

Sensations induced by medium and long chain triglycerides: role of gastric tone and hormones

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Abstract

Background—The relative roles of gastric relaxation and the neuroendocrine signals released by the small intestine in the perception of nutrient induced sensations are controversial. The different effects of long chain (LCT) and medium chain (MCT) triglyceride ingestion on perception, gastric relaxation, and hormonal release may help to elucidate the mechanisms underlying nutrient induced sensations.

Aims—To compare the effects of intraduodenal LCT and MCT infusions on perception, gastric tone, and plasma gut hormone levels in healthy subjects.

Subjects—Nine fasting healthy volunteers. **Methods**—The subjects received duodenal infusions of saline followed by LCTs and MCTs in a randomised order on two different days. The sensations were rated on a visual analogue scale. Gastric tone was measured using a barostat, and plasma gut hormone levels by radioimmunoassay.

Results—LCT infusion increased satiation scores, reduced gastric tone, and increased the levels of plasma cholecystokinin, gastric inhibitory polypeptide, neurotensin, and pancreatic polypeptide. MCT infusion reduced gastric tone but did not significantly affect perception or plasma gut hormone levels. LCTs produced greater gastric relaxation than MCTs.

Conclusions—The satiation induced by intraduodenal LCT infusion seems to involve changes in gastric tone and plasma gut hormone levels. The gastric relaxation induced by MCT infusion, together with the absence of any significant change in satiation scores and plasma hormone levels, suggests that, at least up to a certain level, gastric relaxation is not sufficient to induce satiation and that nutrient induced gastric relaxation may occur through cholecystokinin independent mechanisms. (Gut 2000;46:32–36)

Keywords: gastric tone; triglyceride; hormones; satiation; cholecystokinin; nutrients

The relative roles of gastric relaxation and the neuroendocrine signals released by the small intestine in the perception of the sensations induced by nutrients are still unclear. Changes in the chemical composition of nutrients infused into the duodenum lead to different sensations despite a similar increase in gastric distensibility, which suggests that the neuroendocrine signals released by the small intestine influence nutrient

induced sensations.^{1,2} Of the various hormones released by the interaction of nutrients with the small intestine, cholecystokinin (CCK) has been shown to play a crucial role in inducing the sensations associated with long chain triglyceride (LCT) ingestion.^{3,4} On the other hand, studies performed using an electronic barostat have shown that changes in gastric tone modulate perception in healthy subjects,⁵ and that impaired gastric relaxation may be involved in the pathogenesis of dyspepsia.^{6,7}

The effects of LCTs on perception, gastrointestinal motility, and plasma hormone levels differ considerably from those of medium chain triglycerides (MCTs). LCTs induce satiation, fullness and nausea,^{1–4} decrease gastric tone,⁸ and increase plasma gastric inhibitory peptide, pancreatic polypeptide, and CCK levels.⁹ MCTs reduce food intake, but this effect does not seem to involve the perception of satiation or fullness¹⁰; furthermore, they only weakly stimulate plasma CCK, and have no effect on gastric inhibitory peptide and pancreatic polypeptide levels.⁹ The effect of MCTs on gastric tone is still not known, but intragastric medium chain fatty acids (10 carbon long chain) have been found to relax the gastric fundus regardless of any concomitant CCK release.¹¹ If intraduodenal MCTs relax the gastric fundus, this would provide an example of gastric relaxation unrelated to significant changes in plasma gut hormone levels and perception, and would support the hypothesis that gastric relaxation per se may occur without any major change in perception.

The aim of our study was to compare the different effects of LCT and MCT duodenal infusions on perception, gastric tone, and the plasma levels of gut hormones in an attempt to identify the relative roles of gastric relaxation and the neuroendocrine signals released by the small intestine in the perception of nutrient induced sensations.

Materials and methods

SUBJECTS

The experiments were performed in nine healthy subjects (three women and six men aged 20–56 years), none of whom complained of dyspepsia, had a past history of any gastrointestinal disease or surgery, or was receiving any medication at the time of the study. The study protocol was previously approved by the ethics committee of Milan's Ospedale Maggiore, and all of the subjects gave their written informed consent to participate.

Abbreviations used in this study: LCT, long chain triglyceride; MCT, medium chain triglyceride; CCK, cholecystokinin.

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RECORDING SYSTEM

The electronic barostat⁸ used to record gastric tone consists of a pressure transducer linked through an electronic feedback mechanism to an air injection-aspiration system driven by a computer (Synectics Visceral Stimulator; Medtronic Synectics Medical, Milan, Italy). The air flow rate was 38 ml/s. The barostat's internal compliance was 0.5 ml/mm Hg, and was linear in the range of pressures from 0 to 55 mm Hg. Air compressibility was taken into account by calculating volume as: volume without correction - (0.5 ml/mm Hg × measured pressure). The pressure transducer and the air injection-aspiration system were independently connected by a double lumen polyvinyl tube (Salem Sump Tube; Sherwood Medical, Petit Rechain, Belgium; outer diameter 4.7 mm) to a highly compliant intragastric bag (Mobile Chemical Company, Pittsford, New York, USA) with a maximum capacity of 1 litre. To measure gastric tone, the barostat was set at a constant pressure: under these conditions, sustained volume expansion reflects a tonic relaxation of the stomach, and vice versa. The intrabag pressure and volume were recorded by a computer at a sampling rate of 16 Hz using version 2.02 of the Polygram for Windows program (Medtronic Synectics Medical). The barostat was equipped with a safety system that blocked any procedure if the intrabag pressure exceeded 55 mm Hg for five seconds.

A single lumen polyvinyl tube (outer diameter 2 mm, length 109 cm; Merck Ltd, Alton, UK), equipped with a side opening located 5 cm from its tip, was used to perfuse saline solution and LCT and MCT emulsions into the duodenum. Duodenal motility was recorded using two manometric catheters (Portex Limited, Hythe, Kent, UK; inner diameter 0.63 mm, outer diameter 1.4 mm), tightly attached to the duodenal infusion tube, and respectively positioned 1 and 5 cm above the infusion port. These catheters were perfused with water through a low compliance pneumohydraulic perfusion pump (Arndorfer Specialities Inc, Greendale, Wisconsin, USA) at a flow rate of 0.5 ml/min. The individual catheters were connected to external pressure transducers (Sensormedics, Anaheim, California, USA), and the pressures were transmitted from the transducers to a computer using a PC Polygraph (Medtronic Synectics Medical). The intraduodenal pressure patterns were used to monitor the position of the infusion port within the proximal part of the duodenum and the timing of the duodenal infusions.

INFUSIONS

Three preparations were tested: 0.9% saline (300 mOsm) and 20% LCT and 22% MCT emulsions. The two emulsions contained the same amount of fatty acids (18%) and lecithin (1.5%). The fatty acids were mainly oleic (26%) and linoleic (52%) in the LCT emulsion and octanoic (56%) and decanoic (40%) in the MCT emulsion. The total glycerol content (4.5%) was equalised by adding respectively 2.5 and 0.95% glycerol to the LCT and MCT emulsions. The two emulsions had the same

energy content and osmolarity (350 mOsm). All three preparations were administered intraduodenally using a syringe pump (Braun, Melsungen, Germany) at a constant rate of 1 ml/min, corresponding to an energy delivery of 8.36 kJ/min for the lipid infusions. The subjects were unaware of the nature of the infusions as the tubing was opaque and the pump was behind the bed.

PROCEDURE

The subjects were studied on two occasions during which their sensory, motor, and endocrine responses were evaluated while the duodenum was perfused with saline and then LCT or MCT emulsion. The order of the studies was randomised, and they were separated by a time interval of at least one week. After an overnight fast, the probe used for the duodenal infusions was introduced through the nose on the morning of the study, and its position checked by fluoroscopy; the infusion port was close to the ligament of Treitz about 20 cm distal to the pylorus. Once the duodenal tube was in position, the subjects swallowed the tube of the barostat with the tied bag tightly wrapped around its end. The bag was positioned in the fundus of the stomach and then gradually inflated using less than 600 ml of air; it was then completely deflated and connected to the barostat. The experiment started with the subject in a recumbent position at 30°. The individual recording pressure was determined by stepwise inflations of the bag in 1 mm Hg increments. The pressure level that first detected respiratory excursions was considered to be the minimum gastric distending pressure, and the gastric operating pressure was then set 2 mm Hg above this level. The mean operating pressure was 8 mm Hg (range 6–11), and was not perceived by the subjects.

Each experiment consisted of two consecutive 30 minute duodenal infusions, the first of isotonic saline, and the second of LCTs or MCTs, both performed during a phase of quiescence (phase I) or intermittent activity (phase II) of the interdigestive migrating motor complex. At the end of each infusion period, the subjects were asked to rate the level of gastric sensations using a questionnaire, and a blood sample for gastrointestinal hormone determinations was withdrawn through a forearm venous cannula. The subjects tolerated the tubes well. In two patients, the LCT infusion was stopped after 21 and 23 minutes because of unbearable nausea; the sensation scores were recorded and the blood samples taken at these times.

SENSATION SCORES

The subjects had no previous experience of comparable studies of visceral sensitivity, and all received standard instructions. The following sensations were measured: satiation (a feeling of repletion, similar to that induced by meal ingestion, that stops further food ingestion), fullness (a feeling of complete satiation, so intense to be uncomfortable), abdominal bloating (a feeling of uncomfortable abdominal distention), nausea (a feeling of sickness with distaste for food and an urge to vomit), and pain. Each sensation was

scored independently on a visual analogue scale consisting of a 100 mm line, with 0 representing “no sensation” and 100 mm the “strongest sensation ever felt”.

GASTROINTESTINAL HORMONES

The blood samples were collected in ice chilled tubes containing EDTA (1 mg/ml) and aprotinin (500 KIU/ml). The plasma was separated by centrifugation at 4°C and stored in aliquots at -80°C until assayed. Gastrointestinal peptides were measured by radioimmunoassay in plasma extracted on SepPak C₁₈ cartridges.¹² Commercially available kits (Peninsula Laboratories, Inc, Belmont, California, USA) were used for the somatostatin, pancreatic polypeptide, neurotensin, and gastric inhibitory peptide assays. CCK was measured as previously described¹³ using a commercially available antibody (C2581; Sigma Chemical Co, St Louis, Missouri, USA) raised in rabbits against synthetic sulphated CCK-8. The 95% confidence limits of detection were respectively 1.5, 1.4, 0.95, 8.0, and 1.2 pg/tube, and the intra- and inter-assay coefficients of variation were respectively 7.1, 9.5, 4.4, 7.2, and 6.4% and 5.2, 9.6, 5.9, 9.8, and 11.7%.

DATA HANDLING AND STATISTICAL ANALYSIS

The mean gastric volume during the last five minutes of each infusion was used to measure gastric tone. The effects of LCTs and MCTs were compared after correction for the effects of the saline infusion. Analysis of variance for a cross over design¹⁴ was performed on the differences between the effects of LCTs and MCTs and those of the respective saline infusions considered as the baseline. The

Table 1 Sensation scores (mm on a visual analogue scale with 0 mm representing “no sensation” and 100 mm “strongest sensation ever felt”) after intraduodenal infusions of saline and long and medium chain triglycerides (LCT and MCT)

	Saline	LCT	Saline	MCT	p Value
Satiation	13 (15)	69 (37)	8 (18)	20 (35)	0.006*
Nausea	3 (7)	43 (41)	6 (10)	13 (21)	0.024
Bloating	27 (24)	32 (30)	16 (15)	22 (14)	0.583
Fullness	28 (25)	37 (32)	15 (12)	21 (19)	0.874
Pain	2 (6)	3 (10)	4 (2)	2 (6)	0.045

Data are mean (SD).

*Considered as statistically significant as it is lower than the statistically significant threshold ($p = 0.01$) according to Bonferroni's correction for multiple comparisons. Moreover, satiation scores after LCT infusion were significantly greater than after saline infusion ($p = 0.001$); all of the other comparisons between the triglycerides and their related saline infusions were not statistically significant.

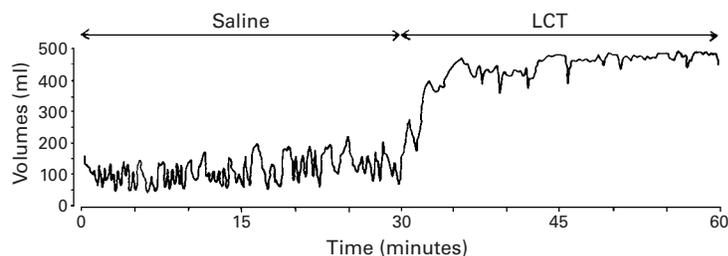


Figure 1 Changes in gastric tone during intraduodenal saline and long chain triglyceride (LCT) infusion in one subject. Note the immediate and sustained gastric relaxation shown by the increase in gastric volume of the barostat bag in response to the lipid infusion. The operating pressure (not shown in the figure) was 8 mm Hg throughout the experiment.

statistical analysis was performed after the logarithmic transformation of gastric volumes and plasma gastrointestinal hormone levels, and after the square root transformation of sensation scores, in order to achieve a Gaussian distribution of the investigated variables. For the sake of clarity, the data are reported as mean (SD) of the non-transformed data. To improve the confidence level of our conclusions, Bonferroni's correction for multiple comparisons was applied within each group of variables (visual analogue scale, gastric tone, and hormone measures).

Results

SENSATION SCORES

Table 1 shows the sensation scores after the intraduodenal infusions of saline, LCTs, and MCTs. The 56 (33) mm increase in satiation score after LCT infusion was significantly different from the 12 (18) mm increase after MCT infusion ($p = 0.006$); furthermore, the satiation scores after LCT infusion were also significantly greater than after saline infusion ($p = 0.001$). The changes in nausea and pain after LCT and MCT infusions (40 (40) mm *v* 7 (12) mm and 1 (23) mm *v* -2 (26) mm respectively) were not considered statistically significant according to the conservative approach chosen; bloating and fullness after the two triglyceride infusions were not significantly different. With the exception of satiation after LCT infusion, none of the comparisons between the triglyceride infusions and their saline counterparts was statistically significant.

GASTRIC TONE

Figure 1 is a representative tracing of the changes in gastric volume during the intraduodenal infusions of saline and LCTs. Gastric volume was unaffected by the former, but the latter induced a rapid and sustained relaxation of the stomach. Gastric volumes after the intraduodenal infusions of saline and LCTs were respectively 144 (35) ml and 480 (216) ml, and after the infusions of saline and MCTs 156 (42) ml and 264 (71) ml. The increase in gastric volume after LCT infusion (336 (193) ml) was significantly greater than that observed after MCT infusion (108 (52) ml) ($p = 0.001$). The relaxation after both LCT and MCT infusions was significantly greater than after saline infusion ($p = 0.0001$ and 0.0002 respectively).

Figure 2 shows the pattern of the changes in satiation scores and gastric volumes in each subject after MCT and LCT infusions. After MCT infusion, the satiation scores increased by 20–50 mm in three subjects and did not change in the others; the concurrent gastric volumes increased by between 25 and 200 ml. After LCT infusion, the satiation score increased by more than 30 mm in all but one subject and gastric volume by more than 200 ml in all but two.

GASTROINTESTINAL HORMONES

Figure 3 shows the changes in plasma hormones during LCT and MCT infusions over the respective saline infusion. The changes in plasma CCK, gastric inhibitory peptide,

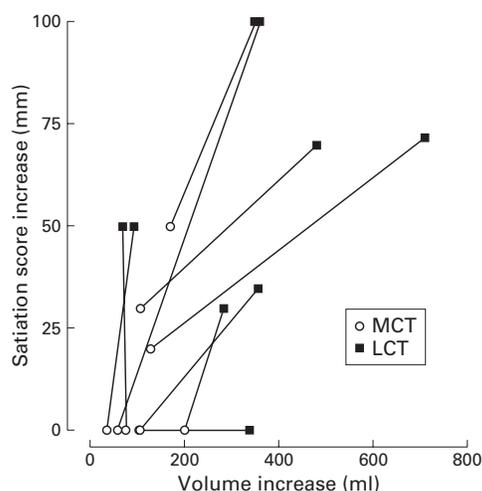


Figure 2 Increases in satiety scores and gastric volumes after intraduodenal infusions of medium and long chain triglycerides (MCT and LCT) over the respective saline infusions in each subject. Each line represents one subject.

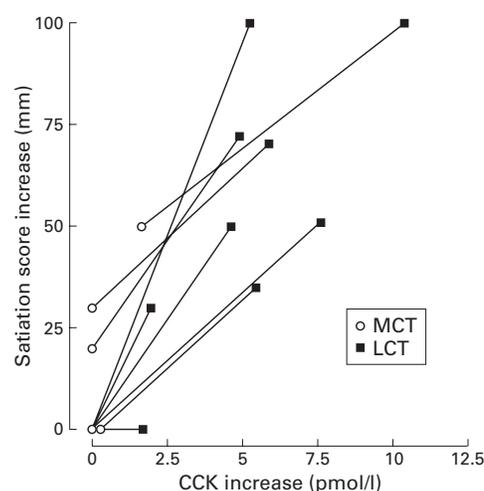


Figure 4 Increases in satiety scores and plasma cholecystokinin (CCK) levels after intraduodenal infusions of medium and long chain triglycerides (MCT and LCT) over the respective saline infusions in each subject. Each line represents one subject.

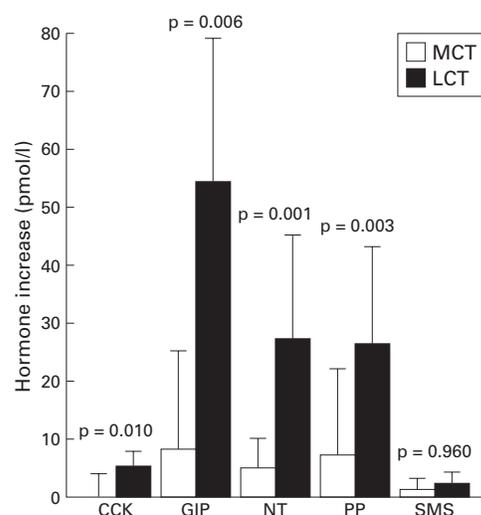


Figure 3 Increases in plasma hormone levels after intraduodenal infusions of medium and long chain triglycerides (MCT and LCT) over the respective saline infusions. Data are mean (SD). The probabilities of the differences between MCT and LCT infusions are reported. CCK, cholecystokinin; GIP, gastric inhibitory peptide; NT, neurotensin; PP, pancreatic polypeptide; SMS, somatostatin.

neurotensin, and pancreatic polypeptide, but not those in plasma somatostatin, were significantly different after LCT infusion from those after MCT infusion ($p = 0.010, 0.006, 0.001, 0.003, \text{ and } 0.960$ respectively; fig 3). Plasma CCK, gastric inhibitory peptide, neurotensin, and pancreatic polypeptide levels were significantly greater after LCT than after saline infusion ($p = 0.0100, 0.0001, 0.0008, \text{ and } 0.0001$ respectively); on the other hand, plasma levels of CCK, gastric inhibitory peptide, neurotensin, and pancreatic polypeptide after MCT infusion were not significantly different from those observed after saline infusion. Plasma somatostatin levels after both LCT and MCT infusion were similar to those recorded after saline infusion.

Figure 4 shows the pattern of the changes in satiety scores and plasma CCK levels in each subject after MCT and LCT infusions. After MCT infusion, the satiety scores increased in

three subjects and did not change in the others, without any concurrent change in plasma CCK levels. After LCT infusion, the satiety scores increased in all but one subject, and plasma CCK levels in all but two.

Discussion

This study confirms that an intraduodenal LCT infusion induces satiety, relaxes the gastric fundus, and releases various hormones including CCK, in line with the results of previous experiments.^{1-4 8 9} These data, together with observations of partially blocked LCT induced sensations after the administration of the CCK-A receptor antagonist loxiglumide,^{3 4} suggest that CCK plays a role in LCT induced satiety, possibly through the stimulation of peripheral vagal afferents¹⁵ or centrally in the area postrema.¹⁶ The considerable relaxation of the gastric fundus induced by LCTs, together with other LCT induced effects on gastric motor function (not assessed in our study) such as changes in antropyloric motility,¹⁷ may also play a role, as antral distention seems to correlate well with satiety.^{13 18} Moreover, LCTs significantly increased plasma gastric inhibitory peptide, neurotensin, and pancreatic polypeptide levels. Gastric inhibitory peptide and neurotensin have an inhibitory effect on gastric motor function^{19 20}; on the other hand, their effects on nutrient induced sensations are still not known and studies with selective antagonists would be advisable.

The confirmatory results obtained after intraduodenal LCT infusion support the validity of our experimental model of assessing lipid induced changes in perception, gastric tone, and hormone plasma levels. Using the same model, we also observed the relaxation of the gastric fundus after intraduodenal MCT infusion, although the degree of this relaxation was significantly smaller. Interestingly, MCT induced relaxation occurred without any concomitant increase in satiety scores or plasma gut hormone levels including CCK. What does this result tell us about the mechanisms

underlying nutrient induced sensations? At least up to a certain point (108 (52) ml), gastric relaxation does not seem to be sufficient to induce satiation, a conclusion that is in line with the results of previous studies in which nutrient induced sensations have been found to change according to the different composition of the meal despite a similar degree of gastric relaxation.^{1,2} It is therefore conceivable that gastric relaxation needs to be greater than that observed after MCT infusion, or be concomitant with changes in plasma gut hormones, in order to induce sensations.

Nutrient induced relaxation of the gastric fundus follows a vagal reflex pathway²¹ and requires the activation of intrinsic nitrergic neurones in the stomach.²² Previous studies have shown that nutrient induced gastric relaxation can be largely, but not completely, inhibited by CCK-A receptor blockade.²³⁻²⁴ Our results suggest that nutrient induced gastric relaxation can also occur regardless of the release of the gut hormones we tested including CCK, and are in agreement with those of other studies that have found that medium chain fatty acids (10 carbon long chain) can activate CCK-independent relaxation of the proximal stomach.¹¹

Caution is required when extrapolating the conclusions obtained using our experimental model for the short term effect of intraduodenal LCT and MCT infusion on satiation (the process that brings eating to an end) to the clinical control of satiety (the inhibition of further eating). In our study the duodenum was perfused at a rate that did not exceed the estimated maximum during normal gastric emptying,^{25,26} but bypassed oral sensory stimulation and the passive distention of the gastric fundus and the antrum. Furthermore, MCTs are more potent than LCTs in inhibiting the consumption of a test meal 30 minutes after a fat preload,¹⁰ and, similarly, the isoenergetic substitution of MCTs for LCTs in high fat diets limits excess food intake over a period of two weeks and allows better control of body weight.²⁷ Finally, an increase in the dietary MCT to LCT ratio in healthy subjects leads to a proportional increase in energy expenditure and urinary noradrenaline (norepinephrine) excretion.²⁸ It is thus likely that factors other than CCK (such as the activation of the sympathetic nervous system, or different triglyceride oxidation rates) are involved in regulating long term energy balance when fats of different chain lengths are consumed.

In conclusion, our study confirms that the satiation induced by intraduodenal LCT infusion may involve various mechanisms, such as changes in gastric tone and plasma levels of gut hormones including CCK. It also shows for the first time that MCT infusion relaxes the gastric fundus and that this occurs without any concomitant increase in satiation scores or the plasma levels of gut hormones including CCK. These results suggest that nutrient induced gastric relaxation may occur through the activation of CCK independent mechanisms

and that, at least up to a certain degree, gastric relaxation does not induce satiation.

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