# Physiology and pathophysiology of the ileal brake in humans

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*Chapter 2*

# DOES THE INTESTINAL SITE OF FAT DELIVERY INFLUENCE FEEDBACK CONTROL ON GASTROINTESTINAL MOTILITY IN HUMANS ?

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**ABSTRACT**

This study was performed to compare in healthy volunteers the effect of intrajejunal versus intraileal fat administration on gastrointestinal and gallbladder motility. Eight healthy volunteers (age 22±5 yr) participated in three experiments, performed in random order with: 1) intrajejunal fat 2) intraileal fat and 3) placebo after oral ingestion of a mixed liquid meal. Antroduodenojejunal motility, gallbladder volumes, and plasma cholecystokinin (CCK) and peptide YY (PYY) were measured. *Results*: 1) both intrajejunal and intraileal fat significantly ($p<0.01$) prolonged the duration of the fed motor pattern. The duration of the fed pattern correlated significantly with PYY but not with CCK secretion; 2) intrajejunal fat significantly ($p<0.05$) prolonged MMC cycle length while intraileal fat shortened MMC cycle length; 3) postprandial gallbladder emptying was significantly ($p<0.01$) reduced with intraileal fat and increased with intrajejunal fat. *Conclusion*: Feedback control mechanisms on gastrointestinal motility and hormone release, evoked by intestinal fat, are qualitatively and quantitatively dependent on the site of fat delivery (jejunum versus ileum).

## INTRODUCTION

Feedback control mechanisms triggered by intraluminal nutrients have an important role in the proces of digestion and absorption. The responses evoked by intraluminal nutrients differ with respect to the intestinal site. For instance, fat administration in the duodenum stimulates exocrine pancreatic secretion, gallbladder contraction and intestinal transit (1-3) while administration of fat into the ileum inhibits exocrine pancreatic secretion and intestinal transit (4-6). The latter is called the "ileal brake", a negative feedback loop from the distal to the proximal gut.

In addition to the ileal brake, the existance of an inhibitory feedback control located in the proximal half of the small intestine, the so called "jejunal brake" has also been proposed (7-9). Intrajejunal nutrients inhibit exocrine pancreatic secretion and prolong intestinal transit in both humans and dogs (7-9). It has been shown in a study in dogs that intestinal transit is more potently inhibited by fat delivered in the distal than in the proximal small intestine, suggesting a more potent inhibitory feedback mechanism of the ileal brake compared to the jejunal brake (10). Although in humans both jejunal and ileal brake are operative, they have not been compared quantitatively.

The present study was undertaken to compare in healthy volunteers the effects of intrajejunal versus intraileal fat administration on gastrointestinal and gallbladder motility. The latter plays a role in delivering bile acids into the duodenum for the digestion of dietery fats. It is generally accepted that the proximal gut peptide cholecystokinin (CCK) is the most potent hormonal stimulator of gallbladder contraction (11,12). In addition, there is also evidence for the involvement of the distal gut peptide PYY in the regulation of gallbladder emptying (13,14).

However, little is known about the effect of the ileal brake on gallbladder motility. In the present study, plasma levels of CCK and PYY were measured and related to gastrointestinal and gallbladder motility data.

## SUBJECTS

Eight healthy volunteers (2 male, 6 female; mean (±SEM) age 22±5 year; mean (±SEM) BMI 22±2) participated in this study. None of the subjects had gastro-intestinal complaints or history of abdominal surgery. Informed consent was obtained from each person and the study protocol had been approved by the ethical committee of the Leiden University Medical Center.

## METHODS

### Antroduodenojejunal manometry

Antroduodenojejunal motility was recorded by stationary perfusion manometry using an ileal catheter (outer diameter 4 mm; length 350 cm) consisting of a central perfusion port, 12 side holes, a stainless steel tip weight and a distal inflatable balloon. The 12 side holes are divided in three clusters each consisting of four side hole openings spaced 2,5 cm apart (antrum) and 5 cm apart (duodenum/jejunum). The manometry catheter was connected to a low-compliance pneumohydraulic perfusion system (Arndorfer Medical Systems) and perfused with distilled water at a rate of 0.3 ml/min. Resistance to infusion within the system was detected with pressure transducers (Medex, Hilliard, Ohio, USA). The output of the pressure transducers was translated in a polygraph (PC Polygraph, Metronics, Denmark) and displayed continuously on a monitor. Data were stored on a personal computer for analysis.

**Gallbladder measurements**

Gallbladder volumes were measured by real time ultrasonography (Toshiba, 3.75 MHz transducer) and calculated by the sum of cylinders method using computerized system (15,16). In this method the longitudinal image of the gallbladder is divided into series of equal height, with diameter perpendicular to the longitudinal axis of the gallbladder image. The uncorrected volume is the sum of volumes of these separate cylinders. To correct for the displacement of the longitudinal image of the gallbladder from the central axis, a correction factor is calculated from the longitudinal and transversal scans of the gallbladder. Gallbladder volume is calculated by multiplication of the uncorrected volume with the square of the correction factor. The mean of two measurements was used for analysis. The assumptions and the mathematical formula used to calculate gallbladder volume have been described and validated previously 15,16).

**Study design**

Each subject participated in three experiments, performed in random order on three consecutive days in a single blind manner. The experiments started at 7:45 AM.

*Day 0: Catheter intubation*

Subjects were intubated transnasally with the ileal catheter after an overnight fast. Once the tip of the catheter passed the ligament of Treitz, the distal balloon was inflated with 10 ml air to facilitate further progression of the tube through the small intestine. The progression of the tube was monitored by fluoroscopy. The tip of the catheter was located so that the most distal cluster of four side hole openings was in the jejunum, the second one was in the

duodenum and the most proximal cluster was situated in the antrum. The time required for the tube to reach the distal ileum varied between 10-24 hours. Correct position was verified by fluoroscopy on day 0 and at the start of day 1, 2 and 3. Additionally, the correct position of the tube was fluoroscopically checked at the end of each experiment.

*Day 1, day 2, day 3 and day 4: manometry measurements*

Measurements were performed in random order with intrajejunal saline, intraileal saline, intrajejunal fat, or intraileal fat.

After the correct position of the catheter was verified, an intravenous cannula was inserted into the antecubital vein of one arm for blood sampling. The spontanous occurrence of a phase III was defined as the start point for all the experiments. During measurements subjects were lying comfortably in a bed.

At time 0 min (15 min after the occurrence of the spontanous phase III) the study was started with oral ingestion of 400 ml of a commercially available polymeric liquid meal (Nutrison; Nutricia Zoetermeer, The Netherlands) containing 16 g protein, 48 g carbohydrates and 12 g of saturated and unsaturated triglycerides (400 ml = 400 kcal; osmolality 260 mOsm). At the same time intrajejunal or intraileal infusion with fat emulsion (Intralipid 20%) or saline was started and continued for three hours at a rate of 1 ml/min (2 kcal/min). Intralipd 20% (Pharmacia & Upjohn BV, Woerden) consists of 20 g soybean-oil, 12 g partitionated egg-phospholipids and 22 g glycerol anhydrates per 100 ml.

Gallbladder volume was measured and blood was sampled at regular intervals at : t=-15, 0, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360 min. Antroduodenojejunal motility was recorded for at least 6 hr after ingestion of the liquid meal.

**Hormone assays**

Plasma CCK was measured by a sensitive and specific radioimmunoassay. This antibody binds to all CCK peptides including sulfated CCK octapeptide, but not with gastrin. The detection limit of the assay is 0.1 pmol/l plasma. The intra-assay variation ranges from 4.6 to 11.5% and the inter-assay variation from 11.3 to 26.1% (17). Plasma PYY was measured by radioimmunoassay. PYY antiserum was generated in rabbits by intracutaneous injections of synthetic human PYY (BACHEM Biochemica GmbH, Switzerland). PYY was labelled with $^{125}$Iodine with chloramine T. The assay is highly specific. There is no cross-reactivity with PP or VIP. The detection limit is 10 pmol/l. Both PYY (1-36) and PYY (3-36) bind to the antibody in dilutions up to 250000.

**Analysis of manometric data**

Motility patterns from antroduodenojejunal manometry were analyzed both visually and by computer. Pressure waves with an amplitude ≥ 10 mmHg and duration ≥ 1.5 sec were considered as true contractions. Artifacts due to increments in intra-abdominal pressure or any other reason were excluded from analysis.

The postprandial period was defined as the time interval between the end of the meal and the occurrence of the first small intestinal phase III propagated over at least two channels, independent of the intestinal site of onset. The motility indices (MI) of the postprandial period were calculated semi-automatically for antrum, duodenum and jejunum using the formula MI= Ln(Σ(mmHgxsec)/min).

Phases of the MMC were defined as follows: phase I, no more than 1 contractions per 5 min for at least 5 min and preceded by phase III; phase II: irregular contractile activity at a frequency of more than 2 per 10 min and

amplitude above 10 mmHg; phase III: regular contractile activity at a frequency of 10-12 contractions per min for at least 2 min. Phase III activity had to be propagated over at least 2 recording sites. Antral phase III activity was defined as rhythmic contractile activity at maximum frequency (3 contractions/min) for at least 1 min in temporal relationship with duodenal phase III activity (18). The duration of the MMC cycle was calculated as the interval between the beginning of phase III in the duodenum or jejunum until the beginning of the next phase III cycle.

**Data and statistical analysis**

Results are expressed as mean ± SEM. Postprandial gallbladder contraction was calculated as percentage decrement over basal gallbladder volume. Integrated incremental values for plasma hormone secretion and postprandial gallbladder contraction were calculated as the area under the plasma concentration and percentage gallbladder contraction curve respectively after subtraction of the basal value. For all parameters, multiple analysis of variance (MANOVA) was used to test for statistical significance. When this indicated a probability of less than 0.05 for the null hypothesis, Student-Newman-Keuls analyses were performed to determine which values between or within subjects differ significantly. Coefficient of linear correlation (Spearman) was used to calculate correlations between motility parameters and integrated plasma hormone secretions. The significance level was set at $p<0.05$.

## RESULTS

### Gastrointestinal motility

#### *Digestive pattern*

After meal ingestion, fed motor patterns were observed in all experiments. However, the duration of the fed motility pattern was significantly ($p<0.01$) prolonged after intrajejunal fat (377±39 min) and intraileal fat administration (326±44 min) compared to control (238±17 min). No significant difference was found in the duration of the fed pattern between the intrajejunal and intraileal fat experiment.

The postprandial duodenal and jejunal MI were significantly ($p<0.05$) decreased in both the intrajejunal and intraileal fat experiment compared to the control (Table 1). The reduction in MI was more pronounced during intraileal fat infusion. The difference in postprandial MI between intraileal and intrajejunal fat was significant ($p<0.05$) from 120-180 min in the duodenum and during the first two postprandial hours in the jejunum (Table 1). In contrast to intestinal MI, postprandial antral MI during intrajejunal and intraileal fat infusion did not differ between the two experiments and controls (Table 1).

#### *Interdigestive pattern*

After transition from a digestive into an interdigestive motility pattern 17 complete MMC cycles were observed in the control, six complete MMC cycles in the intrajejunal fat and seven complete MMC cycles in the intraileal fat experiment. Complete MMC cycles were found in all eight subjects in the control experiment but only in two subjects in the intrajejunal fat and three subjects in the intraileal fat experiment. The duration of the MMC cycles was significantly ($p<0.05$) prolonged

***Table 1.*** *Postprandial antral, duodenal and jejunal motility index (MI= Ln(Σ(mmHgxsec)/min) in 60 min periods and for the total fed period, after ingestion of a liquid meal in the intrajejunal fat, intraileal fat and control experiment. * p<0.05 compared to controls; # p<0.05 compared to intrajejunal fat*

| **MI** | **Control** | **Intrajejunal fat** | **Intraileal fat** |
|---|---|---|---|
| antrum 0-60 min | 5.4±0.5 | 5.0±0.5 | 5.3±0.2 |
| antrum 60-120 min | 5.3±0.4 | 5.1±0.4 | 5.4±0.2 |
| antrum 120-180 min | 5.0±0.5 | 5.0±0.3 | 5.2±0.1 |
| total fed period | 5.1±0.6 | 5.1±0.3 | 5.3±0.3 |
| | | | |
| duodenum 0-60 min | 5.7±0.3 | 5.1±0.1 | 4.4±0.2 |
| duodenum 60-120 min | 5.2±0.2 | 4.2±0.1* | 4.0±0.3* |
| duodenum 120-180 min | 5.4±0.3 | 4.3±0.3* | 3.9±0.2*# |
| total fed period | 5.5±0.3 | 4.8±0.3* | 4.3±0.2* |
| | | | |
| jejunum 0-60 min | 5.4±0.2 | 5.1±0.3 | 3.8±0.1*# |
| jejunum 60-120 min | 5.2±0.3 | 4.3±0.4* | 3.8±0.2*# |
| jejunum 120-180 min | 5.5±0.2 | 4.1±0.3* | 3.9±0.2* |
| total fed period | 5.5±0.3 | 4.2±0.4* | 3.9±0.2* |

in the intrajejunal fat compared to the control experiment. In contrast, the duration of the MMC cycle in the intraileal fat experiment was significantly ($p<0.05$) shorter compared to the control experiment (Table 2). The differences

in MMC cycle length between the experiments result from significant ($p<0.05$) differences in the duration of phase II (Table 2).

***Table 2**. Characteristics of MMC cycles (mean±SEM; min) during the intrajejunal fat, intraileal fat and the control experiment. * $p<0.05$ compared to the control experiment ; # $p<0.01$ compared to the intrajejunal experiment.*

| **MMC** | **Control (n=17)** | **Intrajejunal fat (n=6)** | **Intraileal fat (n=7)** |
|---|---|---|---|
| **Cycle length** | 86±9 | 129±26* | 58±4*# |
| **Phase I** | 16±2 | 18±3 | 16±5 |
| **Phase II** | 65±10 | 107±25* | 38±4*# |
| **Phase III** | 5±0.5 | 4±1 | 4±0.2 |

**Gallbladder volumes**

Basal gallbladder volumes were not significantly different between the saline (18.7±2.4 ml), the intrajeunal fat (18.2±2.4 ml) and the intrailela fat experiments (18.0±3.0 ml). After meal ingestion, gallbladder volumes significantly ($p<0.01$) decreased compared to basal volumes in the control and the fat experiments (Figure 1). Postprandial gallbladder volumes in the intrajejunal fat experiment were significantly ($p<0.01$) smaller compared to those in the intraileal fat experiment from 30 to 240 min and to those in the control experiment from 90 to 240 min. Postprandial gallbladder volumes in the intraileal fat experiment were significantly ($p<0.05$) larger compared to control during the period from 30 to 60

min (Figure 1). Integrated gallbladder contraction during the 6 hour postprandial period was significantly ($p<0.05$) increased in the intrajejunal fat (20949±2395 %*360 min) compared to the intraileal fat (12224±2943%*min) and the control experiment (12888±2559%*min). The difference in integrated gallbladder contraction during the 6 hour postprandial period was not significant between the control and the intraileal fat experiment.

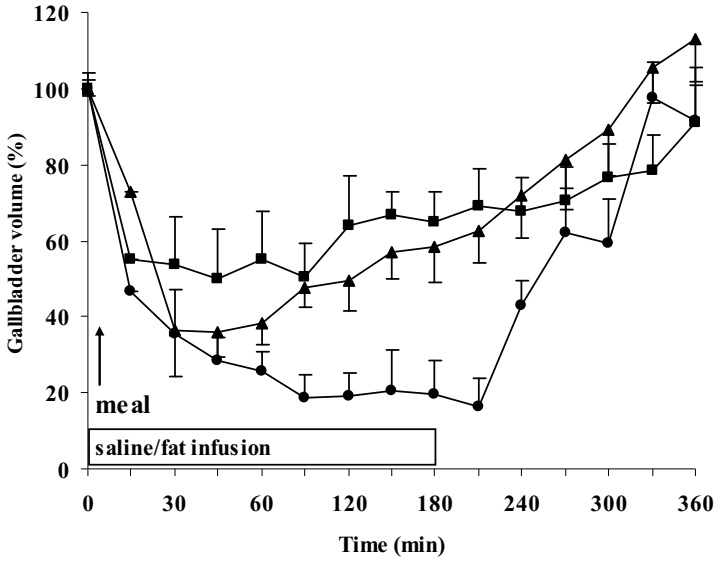


***Figure 1.*** *Gallbladder emptying (%; mean±SEM) after meal ingestion during perfusion of intrajejunal fat (circles), intraileal fat (squares) and placebo (triangles*).

## Plasma CCK

Basal plasma CCK levels were not significantly different between the saline, the intrajejunal and the intraileal fat experiment (0.7±0.1 pM, 0.9±0.2 pM and 0.7±0.2 respectively; Figure 2). After meal ingestion, plasma CCK levels

significantly ($p<0.01$) increased over basal starting from 15 until 210 min in the control experiment and from 15 until 360 min in the intrajejunal and intraileal fat experiment. Postprandial peak increment in plasma CCK levels was significantly lower ($p<0.05$) in the intraileal fat experiment compared to the intrajejunal fat and the control experiment. Integrated plasma CCK secretion during the first three postprandial hours was significantly ($p<0.01$) higher in the intrajejunal fat experiment (599±61 pM*180 min) compared to the control (212±61 pM*180 min) and the intraileal fat experiment (184±26 pM*180 min). Intergrated plasma CCK secretion during the 6 hour postprandial period was also significantly ($p<0.001$) higher in the intrajejunal experiment (949±96 pM*360 min) compared to the saline (234±134 pM*360 min) and the intraileal experiment (350±55 pM*360 min). Intergrated plasma CCK secretion during the 6 hour postprandial period was not significantly different between the control and the intraileal fat experiment.

**Plasma PYY**

Basal plasma PYY levels were not significantly different between the control, the intrajejunal and the intraileal fat experiment (18.0±3.0 pM, 19.0±2.3 pM and 18.4±1.8 respectively; Figure 3). Plasma PYY levels increased significantly ($p<0.01$) over basal from 15 min after meal ingestion until 210 min in the control experiment and from 15 min until 360 min in the intrajejunal and intraileal fat experiment (Figure 3). During the first postprandial hour, integrated plasma PYY secretion was significantly ($p<0.05$) higher in the intraileal fat experiment (715±110 pM*60 min) compared to the intrajejunal fat (189±57pM*60 min) and to the control experiment (217±54 pM*60 min). Integrated plasma PYY secretion during the 6 hour postprandial period was significantly ($p<0.001$)

higher in the intraileal fat experiment (6182±1250 pM*360 min) and in the intrajejunal fat experiment (5452±439 pM*360 min) compared to control (868±216 pM*360 min). Integrated 360 min plasma PYY secretion between intraileal and intrajejunal fat was not significantly different.

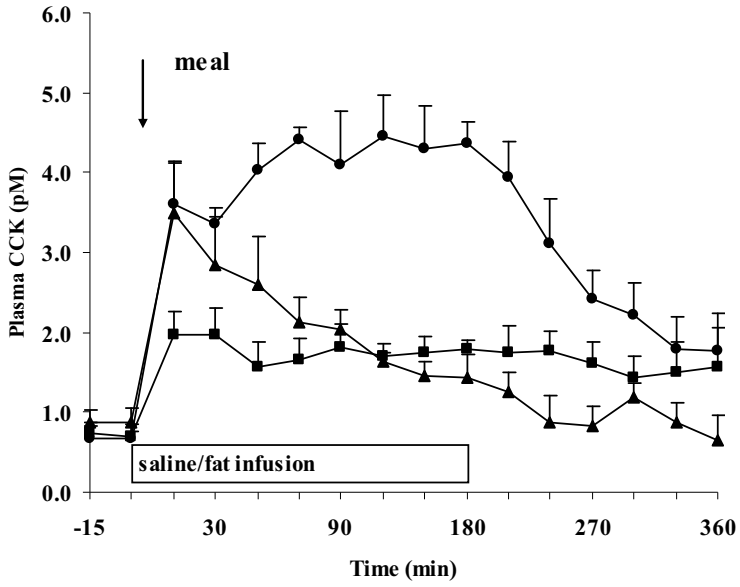


***Figure 2.*** *Fasting and postprandial plasma CCK levels (pM; mean±SEM) during perfusion of intrajejunal fat (circles), intraileal fat (squares) and placebo (triangles).*

## Correlations

*Gallbladder contraction and hormone secretion*

Intergrated postprandial gallbladder contraction significantly correlated with integrated plasma CCK secretions during the 6 hour postprandial period (r=0.62, p=0.03). In contrast, no correlation was found between postprandial gallbladder

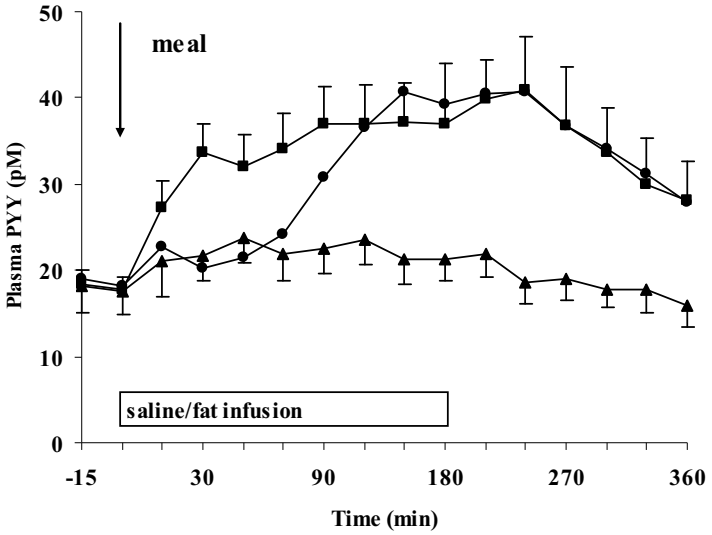


***Figure 3.*** *Fasting and postprandial plasma PYY levels (pM; mean±SEM) during perfusion intrajejunal fat (circles), intraileal fat (squares) and placebo (triangles).*

contraction and integrated plasma PYY secretions during the postprandial period (r=0.08; p=0.7).

*Gastrointestinal motility and hormone secretion*

The duration of the fed pattern was significantly correlated with the integrated incremental plasma PYY secretion during the total postprandial period (r=0.58; p=0.005). No significant correlation was found between the duration of the fed pattern and the integrated postprandial CCK release (r=0.35; p=0.1).

Antral MI was not significantly correlated with the integrated plasma CCK or PYY secretion. The duodenal MI strongly correlated with the integrated incremental plasma CCK secretion during the total postprandial period (r=0.85;

p<0.001) but it did not significantly correlate with the integrated plasma PYY secretion (r=0.41; p=0.13). In contrast, jejunal MI significantly correlated with the integrated incremental plasma PYY secretion during the total postprandial period (r=0.54; p=0.03) but did not correlate with the integrated plasma CCK secretion (r=0.43; p=0.10).

## DISCUSSION

Results of the present study show that: 1) intrajejunal and intraileal administration of fat both prolong the duration of the fed pattern induced by an oral liquid meal. The duration of the fed pattern in the fat perfusion experiments correlates significantly with the integrated plasma PYY secretion but not with the integrated plasma CCK secretion; 2) intrajejunal fat prolongs the duration of the MMC length while MMC length was shortened in the intraileal fat experiment; 3) postprandial gallbladder emptying was significantly reduced in the intraileal compared to the intrajejunal fat experiment. Postprandial gallbladder emptying significantly correlates with postprandial plasma CCK but not with plasma PYY release.

We have found in the present study that both continuous intrajejunal and intraileal administration of fat significantly prolonged the duration of the motility fed pattern induced by a liquid meal. The prolonged postprandial motility patterns are likely to result from delayed gastric emptying and increased small intestinal transit time induced by the intestinal feedback. Previous studies in humans have shown that intrajejunal and intraileal nutrients inhibit not only gastric emptying but also delay small intestinal transit time (4,5,7,8). Delayed gastric emptying and increased intestinal transit time result in longer intestinal

nutrient exposure time which may contribute to the prolonged duration of the digestive period. It is interesting to observe that the duration of the fed pattern correlated significantly only with postprandial plasma PYY but not with plasma CCK release. In humans, intraduodenal nutrients and subsequent CCK release play a central role in the transition from interdigestive to digestive motility pattern (19-21). On the other hand, mechanisms regulating the transition from digestive to interdigestive state are unclear. There is, however, evidence that the distal small bowel may be involved in the regulation of the late postprandial period and the transition to the interdigestive state (6,22-24). It has been shown by Keller et al (24) that the duration of the digestive motor pattern does not correlate with duodenal or jejunal nutrients but rather with the late postprandial increase in ileal nutrient concentration. Since peptide YY is released in the distal gut and represents ileal brake activation, our findings are in line with those of Keller et al (24).

It is apparent from the results that the postprandial duodenal and jejunal MI were reduced during intrajejunal and intraileal fat infusion while no significant changes were observed concerning antral MI. Furthermore the reduction in jejunal MI was more pronounced in the intraileal fat experiment. This finding is in line with those of Lin et al demonstrating that in dogs, fat induced ileal brake is more potent than the fat induced jejunal brake (10). Our results further show that duodenal MI correlated more with plasma CCK secretion than with plasma PYY secretion while jejunal MI correlated more with plasma PYY than with plasma CCK secretion. These findings suggest regional small intestinal heterogeneity in responsiveness to gut peptides. An earlier study in rats has shown that intravenous infusion of PYY had less effect on duodenal motility but

almost totally abolished the spiking activity in the jejunum (25). Furthermore, one study in humans has demonstrated that motor responses of the intestine to different gut peptides appear to vary regionally (26). Our results are, on the one hand, consistent with those found by Welch et al demonstrating that fat infusion into the ileum reduces the postprandial contractile activity of the jejunum (27). On the other hand, we also found a decrease in postprandial duodenal motility while in the study by Welch et al. duodenal motility was not affected. Differences in study design such as a shorter duration of intraileal fat infusion (20 min by Welch et al versus 180 min in the present study) may account for this difference in results. It is conceivable that the degree of activation of the ileal brake also determines the extent of the inhibitory action.

Delayed gastric emptying induced by intrajejunal and intraileal fat has repeatedly been demonstrated. Although a reduced antral MI would be expected during ileal or jejunal fat perfusion, we did not observe differences in antral MI between the intrajejunal, intraileal fat and the control experiment. The reason underlying this finding is not obvious. However, delayed gastric emptying may result from factors other than impaired antral motor activity such as increased pyloric tone, disturbed antro-pyloro-duodenal coordination. In animals, activation of the ileal brake through infusion of PYY inhibits interdigestive but not postprandial antral motility (28,29). It has been shown in pigs that ileal fat infusion increases pyloric tone (30). In humans, the effect of the ileal brake on pyloric motility has not been studied .

In contrast to the prolonged MMC cycle length induced by intrajejunal fat, intraileal intralipid significantly shortened MMC cycle length by reducing the duration of phase II. The mechanism underlying this difference is not apparent.

To date, we confirm the results of Layer et al reporting a shorter duration of the MMC cycle with shorter phase II during intraileal fat infusion (6). Moreover, similar changes in MMC cycle length have been observed in patients with malabsorption disorders with increased ileal fat delivery (31,32). These data consistently point to a shortened MMC cycle length during ileal brake activation. The prolonged MMC cycle length induced by intrajejunal fat results from prolonged duration of phase II. This finding is difficult to explain. One possibility is that the plasma CCK levels that remained elevated after the transition from fed to a fasting motor pattern in the intrajejunal fat experiment, have contributed to the prolongation of phase II. This is plausible since CCK is known to induce fed like motor activity (20,21) and the irregular contractions observed during phase II resemble the fed intestinal motor pattern. This concept is in line with the results found by Defilippi et al showing that in dogs, MMC cycle length was prolonged with an increased duration of phase II during intraduodenal infusion of nutrients of low caloric load (33). The study by Defilippi et al also demonstrated that the number of MMC cycles further decreased and was completely suppressed when higher caloric loads were administered in the duodenum. Although plasma CCK levels were not measured in that study, the stepwise increasing inhibitory effect on the MMC cycle induced by intraduodenal caloric loads may well have been mediated by CCK. It is well known that the number of CCK producing cells is highest in the duodenum (34).

Ingestion of a liquid meal significantly decreased gallbladder volumes which gradually returned to basal at the end of the postprandial period. Fat in the jejunum significantly increased postprandial gallbladder emptying compared to

the intraileal fat experiment and to control especially in the early postprandial period. A similar pattern was observed for the proximal gut hormone CCK. Since gallbladder contraction is merely dependent on CCK secretion (11,12) these results indicate that increased postprandial gallbladder emptying results from increased plasma CCK release. Indeed, postprandial gallbladder emptying strongly correlated with postprandial plasma CCK levels. Moreover, the significantly higher plasma CCK levels during intrajejunal fat infusion indicate that CCK is not only released in the duodenum but also in the more distal small intestine.

No significant correlations were found between gallbladder emptying and PYY secretion neither in the early nor in the late postprandial period. This finding is in line with previous studies in humans and dogs showing that PYY did not inhibit gallbladder contraction stimulated by exogenous or endogenous CCK (13, 35). However, it is worth noticing the delayed peak plasma PYY level obtained in the intrajejunal intralipid experiment compared to the intraileal experiment. This time-related difference reflects the time needed for intralipid to reach the ileum and stimulate PYY release.

In conclusion, the data obtained in the present study demonstrate that intestinal feedback control mechanisms evoked by the fat induced ileal brake on proximal small intestine, postprandial gallbladder motility and hormone release differ qualitatively and quantitatively from those evoked by the fat induced jejunal brake.

## REFERENCES

1. Ledeboer M, Masclee AA, Coenraad M, Vecht J, Biemond I, Lamers CB.

Antroduodenal motility and small bowel transit during continuos intraduodenal or intragastric administration of enteral nutrition. Eur J Clin Invest 29:615-623, 1999

2. Ledeboer M, Masclee AA, Biemond I, Lamers CB. Effect of intragastric or intraduodenal administration of a polymeric diet on gallbladder motility, small-bowel transit time, and hormone release. Am J Gastroenterol 93:2089-2096, 1998
3. Kerstens PJ, Lamers CB, Jansen JB, de Jong AJ, Hessels M, Hafkenscheid JCPhysiological plasma concentrations of cholecystokinin stimulate pancreatic enzyme secretion and gallbladder contraction in man. Life Sci 36:565-569, 1985
4. Pironi L., V. Stanghellini, M. Miglioli, R. Corinaldesi, R. De Giorgio, E. Ruggeri, G. Tosetti, G. Poggioli, A. M. M. Labate, N. Monetti, G. Gozetti , L. Barbara, and V. L. W. Go. Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to the plasma level of peptide YY. Gastroenterology 105:733-739, 1993
5. Read N. W., A. MacFarlane, and R. Kinsman. Effect of infusion of nutrient solutions into the ileum on gastrointestinal transit and plasma levels of neurotensin and enteroglucagon in man. Gastroenterology 86:274-280, 1984
6. Layer P, Schlesinger T, Groger G, Goebell H. Modulation of human periodic interdigestive gastrointestinal motor and pancreatic function by the ileum. Pancreas 8:426-432, 1993
7. Vidon N, Pfeiffer A, Chayvialle JA, Merite F, Maurel M, Franchisseur C, Huchet B, Bernier JJ. Effect of jejunal infusion of nutrients on gastrointestinal transit and hormonal response in man. Gastroenterol Clin

Biol 13:1042-1049, 1989

8. Vidon N, Chaussade S, Merite F, Huchet B, Franchisseur C, Bernier JJ. Inhibitory effect of high caloric load of carbohydrates or lipids on human pancreatic secretions: a jejunal brake. Am J Clin Nutr 50:231-236, 1989
9. Lin HC, Zhao XT, Wang L. Jejunal brake: inhibition of intestinal transit by fat in the proximal small intestine. Dig Dis Sci 41:326-329, 1996
10. Lin HC, Zhao XT, Wang L. Intestinal transit is more potently inhibited by fat in the distal (ileal brake) than in the proximal (jejunal brake) gut. Dig Dis Sci 42:19-25, 1997
11. Niederau C, Heintges T, Rovati L, Strohmeyer G. Effects of loxiglumide on gallbladder emptying in healthy volunteers. Gastroenterology 97:1331-1336, 1989
12. Jebbink MC, Masclee AA, van der Kleij FG, Schipper J, Rovati LC, Jansen JB, Lamers CB. Effect of loxiglumide and atropine on erythromycin-induced reduction in gallbladder volume in human subjects. Hepatology 16(4): 937-42, 1992
13. Hoentjen F, Hopman WP, Jansen JB. Effect of circulating peptide YY on gallbladder emptying in humans. Hoentjen F, Hopman WP, Jansen JB. Scand J Gastroenterol 36:1086-1091, 2001
14. Conter RL, Roslyn JJ, Taylor IL. Effects of peptide YY on gallbladder motility. Am J Physiol 252: G 736-G741, 1987
15. Everson GT, Braverman DZ, Johnson ML, Kern F, Jr. A critical evaluation of real-time ultrasonography for the study of gallbladder volume and contraction. Gastroenterology 79:40-46, 1980
16. Hopman WPM, Brouwer WFM, Rosenbusch G, Jansen JBMJ, Lamers

CBHW. A computerized method for rapid quantification of gallbladder volume from real-time sonograms. Radiology 154:236-237, 1985

17. Jansen J B M J, Lamers C B H W. Radioimmunoassay of cholecystokinin in human tissue and plasma. Clin Chim Acta 131:305-316, 1983
18. Kellow J. E., J. F. Borody, S. F. Phillips, R. L. Tucker, and A. C. Haddad. Human interdigestive motility: variations in patterns from esophagus to colon. Gastroenterology 91:386-395, 1986
19. Behrns KE, Sarr MG. Duodenal nutrients inhibit canine jejunal fasting motor patterns through a hormonal mechanism. Dig Dis Sci 39:1665-1671, 1994
20. Schmidt WE, Creutzfeldt W, Schleser A, Choudhury AR, Nustede R, Hocker M, Nitsche R, Sostmann H, Rovati LC, Folsch UR. Role of CCK in regulation of pancreaticobiliary functions and GI motility in humans: effects of loxiglumide. Am J Physiol 260:G197-G206, 1991
21. Thor P, Laskiewicz J, Konturek P, Konturek SJ. Cholecystokinin in the regulation of intestinal motility and pancreatic secretion in dogs. Am J Physiol 255:G498-G504, 1988
22. Holgate AM, Read NW. Effect of ileal infusion of intralipid on gastrointestinal transit, ileal flow rate, and carbohydrate absorption in humans after ingestion of a liquid meal. Gastroenterology 88:1005-1011, 1985
23. Spiller RC, Trotman IF, Adrian TE, Bloom SR, Misiewicz JJ, Silk DB. Further characterisation of the 'ileal brake' reflex in man--effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptideYY. Gut 29:1042-1051, 1988

24. Keller J, Runzi M, Goebell H, Layer P. Duodenal and ileal nutrient deliveries regulate human intestinal motor and pancreatic responses to a meal. Am J Physiol 272:G632-G637, 1997
25. Al-Saffar A, Hellstrom PM, Nylander G. Correlation between peptide YY-induced myoelectric activity and transit of small-intestinal contents in rats. Scand J Gastroenterol 20:577-82, 1985
26. Kellow JE, Miller LJ, Phillips SF, Haddad AC, Zinsmeister AR, Charboneau JW. Sensitivities of human jejunum, ileum, proximal colon, and gallbladder to cholecystokinin octapeptide. Am J Physiol 252:G345-G356, 1987
27. Welch IM, Davison PA, Worlding J, Read NW. Effect of ileal infusion of lipid on jejunal motor patterns after a nutrient and nonnutrient meal. Am J Physiol 255:G800-G806, 1988
28. Zai H, Haga N, Fujino MA, Itoh Z. Effect of peptide YY on gastric motor and secretory activity in vagally innervated and denervated corpus pouch dogs. Regul Pept 61:181-188, 1996
29. Suzuki T, Nakaya M, Itoh Z, Tatemoto K, Mutt V. Inhibition of interdigestive contractile activity in the stomach by peptide YY in Heidenhain pouch dogs. Gastroenterology 85:114-121, 1983
30. Cuche G, Malbert CH. Ileal short-chain fatty acids inhibit transpyloric flow in pigs. Scand J Gastroenterol 34:149-55, 1999
31. Vu MK, Vecht J, Eddes EH, Biemond I, Lamers CB, Masclee AA. Antroduodenal motility in chronic pancreatitis: are abnormalities related to exocrine insufficiency?. Am J Physiol Gastrointest Liver Physiol 278:G458-G466, 2000
32. Layer P, von der Ohe MR, Holst JJ, Jansen JB, Grandt D, Holtmann G,

Goebell H. Altered postprandial motility in chronic pancreatitis: role of malabsorption. Gastroenterology 112:1624-1634, 1997

33. Defilippi C. Canine small bowel motor activity in response to intraduodenal infusion of nutrient mixtures of increasing caloric load in dogs. Dig Dis Sci 48:1482-1486, 2003
34. Larsson LI, Rehfeld JF. Distribution of gastrin and CCK cells in the rat gastrointestinal tract. Evidence for the occurrence of three distinct cell types storing COOH-terminal gastrin immunoreactivity. Histochemistry 58:23-31, 1978
35. Lluis F, Fujimura M, Lonovics J, Guo Y, Gomez G, Greeley GH, Townsend CM, Thompson JC. Peptide YY and gallbladder contraction. Studies in vivo and in vitro. Gastroenterology 94:1441-1446, 1988