Adaptation to high-fat diet accelerates emptying of fat but not carbohydrate test meals in humans

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Castiglione, K. E., N. W. Read, and S. J. French. Adaptation to high-fat diet accelerates emptying of fat but not carbohydrate test meals in humans. Am J Physiol Regulatory Integrative Comp Physiol 282: R366–R371, 2002; 10.1152/ajpregu.00190.2001.—Previous work has shown that the gastric emptying rate in animals and humans can adapt due to previous dietary intake. The present study investigated whether adaptation in gastric emptying rate due to consumption of a high-fat diet (HFD) is nutrient specific in humans. Gastric emptying of high-fat and high-carbohydrate test meals was measured (using gamma scintigraphy) before and after consumption of an HFD for 14 days in eight free-living male volunteers. Visual analog ratings of appetite were recorded throughout each test. There was no effect of HFD on any parameters of gastric emptying rate (lag phase, half-emptying time, and linear emptying rate) measured for carbohydrate test meals. HFD led to an acceleration of the linear emptying rate of the high-fat test meal (0.36 vs. 0.47%/min; P < 0.05). All meals reduced appetite ratings, but there were no differences between tests. These results support our previous findings of accelerated gastric emptying of high-fat test meals following an HFD and show that these changes appear to be nutrient specific, confirming recent studies in rats.

Previous work from our department has shown that human subjects display an adaptive change in the emptying rate of nutrients from the stomach due to previous dietary macronutrient intake. Consumption of a high-fat diet (HFD) for a 2-wk period led to an acceleration in the gastric emptying rate of high-fat test meals (11). Short-term supplementation of the diet with glucose (400 g for 3 days) in humans led to an increase in the gastric emptying rate of a glucose test meal, whereas the emptying rate of a protein drink was unchanged (12). Further work has shown that plasma levels of the gastrointestinal hormone CCK, a potent inhibitor of gastric emptying, are raised after ingestion of a fatty test meal following an HFD (14). Because this raised CCK level was not associated with a reduction of gastric emptying, the combined data suggest that subjects may be desensitized to the effects of CCK following a period of high-fat consumption.

There is evidence from studies in rats that adaptive changes in gastric emptying rate are nutrient specific. A high-protein diet has been shown to lead to an acceleration of emptying of a peptone meal but not of glucose or methylcellulose (29). Covasa and Ritter (9) recently demonstrated in rats that the delay in gastric emptying of saline caused by both intestinal oleate infusion and intraperitoneal CCK is attenuated by prior consumption of an HFD (54% energy from fat), whereas the delay in gastric emptying caused by intestinal infusion of maltotriose was unaffected (10). The same authors also demonstrated reduced sensitivity to the satiating effects of intestinal oleate following maintenance on an HFD (34 and 54% energy from fat) in rats.

A number of other digestive functions has been shown to adapt to changes in dietary macronutrient composition. High-fat intake leads to an increase in the secretion of pancreatic lipase (27, 31) and an increased capacity for the absorption of triacylglycerol (TAG) (1, 28, 30). Considering the close relationship between dietary fat intake and total energy intake and obesity in humans (3, 4), understanding the influence of dietary fat intake on the digestive processes relating to fat and subsequent regulation of food intake is of importance. We previously showed that food intake is increased following an HFD (14). As gastric distension is a potent signal to inhibit feeding (15), this may result from the previously observed acceleration in gastric emptying and/or a possible desensitization to released CCK; as good evidence exists that CCK can act directly as a satiety hormone (2). Furthermore, recent evidence suggests that elevated postprandial TAG concentrations are associated with a greater risk of atherosclerosis than elevated fasting concentrations (20, 25). Thus increased lipid absorption due to adaptation to an HFD could lead to an increased risk of atherosclerosis and coronary artery disease.

Currently, there is no evidence in humans to determine whether dietary adaptation of gastric emptying following an HFD is nutrient specific. If emptying of carbohydrates is also accelerated, this may have important implications for postprandial glycemic and in-
sulinemic responses in individuals already at risk for weight gain and atherogenesis. Therefore, the aim of the present study was to investigate the gastric emptying rates of high-fat and high-carbohydrate test meals following consumption of an HFD.

METHODS

Subjects

Studies were carried out on eight healthy, free-living male volunteers between the ages of 19 and 26 yr and within the normal range for body mass index (BMI) (23.0 ± 0.7 kg/m²). Only subjects who were in good health, between the ages of 18 and 35 yr, with a BMI of between 20 and 25, nonsmokers, and nonrestrained were recruited. Dietary fat intake was assessed before the study by completion of a 6-day weighed intake diary that was analyzed using the Foodbase dietary analysis programme (Institute of Brain Chemistry and Human Nutrition, Queen Elizabeth Hospital, London, UK). Subjects were recruited into the study based on an intake of dietary fat between 30 and 40% of total calories ingested.

Subjects had a mean restraint score of 3.1 (±0.7) as measured by the Three-Factor Eating Questionnaire (32), indicating that subjects had a low level of dietary restraint. This questionnaire measures three factors associated with abnormal eating behavior: disinhibition (loss of control of eating and possible binging behavior), restraint (conscious control over food intake/dieting behavior), and abnormal hunger. A restraint score of 10 indicates that a person has a considerable level of dietary restraint and was chosen as a cut-off point for the rejection of subjects in this study. In addition, subjects were questioned to ensure they liked the test meal of strawberry milkshake. A novel liquid test meal was chosen to make it easier to manipulate the energy and macronutrient content by the addition of fat in the form of cream or carbohydrate in the form of maltodextrin.

Protocol

The dietary protocol consisted of a “run-in” period during which time subjects were requested to consume their normal diet, i.e., to consume foods they would normally eat from day to day and to avoid bingeing. After this, subjects consumed a high-calorie, high-fat diet for 14 days. The diet provided 55% energy from fat and an energy intake of 133% of requirement based on prior nutritional analysis and activity levels (mean = 17.48 MJ; range = 15.65–19.73 MJ). Subjects took part in four laboratory sessions: two sessions in the run-in week, one on day 12 of the dietary intervention period, and one session on the day after (day 15) the intervention period (Fig. 1). On each occasion, subjects were asked to consume a test meal of strawberry milkshake labeled with 1.5 MBq Technetium tin colloid. Subjects received high-carbohydrate and high-fat test meals before and after the diet in a randomized order with the subject blind to the composition of the test meal. The composition of the high-fat test meal was 55% energy from fat, 32% energy from carbohydrates, and 13% energy from protein, and it consisted of 354 g Safeway strawberry milkshake (Safeway, Hayes, Middlesex, UK) and 46 g Safeway double cream. The composition of the high-carbohydrate test meal was 25% energy from fat, 62% energy from carbohydrates, and 13% energy from protein, and it consisted of 348 g Safeway strawberry milkshake, 38 g maltodextrin (Polycal, Cow and Gate Nutricia, Towbridge, Wiltshire, UK), and 14 g double cream. The ingredients for each test meal were blended together for 30 s using a handblender (Braun handblender MR555 CA, Braun, Isleworth, Middlesex, UK) immediately before labeling with the radioisotope.

Subjects were required to fast overnight (from 2100 on the night before the study) and to arrive at the center at 0930 on the morning of the test day. On arrival, measurements of weight and percentage of body fat were made. Subjects were weighed on a digital foot balance (Soehnle, Murrhardt, Germany) and had their height measured using a stadiometer. Body fat percentage was determined using the bioelectrical impedance technique (Bodystat 1500, Bodystat, Douglas, Isle of Man, UK).

Analysis of gastric emptying rate. Subjects were asked to sit upright against a posteriorly positioned gamma camera. At ~1000, subjects were presented with 400 g of test meal and asked to consume it within 5 min. Measurement of gastric emptying began as soon as the subject started to consume the test meal.

Sequential images of the abdominal distribution of radioactivity were collected over 180 min (at 1-min intervals for the first 20 min, at 2-min intervals for the next 40 min, and at 5-min intervals for the remaining 2 h) and stored on a dedicated microcomputer. At the end of each study, the images were corrected for gamma emission attenuation by the subject’s tissues as the stomach contents moved from the more posterior location of the fundus to the more anterior position of the antrum, using a technique previously described by Collins et al. (7). Subjects were required to drink 200 ml of water containing a further 1 MBq Technetium tin colloid while they were seated with their left side against the collimator head of the gamma camera to acquire a static left lateral image of the stomach. The stored images of distribution of the radioactivity were redisplayed, and an integrated image of the early frames was used to identify and outline the position of the stomach. The counts within this region were then calculated for each frame throughout the study and corrected for the decay rate of the isotope and tissue attenuation. The counts were expressed as a percentage of the total radioactivity derived from the maximum counts in the region of interest shortly after ingestion, and these were used to construct the profile of the gastric emptying. Half-emptying time (T½), lag phase, and percentage emptied per minute were calculated from the profile of gastric emptying generated by the computer. T½ was calculated as the time it took for the stomach to empty 50% of its contents. The lag phase was determined visually as the frame preceding that in which activity appeared in the proximal small intestine (8, 18). Percentage of meal emptied per minute was calculated by drawing the line of best fit through the linear phase of emptying for individual curves. All studies were coded, and analyses were made blind of particular treatment conditions.

Analysis of visual analog ratings. During the study, subjects were asked to rate a range of subjective feelings including hunger, fullness, desire to eat, and how much food they felt they could eat at that time (prospective consumption) on 100-mm visual analog scales. These scales are widely used in appetite measurement (16). Subjects also rated other feelings of general well-being such as nausea and dizziness. Subjects placed a vertical mark on the scale to indicate their response...
to the particular question at that time. Scales were anchored with the descriptors “not at all” at the left-hand side and “extremely” at the right-hand side or “none” and “very large amount” for prospective consumption ratings. For example, subjects were asked to rate their hunger on a scale from “not at all” to “extremely” in response to the statement “I feel hungry.” Questionnaires were completed immediately before presentation of the test meal ($t = 0$), every 15 min for the first hour of the study, and then every half hour until the end of the experiment. The position on the scale was measured in millimeters from the left-hand side to give a numerical score.

**Statistical Analysis**

**Body weight and composition.** Student’s paired $t$-tests were used to detect any differences in body weight or body composition before and after consumption of the HFD.

**Gastric emptying.** Gastric emptying profiles were analyzed using two-way ANOVA, with condition and time as within-subject factors. One-way ANOVA was used to detect any significant differences in T1/2, lag phase, and percentage of the meal emptied per minute during the linear phase. Where differences between treatments were observed, post hoc analysis was carried out using Student-Newman-Keuls tests.

**Appetite ratings.** Repeated-measures ANOVA (2-way ANOVA) was used to test for significant differences in ratings of hunger, fullness, prospective consumption, and nausea with time and condition as within-subject factors.

**RESULTS**

**Body Composition**

Consumption of the HFD for 2 wk led to a small, non-significant increase in body weight [$76.7 \pm 3.4$ vs. $77.2 \pm 3.6$, $t(7) = -1.66$, $P = 0.141$] and percentage of body fat [$13.7 \pm 1.08$ vs. $14.2 \pm 1.22$, $t(7) = -1.67$, $P = 0.139$].

**Gastric Emptying**

ANOVA indicated there was no significant overall difference in gastric emptying profiles on different occasions [$F(3,21) = 0.59$, $P = 0.628$]; however, analysis revealed a significant condition by time interaction [$F(189;1,134) = 1.67$, $P = 0.000$; Fig. 2]. Initially, a small amount of all meals emptied relatively rapidly; this was followed by a period of little emptying before drinks began to empty in an approximately linear manner.

There was no significant difference in T1/2 between conditions [$F(3,21) = 0.87$, $P = 0.475$; Fig. 3], although it can be seen that there is a trend for faster half-emptying of the high-fat test meal after the HFD [$162 (\pm 21.6)$ vs. $138.6 (\pm 11.3)$ min]. Half-emptying rate of the high-carbohydrate test meal was similar before and after the diet [$161.3 (\pm 20.5)$ vs. $165.0 (\pm 13.2)$ min]. Test meals emptied after a short lag phase on all occasions. The high-carbohydrate test meals before and after the diet and the high-fat test meal before the diet all had a lag phase of $\sim 6$ min [$6.3 (\pm 0.9)$, $6.0 (\pm 0.8)$, and $6.4 (\pm 0.8)$ min, respectively]. The high-fat test meal had a slightly shorter lag phase after the diet compared with other conditions [$4.2 (\pm 0.4)$ min]. Analysis using ANOVA revealed that this difference was not significant [$F(3,21) = 2.42$, $P = 0.095$; Fig. 3]. In addition, it was shown that the slope of emptying of the test meals during the linear portion of the profile was significantly different on the four occasions [$F(3,21) = 4.86$, $P = 0.01$; Fig. 3]. Post hoc tests indicated that emptying of the high-fat test meal was significantly faster following the diet rather than before the diet [$0.47 (\pm 0.03)$ vs. $0.36 (\pm 0.05)$%/min, respectively] such that following the diet, the slope of emptying was similar to that for high-carbohydrate meals. There was no difference in the emptying rate of carbohydrate meals before and after the diet [$0.50 (\pm 0.07)$ vs. $0.56 (\pm 0.07)$%/min].

**Appetite Ratings**

Similar feelings of hunger and fullness were reported at baseline on all occasions (Fig. 4). Other measures of appetite (desire to eat and prospective consumption) showed similar patterns to those described below.

Ratings of hunger were moderately suppressed (by $\sim 15$ mm) immediately after consumption of high-fat and high-carbohydrate test meals. Analysis showed there was no significant difference in hunger ratings between occasions [$F(3,21) = 0.19$, $P = 0.902$]. As expected, hunger ratings changed significantly over time [$F(8,56) = 6.88$, $P = 0.000$]. Fullness ratings were increased by consumption of the test meals, but they returned to baseline levels by the end of the experiment. ANOVA indicated that there was no significant effect of condition on fullness ratings [$F(3,21) = 0.59$, $P = 0.631$]. As expected, ratings changed significantly over time [$F(8,56) = 7.18$, $P = 0.000$].

Feelings of nausea were not reported during any of the conditions. Analysis confirmed that ratings did not
differ significantly between conditions \( F(3,21) = 1.84, P = 0.172 \).

DISCUSSION

The results of this study show that consumption of an HFD for 2 wk produces a significant acceleration of gastric emptying during the linear phase of emptying of a high-fat test meal and a trend toward an acceleration in the lag phase following HFD. In contrast, there were no detectable changes in the pattern of emptying of the high-carbohydrate test meal. To our knowledge, this is the first demonstration of a nutrient-specific adaptation to gastric emptying of fat in humans. There was no effect of diet in this study on appetite responses to the test meals given. Analysis of the overall emptying curve does not demonstrate a significant treatment effect; this probably relates to the extended plateau in emptying following initial emptying and before linear emptying.

This study confirms previous findings in humans that an HFD leads to an acceleration of the gastric emptying rate of fatty test meals (11). Furthermore, these results extend to humans the recent findings of a fat-specific acceleration in emptying in rats due to an HFD (10).

Feedback mechanisms due to the presence of nutrients in the small intestine exert a powerful influence on the gastric emptying rate (23). Furthermore, the length of intestine exposed to nutrients has previously been shown to influence the inhibitory effects on gastric emptying (21, 22). Thus one possible explanation for the present results may relate to changes in the

Fig. 3. Effect of a high-fat diet on the half-emptying time, lag phase, and percent emptied per minute of high-fat and Cho test meals. Data are means ± SE, \( n = 8 \). *\( P < 0.05 \) vs. pre-diet condition.

Fig. 4. Effect of a high-fat diet on appetite ratings after consumption of high-fat and Cho test meals.
capacity of the small intestine to absorb fat. It has previously been shown that the rate of absorption of fat is increased following a period of consumption of an HFD (1, 28, 30). This may be secondary to an increase in the production of pancreatic lipase (31). Therefore, increased clearance of TAG from the small intestine could reduce the time or area of exposure to the mucosal surface leading to a reduction in the inhibitory signals on gastric emptying. Previous work suggested that the intestinal feedback due to nutrients is particularly involved in the reduction of the linear portion of emptying of energy-containing liquids (5). Thus the observation in the present study that the rate of the linear emptying portion was significantly increased following HFD consumption supports the idea that a change in interaction between nutrients and the intestinal mucosa is involved in this adaptive process.

CCK is an important feedback signal in the inhibition of gastric emptying due to the presence of fats in the small intestine (26, 33). Our previous studies measuring plasma CCK responses due to a high-fat test meal following an HFD have shown an increase in circulating levels following the diet (14). This may either represent a desensitization of receptors to the release of CCK (as gastric emptying is also accelerated) or it may reflect an effect secondary to the acceleration of gastric emptying, i.e., an effect mediated by the increased delivery rate of nutrients to the small intestine. We recently attempted to investigate this by measuring plasma CCK levels due to a controlled intestinal infusion of fat before and after an HFD (Castiglione KE and French SJ, unpublished observations). This study showed a trend toward an attenuation of the plasma CCK response following the HFD [424 ± 57, 447 ± 94, 265 ± 29, 120 min/pmol; area under CCK curve 0, 7, 14 days HFD; \( F(2,10) = 3.21; P = 0.084 \)] that could also be explained by an increase in the rate of absorption of fat, resulting in reduced exposure of CCK-releasing cells to fat. Thus changes in CCK release due to accelerated fat absorption (although not measured in the present study) may be involved in the adaptive process observed.

If a change in the absorption rate of TAG and/or a change in the release of or receptor sensitivity to CCK are involved in the observed effects of HFD on the emptying rate of fats, these effects may also explain the lack of effect on the emptying rate of carbohydrates. Intestinal carbohydrates are a weak signal for the release of CCK in mammals (17, 24). Thus it is unlikely that a change in the sensitivity of feedback mechanisms on gastric emptying relating to fat absorption or CCK response would influence the emptying rate of carbohydrates. The effects of HFD on the absorption rate of carbohydrates from the small intestine have not, however, been tested at present.

All test meals produced a similar reduction in hunger and induction of fullness. These findings do not correspond with our previously published work showing that food intake measured by food diary over a 14-day period was increased following an HFD (14). It may be that changes are too subtle to be observed with the relatively crude method of visual analog rating, especially at a single meal within the novel laboratory environment. We previously showed that manipulations that do not cause an observable change in visual analog ratings of appetite can still affect meal intake at a subsequent test meal (6, 13). Therefore, in future studies, the measurement of food intake subsequent to the dietary and preload manipulations may provide further information regarding the interaction between gastric emptying rate and appetite. The purpose of the present study, however, was to determine the emptying over a long period (3 h), and hence the incorporation of an ad libitum test meal was not possible.

It is now widely accepted that HFDs promote the development of obesity and its increased risks of diabetes, cancer, and atherosclerosis (e.g., Ref. 4). Recently, it has been suggested that the degree of postprandial lipemia is a better predictor of the degree of atherogenicity than fasting TAG levels (20, 25). Evidence suggests that the increased risk of atherosclerosis due to elevated postprandial TAG levels is due to the delayed clearance of potentially atherogenic chylomicrons and chylomicron remnants (see Ref. 19 for review). Thus adaptation to an HFD may be an important factor in this increased risk due to an increase in the rate of delivery and absorption of fats and a possible reduction in the feedback inhibition of food intake as shown in this and our previous studies (11, 14). The likely consequences of these adaptations are an increase in both the amount and rate of entry of dietary fat as chylomicrons into the circulation, resulting in increased competition for their clearance from the circulation.

**Perspectives**

Obesity is a complex disease with multiple causes; genetic, metabolic, behavioral, dietary, and physiological factors have all been implicated in its development. Consumption of HFDs has been strongly implicated in the etiology of obesity, and it is possible that HFD may lead to gastrointestinal and physiological adaptations that might serve to increase food intake and therefore predispose to weight gain. We demonstrated an acceleration in the gastric emptying rate of a fatty test meal following consumption of an HFD for 2 wk. Previous investigations demonstrated an increase in the absorptive capacity for fat from the intestine after consumption of an HFD (1, 28, 30). These adaptations may lead to reduced feedback inhibition on feeding, resulting in increased food intake and storage of fat and therefore predispose to weight gain and obesity when an HFD is consumed. The present study investigated the effects of the consumption of an HFD over a relatively short period of 2 wk. Whether the observed adaptation in gastric emptying would persist, undergo further adaptation, or readapt if an HFD was consumed over a prolonged period of time requires further investigation. In contrast to HFDs, high-carbohydrate diets are less energy dense, are more satiating, and promote weight loss. Current dietary advice to switch to a high-carbo-
hydrate, low-fat diet to aid weight reduction may have additional benefits suggested by the current findings that carbohydrates appear to be resistant to the adaptive changes observed due to an HFD.

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REFERENCES