Enhancement of intragastric acid stability of a fat emulsion meal delays gastric emptying and increases cholecystokinin release and gallbladder contraction

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1Wolfson Digestive Diseases Centre, Queen’s Medical Centre University Hospital, and 2Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham; 3Institute of Food Research, Norwich; 4School of Biomedical Sciences, University of Nottingham, Nottingham; and 5Division of Surgery, Queen’s Medical Centre University Hospital, Nottingham, United Kingdom

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Marciani L, Wickham M, Singh G, Bush D, Pick B, Cox E, Fillery-Travis A, Faulks R, Marsden C, Gowland PA, Spiller RC. Enhancement of intragastric acid stability of a fat emulsion meal delays gastric emptying and increases cholecystokinin release and gallbladder contraction. Am J Physiol Gastrointest Liver Physiol 292: G1607–G1613, 2007. First published March 1, 2007; doi:10.1152/ajpgi.00452.2006.—Preprocessed fatty foods often contain calories added as a fat emulsion stabilized by emulsifiers. Emulsion stability in the acidic gastric environment can readily be manipulated by altering emulsifier chemistry. We tested the hypothesis that it would be possible to control gastric emptying, CCK release, and satiety by varying intragastric fat emulsion stability. Nine healthy volunteers received a test meal on two occasions, comprising a 500-ml 15% oil emulsion with 2.5% of one of two emulsifiers that produced emulsions that were either stable (meal A) or unstable (meal B) in the acidic gastric environment. Gastric emptying and gallbladder volume changes were assessed by MRI. CCK plasma levels were measured and satiety scores were recorded. Meal B layered rapidly owing to fat emulsion breakdown. The gastric half-emptying time of the aqueous phase was faster for meal B (72 ± 13 min) than for meal A (171 ± 35 min, P < 0.008). Meal A released more CCK than meal B (integrated areas, respectively 1,095 ± 244 and 531 ± 111 pmol·min−1, P < 0.02), induced a greater gallbladder contraction (P < 0.02), and decreased postprandial appetite (P < 0.05), although no significant differences were observed in fullness and hunger. We conclude that acid-stable emulsions delayed gastric emptying and increased postprandial CCK levels and gallbladder contraction, whereas acid-instability led to rapid layering of fat in the gastric lumen with accelerated gastric emptying, lower CCK levels, and reduced gallbladder contraction. Manipulation of the acid stability of fat emulsion added to preprocessed foods could maximize satiety signaling and, in turn, help to reduce overconsumption of calories. This could also lead to improved design of slimming products.

A significant proportion of the fat in the modern diet is incorporated within the food structure in the form of surfactant-stabilized lipid emulsions. Examples of this are spreading fats, imitation creams, salad dressings, gravies, sauces, soups, and cream desserts. Little is known about the intragastric behavior of such lipid emulsions and the relationship between this and the mechanisms of satiety.

Recently we have validated MRI methods to study the intragastric behavior of oil-in-water emulsion test meals both in vitro and in vivo (6, 34, 35). MRI represents a unique tool to carry out such investigations because it is a noninvasive, nonionizing method that can noninvasively reveal the spatial distribution of fat in the gastric lumen and the subsequent lipid delivery to the gut. MRI methods have also been used to study the effect of saturated fatty acids on satiation and to investigate the mechanisms underlying postprandial hunger (29). MRI is particularly well suited to the present investigation because the spatial distribution of the fat emulsion can be monitored over the whole meal and during the postprandial interval.

The physical state of a meal is a critical factor influencing satiety and CCK release (42). Early gamma scintigraphy studies using labeled, lipid-phase markers (14, 26, 28) showed that where fat is an integral part of the food, the fat component of the meal is emptied with the solid phase of the meal (16). However, if the fat component is free and liquid at body temperature it can separate from the solid food component and may empty much more slowly than the aqueous phase of the meal (14, 28). Recently several groups have begun to exploit the developments in MRI to describe this process in more detail and have shown that the oil phase floats above the aqueous phase in the gastric fundus and hence empties last (6). The order of ingestion of different meal components may also influence gastric emptying and the intragastric spatial distribution of fat (29). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

CONSUMPTION OF PREPROCESSED foods high in added fat is steadily increasing in the developed countries. Fatty foods have high energy density and palatability but exert a relatively weak effect on satiation (compared calorie per calorie with protein and carbohydrate loads), which may encourage calorie overconsumption (5). This, in turn, may be one important factor contributing to the current epidemic of obesity in the Western population (38). Weight gain management rightly focuses on a healthy balanced diet, sensible portion sizes, and exercise. However, it would be desirable also to be able to maximize the satiating properties of fatty meals themselves. This could help to reduce postprandial hunger and, in turn, snacking, and it could also lead to improved design of slimming products.

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well-established method to gain insights into the spatial distribution of intraluminal contents and to follow gastric emptying (17, 33, 44). Furthermore, MRI has high spatial resolution and can by virtue of its unique sensitivity to changes in the proton environment discriminate well between the water and the fat components of a meal (6, 7, 17, 19, 27, 29, 45, 46).

On the basis of our previous work on fat emulsions, the aim of this study was to investigate whether it would be possible to manipulate the intragastric distribution of fat and hence gastric emptying, CCK levels, gall bladder contraction, and satiety feelings in healthy volunteers by simply modifying the intragastric acid stability of ingested fat emulsions.

MATERIALS AND METHODS

**Oil emulsion test meals.** The volunteers were fed 500 ml of the olive oil-in-water emulsion test meals that we have characterized previously both in vitro and in vivo (34, 35). They have equal fat content (hence equicaloric, 675 kcal) and equal lipid droplet size distributions, but opposite acid stability. Emulsion meal A was acid stable and remained intact when exposed to 1 M hydrochloric acid (a concentration found in gastric secretions), retaining both its emulsion structure and oil droplet dimension distribution. Emulsion meal B was acid unstable and broke rapidly into two distinct phases on the addition of hydrochloric acid, with the oil layer floating above the aqueous phase.

The two fat emulsion test meals were prepared at room temperature by mixing 15% wt/wt olive oil and 2.5% wt/wt surfactant with deionized, sterile water containing trace amounts of sweetener and coffee flavoring in a PB20E Waring blender (Waring, Torrington, CT) for 90 s. The surfactant used was either polyoxyethylene sorbitan monooctenolate Tween 60 (E491) surfactant (Macphie, Glenbervie, UK) for the acid-stable emulsion meal A or sorbitan monooleate Span 80 (E494) surfactant (Esterchem, Leek, UK) for the acid-unstable emulsion meal B. After preparation, the emulsion samples were left to equilibrate for 15 min in a 37°C water bath while being slowly stirred with a laboratory minitrirrer. Our previous studies (34) showed that although both emulsions had the same initial mean oil droplet size (3.6 μm), after acidification the acid-unchable one had no remaining oil droplets with complete separation of oil and water layers whereas the acid-stable emulsion particle size distribution was unchanged.

**Subjects and study design.** Nine healthy male volunteers (age 26 ± 3 yr), with normal body mass index (23.3 ± 0.9 kg/m²), free from serious disease and with no history of gastrointestinal disorders, attended after an overnight fast on two separate experimental morning sessions (7 days apart). An 18GA BD Venflon Pro (Becton Dickinson Infusion Therapy, Helsingborg, Sweden) intravenous cannula was placed in a forearm vein. Each volunteer then drank, within 10 min, 500 ml of one of the two emulsion meals, given in random order. The time when meal ingestion started was defined as time (t) = 0 min. At t = 5 h the subjects ingested a standard 500-ml, 460-kcal soup lunch meal by adding hot water to 100 g of dried vegetable soup (12.2 g fat) (Knorr, Crofter’s thick vegetable soup, Unilever Bestfoods UK) together with 25 g of sugar and a glass of still water. The volunteers’ sense of fullness, appetite, and hunger were monitored hourly. The imaging protocol and timings and satiety questionnaires are described below.

This protocol was approved by the University Medical School Research Ethics Committee, and all volunteers gave informed, written consent before experiments.

**Echo-planar magnetic resonance imaging measurements.** Single-shot echo-planar magnetic resonance (EPI) (27) images were acquired on a whole-body 0.5-T purpose-built EPI scanner equipped with actively shielded gradients and a 50-cm diameter birdcage coil. The in-plane resolution was 3.5 mm × 2.5 mm, and a slice thickness of 1 cm was used throughout the experiments. Each image was acquired in 130 ms using a 128 × 128 matrix and an effective echo time of 40 ms. A transverse rapid multislice set of EPI images was acquired from the heart to the kidneys to visualize the gastric lumen and the gallbladder with a total acquisition time of a few seconds. At intervals, T₁-weighted inversion recovery and T₂-weighted spin-echo images were also acquired on a single slice at the level of the gastric corpus to help visualizing the fat spatial distribution.

Volunteers were asked to hold their breath before each image acquisition to minimize movement. The subjects sat upright between scans, lying down only for the time necessary to acquire the images. The volunteers were trained to lie on the scanner bed and then to sit up without raising the right-hand side of the abdomen. We did this to avoid allowing layered oil to float up to the pylorus, which we have previously demonstrated encourages emptying of fat layers (6), something that would not happen when standing or sitting normally. Padding placed on the scanner bed helped the subjects to keep the left-hand side of the abdomen higher than the right side when being imaged. Volunteers underwent the first EPI scan at baseline, then at 10 min after ingesting the test meals, and after that every 20 min up to 10 h. Scanning was not performed when the volunteers were fed the soup lunch meal. After the midday meal, volume scans were collected every 20 min until the stomach appeared empty.

**Plasma collection and CCK assay analysis.** Thirteen venous blood samples (6.5 ml) were collected by syringe at 30-min intervals for the first 2 h and 60-min intervals afterward up to 10 h. The blood was quickly transferred into chilled blood collection tubes containing 0.3 ml EDTA and 5,000 KIU aprotinin. The samples were cooled in an ice bath immediately. The plasma was readily separated by centrifugation at 4°C and then stored at −70°C until assayed.

The plasma samples were extracted before assay to eliminate nonspecific interference from plasma proteins. One milliliter of plasma was added to 2 ml of 96% ethanol, vortex mixed in a glass tube. The tubes were allowed to stand on bench for 10 min, before centrifugation at 1,700 g for 15 min. The supernatant containing CCK was decanted into another glass tube and evaporated to dryness in vacuum before being redissolved in 1 ml of phosphate buffer. The concentrations of CCK were then measured by RIA with commercially available kits according to the manufacturer’s instructions (EURIA-CCK, Euro-Diagnostica, obtained from Immunodiagnostic Systems, Ids, Tyne and Wear, UK). Briefly, the samples and the standards competed with 125I-CCK-8 sulfate in binding to antibodies of CCK-8 sulfate. The antibody bound with 125I-CCK-8 sulfate was separated from the unbound fraction by using a double-antibody solid phase. The radioactivity of the bound fraction was then measured in a gamma counter.

The minimum detectable concentration for CCK was 0.3 pmol/l of sample with intra- and interassay variations less than 6 and 15%, respectively. The antibody was highly specific, cross reactivity being <0.01% to CCK-(26-33) nonsulfated, CCK-(30-33) and gastrin-17, respectively. The antibody was highly specific, cross reactivity being <0.01% to CCK-(26-33) nonsulfated, CCK-(30-33) and gastrin-17, respectively. The antibody bound with 125I-CCK-8 sulfate was separated from the unbound fraction by using a double-antibody solid phase. The radioactivity of the bound fraction was then measured in a gamma counter.

The subjective feelings of the volunteers’ fullness, hunger, and appetite were assessed by use of self-assessment visual analog scales (24, 47). Before meal ingestion, after meal ingestion, and thereafter hourly until t = 10 h, the volunteers were asked to give numbers between 1 and 10 to indicate how full they felt (1 = “not full,” 10 = “extremely full”), 2) how hungry they felt (1 = “not hungry,” 10 = “extremely hungry”), and 3) how much food they would eat (1 = “nothing,” 10 = “an enormous meal”) at that given time. The satiety scores were then plotted against time for each experiment and areas under the curve (AUC) were calculated and averaged for each meal.

**Data analysis and statistical analysis.** Data are expressed as means ± SE. Measurements of the volume of the gastric contents were carried out by manually tracing a region of interest around the meal within the stomach on each image slice with Analyze software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN)
and summing across the slices to determine the total volume at the
different time points. The surrounding organs and gastrointestinal gas
were easily discriminated and excluded from the region of interest.
The time for half emptying was calculated from the plots of volume
against time. The gallbladder volumes were measured similarly with
Analyze software. The mean gallbladder volumes data were then fitted
to a simple model as previously reported (32).

Test for normality of the data was carried out using Prism 4
(GraphPad Software, San Diego, CA), and statistical analysis was
carried out using SPSS 12 (SPSS, Chicago, IL). Statistical analysis of
related variables was performed using the nonparametric two-tailed
Wilcoxon’s signed-rank test for paired comparisons, since normal
distributions of the data could not be assumed. For the same reason
Spearman’s bivariate analysis was used instead of Pearson’s to assess
correlations between variables.

RESULTS

Experimental procedures and imaging. All nine subjects that
completed the study tolerated the experimental procedures
well. A tenth subject enrolled but withdrew during the first
experiment because of dislike of the taste of the test meal.

The images confirmed that the acid-unstable meal B broke
and layered rapidly in the stomach (Fig. 1). The acid-stable
emulsion meal A remained stable in the stomach, although it
showed some creaming (an increase in the number of oil
droplets in the upper part of the meal) in the gastric lumen. In
a previous study we observed that creaming of such an acid-
stable emulsion meal shows aggregation of droplets without
coalescence (34).

Gastric emptying. Figure 2 shows the average gastric emp-
trying curves for both emulsion test meals. No lag phase in
gastric emptying was observed. The average time to empty half
($T_{1/2}$) of the aqueous phase of the acid-unstable
emulsion meal B, 72 ± 13 min, was significantly faster than that of the
acid-stable emulsion meal A, 171 ± 35 min, Wilcoxon’s $P < 0.008$. The AUC (between $t = 10$ min and $t = 220$ min) for the
emptying of the acid-unstable emulsion meal B (29,200 ±
4,798 ml·min) was significantly smaller than the AUC for the
emptying of the acid-stable emulsion meal A (76,417 ± 8,051
ml·min), $P < 0.008$.

Neither of the test meals induced significant changes in the
gastric emptying of the later standard soup meal given to the
volunteers 5 h later. By that time only an average of 70 ml of
the acid-stable emulsion meal A was still present in the stom-
ach, whereas the stomach appeared empty for the acid-unstable
emulsion meal B. $T_{1/2}$ for the soup meal was 90 ± 7 min when
the volunteers had received meal B in the morning and 77 ± 9
min when the volunteers had received meal A ($P < 0.3$). The
mean areas under these curves were also not significantly
different (64,827 ± 6,210 and 72,460 ± 8,431 ml·min, respec-
tively, $P < 0.3$).

Gallbladder contraction. The changes in mean gallbladder
volumes with time between $t = 0$ min (baseline before eating
the emulsion meal) and $t = 220$ min are shown in Fig. 3. The
gallbladder contracted more following ingestion of the acid-
stable emulsion A than following the acid-unstable meal B (P < 0.05 at t = 130 min and overall P < 0.02 between mean time points).

No significant difference in the gallbladder contraction were detected in the afternoon after the soup lunch meal (P < 0.374).

**CCK circulating plasma levels.** Figure 4 shows the plot of the average CCK circulating plasma levels against time for both the acid-stable and the acid-unstable emulsion test meals. The acid-stable emulsion meal A stimulated the release of more CCK than the acid-unstable emulsion meal B for up to 7 h. The difference is significant at individual time points t = 1, 1.5, and 4 h with P < 0.05 and overall for the whole 10 h experiment with P < 0.001. The integrated area under the CCK curve up to t = 5 h (hence integrated between the emulsion test meal and the lunch soup meal) was significantly higher for meal A than for meal B (1,095 ± 244 and 531 ± 111 pmol·min⁻¹·L⁻¹, respectively, difference P < 0.02).

**Relationship between CCK and gallbladder contraction.**

Increased mean CCK plasma levels were correlated with increasing mean gallbladder contraction (e.g., decreased gallbladder volume) as shown in Fig. 5. Spearman’s rho = 0.86, P < 0.001. A cluster of high CCK-high gallbladder contraction data points can be seen for the acid-stable emulsion meal A. The overall linear regression line is also shown in the figure.

**Satiety.** Figure 6 shows the plot of the volunteers’ mean fullness (Fig. 6A), hunger (Fig. 6B), and appetite (Fig. 6C) scores for the acid-stable emulsion meal A and the acid-unstable emulsion meal B. The volunteers’ integrated AUCs of appetite scores between t = 0 and t = 5 h (up to the soup lunch meal) were significantly lower for the acid-stable emulsion meal A (P < 0.05). The scores for fullness and hunger showed a similar trend for increased satiety to be associated with the acid-stable emulsion meal A, although these differences were not significant (P < 0.074 and P < 0.498, respectively). However, the mean satiety scores for the sense of fullness between t = 0 and t = 5 h were correlated with gastric volumes, Spearman’s rho = 0.945, P < 0.001.

**DISCUSSION**

As an increasing proportion of food is commercially prepared, modifying food production methods to alter the postprandial delivery of fats to the intestine, the response of gut peptides and, ultimately, mechanisms of satiety has potential benefits. With this in mind we hypothesized that altering the intragastric stability of fat emulsions by using different emulsifiers could induce significant changes in the gastric emptying, CCK release, gallbladder contraction, and satiety response.

Using our simple model meals we were able to confirm that, compared with an equicaloric acid-unstable emulsion, the acid-stable emulsion meal A was associated with a much slower rate of emptying, increased levels of circulating CCK, and greater gallbladder contraction. There was a significant decrease in postprandial appetite between t = 0 and t = 5 h for the acid-stable emulsion meal A compared with the acid-unstable meal B. There was a corresponding numerically increased...
fullness and decreased hunger with meal A but this was not statistically significant, probably because of insufficient numbers and the inevitable large variability in such subjective scores. The role of endogenous fat-stimulated CCK release in satiety has been shown in some animal models (11) although in other animal studies CCK levels did not correlate with suppression of sham feeding after intraintestinal infusion of nutrients (9). Our previous work showed that the sense of fullness is proportional to postprandial gastric volumes (33), a feature that we were able to reconfirm in this study.

The mechanism for the differences is uncertain. Emulsions that do not break under acid conditions remain longer in the stomach, provide a larger surface area, and therefore may be subject to more intragastric lipolysis ensuring greater concentrations of free fatty acids reaching the duodenum, which is where fatty acids exert their satiating effect. When the acid-stable emulsion meal A enters the proximal small intestine it is still emulsified when it meets bile and pancreatic enzymes, which will further increase the availability of free fatty acid. By contrast, the acid-unstable emulsion meal B coalesces very rapidly in the stomach, dramatically reducing its surface area, which is a critical factor in determining the rate of lipolysis. Furthermore, the floating fat layer is emptied after the underlying water phase and hence delayed compared with the acid-stable emulsion meal A. The coalesced fat layer from the acid-unstable emulsion meal B has a much reduced interface-to-volume ratio compared with the acid-stable emulsion and hence a much reduced lipolysis rate. There may be some degree of reemulsification induced by shearing forces at the pylorus, but this is unlikely to be very efficient and any newly formed droplets would rapidly coalesce again, at least until the pH returns to neutral. Since both surfactants are sorbitol-fatty acid esters, they will be well digested and absorbed through deesterification at the brush border and both will contribute similar amounts of fatty acids and energy.

The net effect of these influences is that the acid-stable emulsion meal A is likely to deliver greater concentrations of free fatty acids more rapidly to the small intestinal fatty acid receptors than the acid-unstable meal B. Free fatty acid in the upper small intestine releases a range of neuropeptides that act via vagal afferents to alter gastric emptying and eating behavior. The best known is CCK, released from CCK-containing enteroendocrine cells whose concentration is maximal proximally. Peptide YY and glucagon-like peptide-1 are other peptides, located more distally, released by nutrients including fat, infusion of which, like CCK, inhibits gastric emptying and feeding (1, 39). The reduced CCK release noted with the acid-unstable meal B likely reflects both the delay in emptying of fat and, possibly, also less active proximal lipolysis, since unemulsified fat is much less efficient in stimulating CCK release (30). If hydrolysis of fat is delayed and occurs in the distal small intestine, then it will be less effective in releasing CCK since few CCK cells are found in the distal small bowel.

Increased CCK release from the acid-stable emulsion meal A was reflected by an associated increase in gallbladder contraction. Such association would be expected (21) and in this case further supports the hypothesis that the acid-unstable meal B delivered fat to the duodenum that was mostly unemulsified and hence unable to provide sufficient fatty acids to stimulate CCK release (30). Preliminary data (unpublished) from our laboratory using the same emulsions containing $^{13}$C-labeled

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**Fig. 6.** Mean self-assessment satiety scores for the acid-stable emulsion meal A (●) and acid-unstable emulsion meal B (□). Graphs show scores for the sense of fullness (A), hunger (B), and appetite (C). The areas under the curve (AUC) of appetite scores between $t = 0$ and the soup lunch meal at $t = 5$ h were significantly lower for the acid-stable emulsion meal A ($P < 0.05$).
palmitic acid tracer indicated that the overall systemic delivery of fat over a 12-h study was similar, suggesting that significant fat malabsorption did not result from the changes in emulsifiers.

The difference in the fat emulsion test meals received in the morning did not have a significant effect on the gastric emptying of the lunch soup meal nor on the corresponding gallbladder contraction.

This study had some limitations. One was the artificiality of the two oil emulsion test meals, which had low palatability. Because we were investigating mechanisms, the test meals and the emulsifiers that were chosen were extremes. However, there are many different emulsifiers commonly used in food preparation with better palatability that could now be evaluated. The second limitation is represented by the need for the subjects to lie down for short intervals in the MRI scanner, which is not a normal postprandial position and might have disturbed the normal intragastric distribution of fat. We minimized the impact of posture by reducing the time that the volunteers spent in the scanner and training them to lie down and sit up on the scanner bed in a way that would avoid layered fat entering the pylorus. By keeping the left side uppermost, fat that layered was retained in the fundus and not allowed to float toward the pylorus, which could have caused the floating fat in meal B to enter the duodenum and delay gastric emptying as we have previously shown (6). This would have reduced the differences between meals A and B; hence the significant difference that we did observe suggests that we were successful in this respect.

Finally, differences in response to the two meals may have been influenced by the different emulsifiers. Each meal contained 75 g of olive oil, which would have provided 54 g of C18:1 and 2.5% C18:0. The monostearate emulsifier (stable) would add ~10 g of stearate (C18:0) and the monoooleate emulsifier (unstable) ~10 g of oleate (C18:1). Thus the stable meal would contain 54 g C18:1 and 12.5 g C18:0 and the unstable meal 64 g of C18:1 and 2.5 g C18:0. Recent studies show no difference in gastric emptying of saturated fatty acid meals vs. oleic acid, indicating that without the difference in physical characteristics of the emulsions it is unlikely that such minor changes in fat composition alone would produce the marked changes in gastric emptying that we observed (41).

In conclusion, this study shows that manipulation of the intragastric acid stability of fat emulsions can significantly alter gastric emptying, CCK release, and gallbladder contraction. We clearly show that the physical distribution of fat in the stomach should be taken into account when comparing the gastrointestinal and hormonal response to feeding different fatty meals.

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