter: 1.0 mm) was used for intraduodenal nutrient infusion (Fig. 2). Six manometric channels, spaced at 1.5-cm intervals, were located in the antrum (channels 1–6), a 4.5-cm sleeve sensor straddled the pylorus (channel 7), and two channels, 1.5 and 3 cm from its orad end, were situated on the back of the sleeve (channels 8 and 9). Seven more distal channels, spaced at 1.5-cm intervals, were situated in the duodenum (channels 10–16); the infusion port was situated a further 2.25 cm beyond this chain of side holes, 11.25 cm from the pylorus. All manometric channels were perfused with distilled, degassed water at 0.08 ml/min except channels 6 and 10 (on either side of the sleeve), which were perfused with 0.9% saline for monitoring TMPD (31).

Data were recorded at 10 Hz using a computer-based system (PowerMac 7100/75; Apple Computer, Cupertino, CA) running commercially available software [MAD; C. Malbert, Unité de Flux Digestifs, Institut National de la Recherche Agronomique, Saint Gilles, France, in Labview 3.0.1 (National Instruments)]. Data were digitized, logged to disk for subsequent analysis, and only analyzed when the assembly was positioned correctly, according to previously described TMPD criteria (22).

Analysis of basal pyloric pressure activity (“tone”) was performed, as previously described (31). Basal pyloric pressure was quantified for each minute using custom written software (MAD) by subtracting the mean pressure (excluding phasic pressures) recorded at the most distal antral side hole (channel 6) from the mean pressure recorded at the sleeve (channel 7) (22); mean values were then calculated for each 15-min time interval. Data were then imported into a novel custom-designed computer program (Trace! 1.1; G. S. Hebbard, Royal Melbourne Hospital, Australia) for the analysis of APD pressures. In Trace!, data are displayed as three-dimensional color-pressure contour plots (2), with time on the y-axis, distance along the assembly on the x-axis, and pressure encoded by color. This allows for a better visual interpretation of the pressure profile along the assembly. APD pressures were analyzed for 1) number and amplitude of isolated PWs in the antrum, pylorus, and duodenum and 2) number and length of propagation of pressure-wave sequences. A phasic PW in the antrum or pylorus was defined as a pressure lasting between 1 and 20 s with an amplitude of ≥10 mmHg. In the duodenum, a PW was defined as lasting between 0.8 and 7 s with an amplitude of ≥6 mmHg (1). PWs 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. A PW sequence was defined as two or more temporally related PWs. Data were analyzed in 15-min segments, including the baseline period (t = −15–0 min) and the first 45 min of the lipid infusion (t = 0–45 min), as we and others have previously established that the major effects of intraduodenal lipid infusion on APD pressures occur during this time (21, 22). All motility analyses were jointly performed by two blinded observers (i.e., both were unaware of the study conditions).

**Assessment of Appetite/Food Intake**

Subjective sensations of appetite/hunger, fullness, desire to eat, prospective consumption (“how much food do you think you could eat if you were given a meal now?”), and nausea were rated by each subject at regular intervals (Fig. 1) on validated VASs (44). The buffet meal, given at the end of the duodenal infusion, contained food in excess of what a subject would normally eat, and each subject was invited to eat as much as he wished until he felt comfortably full (29, 31). The meal consisted of four slices each of brown and white bread, cheese and cold meat, 20 g margarine, 24 g mayonnaise, sliced cucumber and tomato, lettuce leaves, an apple, a banana, 150 g fruit salad, 200 g fruit yogurt, 150 g custard, 300 ml orange juice, 300 ml iced coffee, and 600 ml mineral water. Total energy intake (kcal), the amount eaten (g), and macronutrient composition (%energy and g) were calculated subsequently using commercially available software [Foodworks Version 2.10, Xyris Software (Australia), Highgate Hill, QLD, Australia].

**Measurement of Plasma CCK and GLP-1**

For plasma CCK and GLP-1 determinations, 10-ml samples of venous blood were collected in ice-chilled EDTA dipotassium-treated tubes containing 400 KIU/ml blood aprotinin (Trasylol; Bayer Australia, Pymple, Australia). Plasma was separated by centrifugation (3,000 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 by radioimmunoassay as previously described (31). A commercially available antibody (C2581, Sigma, St Louis, MO) raised in rabbits against synthetic sulphated CCK-8 was employed. The intra-assay coefficient of variation was 9.5% at 50 pmol.

Plasma GLP-1(7–36) (pmol/l) was determined by radioimmunoassay after ethanol extraction of plasma samples (47). The antibody used was provided by S. R. Bloom (Hammermith Hospital, London) and had been raised in rabbits immunized with GLP-1(7–36) conjugated to bovine serum albumin by carbodiimide. The detection limit was 2 pmol/l. The intra-assay coefficient of variation was 17%.

**Statistical Analysis**

VASs, plasma concentrations of CCK and GLP-1 (as obtained during the entire study period), and manometry data (baseline, i.e., t = −15–0 min and t = 0–45 min during the infusions) were analyzed by repeated-measurement ANOVA, with time and treatment as factors. A two-tailed Student's $t$-test was used for statistical analysis of the food intake study.
A paired t-test was used to test for differences between study conditions in food intake (amount and energy consumed and macronutrient distribution). An error probability of $P < 0.05$ was assumed to indicate statistically significant differences. The relationship between scores for both prospective consumption and nausea with food intake was assessed using Pearson’s product moment correlation test, stating the correlation coefficient $r^2$ and assuming $P < 0.05$ to indicate a significant linear relationship.

**RESULTS**

All subjects tolerated the study procedures, including nasoduodenal intubation and fat infusion, well. Nine of the 16 subjects did not experience any side effects. The other seven subjects reported transient side effects including loose, oily stools (4 subjects following FAT-THL and 1 subject following FAT) and abdominal bloating (2 subjects following FAT-THL).

**APD Pressures**

The manometric assembly was positioned correctly for 98% of the recording time. Infusion of FAT resulted in a typically fed motor pattern in which isolated antral and duodenal PWs were inhibited and isolated pyloric PWs (IPPW) were stimulated (Fig. 3, left). In contrast, inhibition of lipase activity (condition FAT-THL) resulted in pronounced propulsive APD activity and reduced tonic and phasic pyloric pressures (Fig. 3, right).

### Isolated Antral PWs

The FAT infusion tended to decrease both the number and amplitude of PWs [time effect: not significant (NS)], whereas the FAT-THL infusion resulted in an increase in both the number and amplitude of PWs (time effect: NS) when compared with baseline. Hence, the FAT-THL infusion resulted in a greater number (treatment effect: $P = 0.005$, treatment $\times$ time interaction: $P = 0.014$) and amplitude (treatment effect: $P < 0.001$) of PWs when compared with the FAT infusion (Table 1).

### Pyloric PWs

The FAT infusion stimulated both the number and amplitude of IPPWs (time effects: NS), with a maximum effect occurring between 15 and 30 min during the infusion, whereas the FAT-THL infusion was not associated with any changes in the number or amplitude of IPPWs (time effects: NS). Overall, the FAT-THL infusion resulted in a smaller number (treatment effect: $P = 0.006$, treatment $\times$ time interaction: $P = 0.024$) and amplitude (treatment effect: $P = 0.023$, treatment $\times$ time interaction: $P = 0.004$) of IPPWs when compared with the FAT infusion (Fig. 4, A and B, and Table 1). The FAT infusion was associated with a marked increase in basal pyloric pressure (time effect: $P = 0.011$) peaking between 15 and 30 min. In contrast,

**Table 1. Characteristics of isolated pressure waves in the antrum, pylorus, and duodenum**

<table>
<thead>
<tr>
<th></th>
<th>Total Number (0–45 min)</th>
<th>Amplitude, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FAT</td>
<td>FAT-THL</td>
</tr>
<tr>
<td>Antrum</td>
<td>$2.8 \pm 1.9$</td>
<td>$17.2 \pm 5.0$</td>
</tr>
<tr>
<td>Pylorus</td>
<td>$50.2 \pm 10.1$</td>
<td>$25.9 \pm 5.2$</td>
</tr>
<tr>
<td>Duodenum</td>
<td>$64.5 \pm 10.4$</td>
<td>$91.5 \pm 9.8$</td>
</tr>
</tbody>
</table>

Data are means $\pm$ SE, $n = 16$ subjects. FAT, triglyceride emulsion without 120 g lipase inhibitor tetrahydrolipostatin (THL); FAT-THL, triglyceride emulsion with 120 g THL; NS, not significant.
during condition FAT-THL, basal pyloric pressure declined steadily (Fig. 4C). The differences between the two conditions were significant (treatment effect: $P = 0.005$).

**Isolated Duodenal PWs**

The FAT infusion was associated with a slight decrease in the number (with a minimum number between 15 and 30 min during the infusion; time effect: $P = 0.038$) and the amplitude (time effect: $P = 0.079$) of isolated duodenal waves. During the FAT-THL infusion, the number of PWs was variable, whereas the amplitude increased, with a maximum between 15 and 30 min (time effect: $P = 0.078$). Overall, the amplitude (treatment effect: $P < 0.001$) but not the number (treatment effect: NS) of isolated duodenal PWs was greater during the FAT-THL infusion when compared with the FAT infusion (Table 1).

**PW Sequences**

The number of APD PW sequences was greater during the FAT-THL condition when compared with FAT (Fig. 5A). Specifically, a greater number of sequences originated in the antrum, pylorus, and duodenum during condition FAT-THL, basal pyloric pressure declined steadily (Fig. 4C). The differences between the two conditions were significant (treatment effect: $P = 0.005$).
lipase activity (condition FAT-THL) prevented the increase in plasma CCK within 15 min of the start of the study days. During FAT infusion, there was an increase in plasma GLP-1 when compared with the FAT condition, with a mean difference in energy intake of ~200 kcal. Greater absolute amounts of carbohydrate (FAT: 141.4 ± 11.9 g, FAT-THL: 161.9 ± 12.1 g, P = 0.045) and protein (FAT: 57 ± 5 g, FAT-THL: 67.6 ± 4.4 g, P = 0.029) were consumed. Fat consumption did not differ (FAT: 49.6 ± 5.2 g, FAT-THL: 57.4 ± 3.5 g, NS), and the percentage of energy derived from the three macronutrients remained unchanged between the two study conditions.

**Appetite/Food Intake**

Scores for “prospective consumption” declined progressively during the FAT infusion to levels that were lower than during the FAT-THL condition (P = 0.037; Fig. 6A). During the FAT-THL condition, scores for prospective consumption did not change from baseline during the infusion period (Fig. 6A). “Nausea” scores were very low throughout both infusion periods, yet statistical analysis showed that nausea was marginally higher during the FAT condition [maximum score (mm); FAT: 10.6 ± 3.6, FAT-THL: 7.8 ± 2.4, P = 0.045, Fig. 6B]. As expected, consumption of the buffet meal was associated with a reduction in scores for prospective consumption, but there were no differences between the two study conditions. Nausea scores were very low following the meal, with no differences between the two study conditions (data not shown).

Energy intake (FAT: 1,237 ± 104 kcal, FAT-THL: 1,433 ± 86 kcal, P = 0.04) and the amount of food consumed (FAT: 1,165 ± 104 g, FAT-THL: 1,335 ± 87 g, P = 0.032) at the buffet meal were greater after the FAT-THL compared with the FAT condition, with a mean difference in energy intake of ~200 kcal. Greater absolute amounts of carbohydrate (FAT: 141.4 ± 11.9 g, FAT-THL: 161.9 ± 12.1 g, P = 0.045) and protein (FAT: 57 ± 5 g, FAT-THL: 67.6 ± 4.4 g, P = 0.029) were consumed. Fat consumption did not differ (FAT: 49.6 ± 5.2 g, FAT-THL: 57.4 ± 3.5 g, NS), and the percentage of energy derived from the three macronutrients remained unchanged between the two study conditions.

**Relationship Between Prospective Consumption and Nausea Scores with Subsequent Energy Intake**

The score for prospective consumption immediately preceding the buffet meal was positively related with (r² = 0.284, P < 0.001), whereas there was no relationship between the score for nausea (r² = 0.009, P > 0.1) and subsequent energy intake.

**Plasma CCK and GLP-1 Concentrations**

**Plasma CCK.** Baseline CCK did not differ during the study days. During FAT infusion, there was an increase in plasma CCK within 15 min of the start of the infusion to levels that were higher than during the FAT-THL condition (P = 0.001; Fig. 7A). Inhibition of lipase activity (condition FAT-THL) prevented the FAT-induced increase in plasma CCK concentrations. Ingestion of the buffet meal increased plasma CCK concentrations during both study conditions, but levels were higher during the FAT condition (P = 0.001, data not shown).

**Plasma GLP-1.** Baseline GLP-1 did not differ between the study days. FAT infusion was associated with an increase in plasma GLP-1 when compared with FAT-THL. This was evident within 30 min of starting the infusion (P = 0.001; Fig. 7B). During FAT-THL, the FAT-induced increase in plasma GLP-1 was prevented. Ingestion of the buffet meal increased plasma GLP-1 concentrations during both study conditions, but levels were higher during the FAT condition (P = 0.001, data not shown).

**DISCUSSION**

Our study confirms that lipase inhibition reduces the inhibitory effect of duodenal fat on appetite and subsequent food intake (32) and diminishes fat-induced effects.
In considering the doses of intraduodenal fat and THL used, the infusion rate approximates the rate at which fat is emptied from the stomach into the small intestine after a high-fat meal (35), and the THL dose of 120 mg is recommended for ingestion with meals to achieve weight loss (7, 25). However, the degree of inhibition of fat absorption in our study (~75%) was substantially greater than that achieved in previous weight loss studies (~30%) (7, 25); this should be taken into consideration in interpreting our data. The fat emulsion was based on soybean oil, which contains exclusively long-chain triglycerides with a chain length ≥16, and a large percentage of oleic acid (24%, monounsaturated fatty acid) and linoleic acid (53%, polyunsaturated fatty acid). Both the chain length and the degree of saturation have been shown to modify the effects of fat on gastric motility, appetite, and CCK secretion. Long-chain fatty acids with a chain length ≥12 but not short chain fatty acids (chain length ≤11) induce gastric relaxation (11, 33), inhibit food intake, and stimulate CCK secretion (11, 32, 33); fat emulsions containing a large percentage of polyunsaturated fatty acids appear to inhibit food intake more than fat emulsions containing monounsaturated fatty acids (15).

It is well established that the presence of nutrients in the small intestine slows gastric emptying. The motor mechanisms associated with the slowing of gastric emptying by intraduodenal fat include proximal gastric relaxation (10, 33), inhibition of antral contractile activity (20, 33), stimulation of phasic and tonic pyloric PWs (13, 21), and conversion of small intestinal activity into a pattern of irregular contractions (1, 4, 27). Although proximal gastric relaxation was not measured in the current study, the other responses were evident. The temporal and spatial organization of APD pressure patterns is a major determinant of gastric emptying and small intestinal transit; changes in gastrointestinal motility in response to food ingestion serve to optimize the interaction of nutrients with small intestinal receptors by slowing gastric emptying and transport of chyme along the gut. Studies in dogs, combining measurement of small intestinal motility using strain gauge transducers with fluoroscopy to monitor movement of chyme along the gut. Studies in dogs, combining measurement of small intestinal motility using strain gauge transducers with fluoroscopy to monitor movement of intestinal contents, have demonstrated that nutrient ingestion shortens the length of PW sequences in the duodenum when compared with a nutrient-free cellulose meal; this is associated with slower transport of intestinal content (4, 27). In contrast to the fat infusion, APD activity during inhibition of lipase activity was characterized by an increased number of PW sequences, inhibition of tonic and phasic pyloric pressures, and stimulation of antral and duodenal pressures. Although the effects of lipase inhibition on small intestinal transit have not been evaluated in humans, lipase inhibition markedly accelerates gastrocolonic transit in rats (36); hence, the demonstrated stimulation of APD PW sequences is likely to be associated with increased propulsion of intestinal content (4, 36). In addition, other studies have shown that increased propagating gastrointestinal motor activity, as induced by the prokinetic drug cisapride (14),

CCK secretion (3, 11, 32). The novel observations are that lipase inhibition abolishes the stimulation of GLP-1 secretion and modifies APD pressure activity in response to intraduodenal fat infusion. In particular, lipase inhibition reduced tonic and phasic pyloric pressures and was associated with a greater number of isolated PWs in the antrum as well as more and longer APD PW sequences, all of which are thought to represent a more propulsive motor pattern.

Input from small intestinal receptors (activated by nutrients and/or neuropeptides) is transmitted to centers in the brain stem, such as the nucleus of the solitary tract and the area postrema, which are both involved in the control of gastrointestinal motility (26), and also conveyed to the hypothalamus (42), which plays a major role in appetite regulation. Our data suggest that lipase inhibition “interrupts” activation of these pathways by triglyceride. The observed effects of lipase inhibition on hormone secretion and APD pressure activity potentially have implications for the use of lipase inhibition in the treatment of obesity.

Fig. 7. Plasma concentrations of CCK (A) and glucagon-like peptide-1 (GLP-1; B). The rise in plasma CCK and GLP-1 levels in response to the FAT infusion was absent during the FAT-THL infusion. Data are means ± SE, n = 16 subjects. *Significantly different from FAT (P = 0.000).
is associated with acceleration of gastric emptying (14, 18). Therefore, it is likely that these motor effects [together with a decreased relaxation of the proximal stomach (11)] are responsible for the acceleration of gastric emptying of fat induced by lipase inhibition (35) or in patients with exocrine pancreatic insufficiency (5). Our study also indicates that duodenally administered fat requires ~30–45 min to exert its maximal modulating effects on APD motility (9). It could, therefore, be postulated that the latency for stimulation of IPPWs during the lipid infusion is accounted for by the time required for digestion, although it is also possible that a threshold “dose” of nutrient (12) or stimulation of a minimum length of intestine (37) is required to interrupt the fasting motor pattern.

Lipase inhibition also prevented the reduction in scores for prospective consumption induced by the duodenal fat infusion and increased energy intake at the buffet meal in our study. These findings are consistent with previous observations that the decrease in hunger and increase in fullness induced during gastric distension and duodenal lipid infusion are diminished by lipase inhibition (11). Moreover, the data are consistent with the findings of two other recent studies that the suppression of food intake by duodenal infusion of olive oil (32) or a high-fat yogurt preload (39) are attenuated when fat digestion is inhibited, underlining the importance of the products of fat digestion in the regulation of appetite perception and food intake by fat. It may be argued that nausea, which was greater in the absence of lipase inhibition, may be responsible for a reduction in food intake. However, although statistically different, nausea scores were very low during both study conditions and unlikely to be relevant. A lack of influence of nausea on food intake is also supported by the fact that there was no relationship between nausea scores at the end of the lipid infusion and the amount eaten at the buffet meal. Furthermore, food intake was substantial in all subjects, i.e., they all ate what would be considered to be a “normal” meal.

Our data suggest that by increasing energy intake at a subsequent meal, subjects largely compensated for the deficit generated by the inhibition of fat digestion. The duodenal infusion administered contained 336 kcal, and it may be assumed that as a result of 75% inhibition of lipase activity, ~250 kcal were not available for digestion and absorption during the FAT-THL condition. Hence, by ingesting an additional ~200 kcal during this condition, subjects compensated for ~80% of the energy deficit.

The regulation of appetite, gastrointestinal motor function, and hormone secretion is complex, interrelated, and modulated by a large number of factors including gut hormones. It has been established that the slowing of gastric emptying by fat is dependent on CCK mechanisms (16); CCK is also regarded as one of the most important satiety hormones (30) and has been shown to be involved in mediating the effects of intestinal fat on perceptions of hunger and fullness (10). Furthermore, fat digestion is required for the stimulatory effects of fat on CCK secretion (11, 32, 33, 40). GLP-1 has received considerable attention in recent years; it is known that, similar to CCK, GLP-1, when infused intravenously, is a potent regulator of gastric emptying and gastrointestinal motility (38, 43) and also inhibits food intake (12, 17). Our data illustrate that lipase inhibition completely abolishes the stimulation of both CCK and GLP-1 by small intestinal fat, and this may potentially account for the increase in food intake observed with lipase inhibition.

THL is effective in both the induction and maintenance of modest weight loss in overweight and obese subjects (7, 25). As a result of inhibition of gastric and pancreatic lipase (19), THL, in a dose of 120 mg with a meal, decreases dietary fat absorption by ~30% (48). However, although the inhibitory effect of THL on lipase activity is maintained during chronic administration, the mean weight loss is less than would be predicted by the degree of inhibition of fat absorption; this was despite the fact that in these studies, subjects were also asked to consume an energy-restricted diet. Therefore, it is possible that some patients taking THL increase their energy intake (28), although the latter has not been formally evaluated in these chronic studies (7, 25). There are a number of potential mechanisms by which THL could affect appetite, and the relative importance of these is likely to vary between individuals, so that some people may reduce their food intake, whereas others increase it. Our data suggest that the observed increase in food intake in the present study is attributable to the reduction in stimuli (such as free fatty acids, CCK, and GLP-1) that act to inhibit food intake. However, a contribution of other factors, e.g., of humoral, psychological, environmental, or psychosocial nature, cannot be excluded. A role for the rate of gastric emptying as a factor per se was eliminated in our study by infusing fat directly into the duodenum.

In summary, our data illustrate how apparently different systems (gastrointestinal motility and appetite regulation) that are commonly studied separately are, at least in part, governed by the same mechanisms and interact intimately. Lipase inhibition prevents the release of free fatty acids from triacylglycerides, which, in turn, affects motility patterns in the APD region, hormone release, and food intake.

We are grateful to Hoffmann-La Roche, Basel, Switzerland, for financial support of the study and the supply of tetrahydrolipstatin. We also thank V. Sharley from the Royal Adelaide Hospital pharmacy for producing the fat emulsions and G. Hebbard, Royal Melbourne Hospital, for providing Trace! and input into the analysis of the pressure data.

C. Feinle is supported by a Florey Research Fellowship from the Royal Adelaide Hospital.

REFERENCES


LIPASE INHIBITION AND ANTRPYLORODUODENAL MOTILITY


39. O’Donovan D, Feinle C, Wishart J, and Horowitz M. Acute effects of lipase inhibition on food intake and plasma cholecy-