Plasma cholecystokinin is associated with subjective measures of satiety in women[1–3]

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ABSTRACT

Background: Cholecystokinin is associated with satiety. Fat stimulates cholecystokinin release, and fiber appears to prolong cholecystokinin elevation during the alimentary period.

Objective: We tested whether adding fiber or fat to a low-fat, low-fiber meal increases cholecystokinin release and enhances subjective measures of satiety and whether the cholecystokinin response correlates with subjective measures of satiety.

Design: Three isoenergetic breakfast meals were tested in a randomized crossover design: low fiber, low fat; high fiber, low fat; and low fiber, high fat. Blood samples were drawn from fasted subjects (7 men and 8 women) before and at different time points after test meal consumption for 6 h. Plasma was analyzed for cholecystokinin, insulin, glucose, and triacylglycerols. Visual analogue scales were used to assess subjects' hunger, desire to eat, fullness, and prospective consumption.

Results: In the women, the meals higher in fiber or in fat resulted in greater feelings of satiety and in significantly higher cholecystokinin responses than did the low-fat, low-fiber meal. In the men, the increase in cholecystokinin concentration did not differ between meals, but the 2 low-fat meals elicited a greater feeling of satiety than did the high-fat meal. The insulin response was significantly higher for the low-fiber, low-fat meal than for the other 2 meals, and the triacylglycerol response was greatest for the high-fat, low-fiber meal.

Conclusion: In women, the feeling of satiety caused by cholecystokinin release is enhanced by increasing either the fiber or fat content of a low-fat, low-fiber meal. *Am J Clin Nutr* 2002;76:659–67.

KEY WORDS Fiber, dietary fat, insulin, cholecystokinin, triacylglycerol, women, men, satiety

INTRODUCTION

Dietary fiber includes plant carbohydrates that are not digested by digestive enzymes in the mammalian small intestine. Within the small intestine, polysaccharides such as pectins, gums, and β-glucans increase the viscosity of the contents. An increase in viscosity has been associated with slowing the rate and altering the site of lipid and carbohydrate absorption. These alterations have been associated with the plasma cholesterol–lowering ability and reduced glycemic effects of viscous polysaccharides (1, 2).

Replacing fat energy with carbohydrate energy in the diet has been shown under certain conditions to reduce energy intake (3–5). Several mechanisms have been proposed for this effect, including an increase in the volume of food associated with high-carbohydrate diets, which creates a greater feeling of gastric fullness, changes in palatability, or both, resulting in a reduced desire to eat. Fiber, as a typical constituent of high-carbohydrate foods, could act through both of these mechanisms to reduce energy intake. In addition, by altering the rate of digestion and absorption, fiber may have physiologic effects that influence the regulation of food intake when low-fat, high-carbohydrate, high-fiber foods are consumed, such as increasing the time that dietary fat is present in the intestine. Prolonging the time for intraluminal presence of fat has been shown to enhance satiety. Rats infused intestinally with equivalent amounts of fat at a slow rate consumed less energy per day, had longer between-meal intervals, and gained less weight over a 2-wk period than after infusion with fat at a more rapid rate (6). French and Read (7) suggest similar associations between satiety and intestinal lipid exposure to intestinal chemoreceptors in humans.

Cholecystokinin is a hormone released from small intestine mucosal cells in response to meals that contain fat and has been implicated as mediator of fat-induced satiety (8). Slower disappearance of lipid from the small intestine due to fiber may enhance the time for the release of cholecystokinin during the alimentary period and contribute to the satiating effect of high-fiber meals (1, 2). Consumption of barley, which contains viscous polysaccharides, resulted in an enhanced cholecystokinin response to low-fat test meals, and consumption of beans as a source of fiber doubled the meal-related cholecystokinin response (9, 10).

The present study was designed to test the hypothesis that the effect of a low-fat meal on satiety can be enhanced by the incorporation of fibers that delay the digestion and absorption of dietary fat. Our objective was to determine whether the incorporation of foods high in fiber into a low-fat meal would enhance its postmeal satiety effects, whether a low-fat meal that was high in fiber would induce a postmeal satiety response that was not different from that of an energy-equivalent high-fat meal, and whether the subjective satiety responses to meals varying in fiber and fat content are related to the plasma cholecystokinin response, a mediator of fat-induced satiety.

TABLE 1
Test breakfast composition[1]

	LFB-LF meal		HFB-LF meal		LFB-HF meal	
	Women	Men	Women	Men	Women	Men
Egg white (g)[2]	65	85	30	35	65	85
Egg yolk (g)	14	17	12	15	14	18
Sausage (g)[3]	25	30	—	—	19	25
English muffin (g)[4]	20	28	—	—	43	56
Wheat bread (g)[4]	—	—	38	50	—	—
Margarine (corn) (g)	10	13	—	—	5	7
Peanut butter (g)	—	—	15	20	—	—
Jelly (g)	8	10	—	—	9	12
Cereal (g)[5]	80	100	52, 19	68, 25	65	85
Milk (g)[6]	300	400	370	490	264, 45	347, 60
Banana (g)	80	100	—	—	—	—
Apple (g)	—	—	167	220	—	—
Dried fruit (g)[7]	—	—	27, 28	35, 38	—	—
Apple juice (g)	65	90	—	—	—	—
Water (g)	333	327	242	204	471	505
Total weight (g)	1000	1200	1000	1200	1000	1200
Protein (g)	32	42	33	43	32	41
Carbohydrate (g)	128	166	131	172	93	122
Fat (g)	16	20	18	23	31	40
Fiber (g/4.2 MJ)	7	7	20	20	8	8
Energy density (MJ/g)	0.003	0.004	0.003	0.004	0.003	0.004
Solid-liquid food weight ratio	0.43	0.49	0.28	0.31	0.28	0.32

[1] Test meal analysis computed by NUTRITIONIST V (version 1.7; First Data Bank, San Bruno, CA). LFB-LF, low fiber, low fat; HFB-LF, high fiber, low fat; LFB-HF, low fiber, high fat.

[2] Precooked (hard boiled) and separated for measurement.

[3] Precooked: LFB-LF, turkey sausage; LFB-HF, pork sausage.

[4] Lightly toasted.

[5] LFB-LF, corn flakes; HFB-LF, oatmeal and oat bran; LFB-HF, granola.

[6] LFB-LF, nonfat; HFB-LF, non-fat; LFB-HF, nonfat and coconut milk.

[7] HFB-LF: raisins and pears.

SUBJECTS AND METHODS

Subjects

The study was approved by the Human Subjects Research Committee of the University of California, Davis (protocol no. 95-508). Participants were recruited through newspapers and posters in the Davis and Sacramento area. Candidates who had any food allergies or intolerances, were currently modifying diet or exercise patterns to gain or lose weight, were excessive exercisers or trained athletes, or were taking any medications that would affect appetite were excluded. Potential participants were invited to attend an information seminar to learn more about the time and effort required, to confirm self-reported weight and height measures for calculation of body mass index (in kg/m^2), and to complete questionnaires related to diet, exercise, and lifestyle habits. Sixteen subjects (8 men and 8 women) were recruited for the study; they had body mass indexes of 22–28, were 20–50 y of age, were moderate to light exercisers, consumed diets with an average dietary fat intake of 30–35% of total energy, and were able to meet the time and effort requirements. Before the beginning of the experimental phase of the study, the study participants were individually trained to keep detailed scale-weighed food records and were acquainted with the study procedures as well as the food items to be served. This prestudy information and training session was required and served as a means of reducing potential nervousness or anxiety on the first study day.

Food records and background diets

Participants were trained to keep 24-h detailed scale-weighed food records for 3 d during each week of the study; these days included days 3 and 1 before a test day and the day after a test day. Food records were collected weekly and analyzed with NUTRITIONIST V (version 1.7; First Data Bank, San Bruno, CA) to determine the average daily energy, macronutrient, and fiber intakes of the subjects. The dietary information was used to monitor food patterns during the study. In addition, half-day food records were kept on the day of each experiment, which reflected everything the subjects consumed after the 6-h study period until midnight. The half-day food records were analyzed to explore compensatory changes in food intake after each test meal.

Test breakfast meals

Three isoenergetic breakfast meals that differed in fat and fiber content were used as test meals in the study. The control meal was low in fiber and fat (LFB-LF) and contained 19% of energy from fat, 17% of energy from protein, 64% of energy from carbohydrate, and 7 g dietary fiber/4.2 MJ. The meal with added fiber (HFB-LF) was similar to the control meal in energy and macronutrient composition but contained 20 g fiber/4.2 MJ. The third meal (LFB-HF) had a low fiber content similar to that of the control meal but was higher in energy from fat (36%) and lower in energy from carbohydrate (47%); the amount of energy from protein was similar to that of the LFB-LF meal. All meals were prepared with commercially available foods to contain approximately one-third of the average daily energy intake of the men (4.1 MJ) and the women (3.2 MJ). The test meals included foods such as breakfast cereals, milk, toast, margarine, jelly, fresh fruit, dried fruit, and juice (**Table 1**). Each meal was accompanied by water, which varied in volume depending on the weight of the meal being served

(Table 1). Meals were considered similar in palatability and were consumed easily by all subjects except in one case: one man had difficulty consuming all of the high-fiber meal in the time allotted. He was excluded from the data analysis for noncompliance with the study guidelines.

Subjective satiety measures

Visual analogue scale (VAS) booklets were provided to each subject to assess appetite and satiety relative to the 3 test meals. VAS booklets were completed immediately before the test breakfast and then at 20, 40, 60, 90, 120, 180, 240, 300, and 360 min thereafter. Participants rated their hunger, fullness, and desire to eat and how much they thought they could eat on 100-mm line scales. Questions such as "How hungry do you feel right now?" or "How strong is your desire to eat right now?" preceded a 100-mm line anchored by opposing phrases such as "not at all hungry" and "extremely hungry" or "very weak" and "very strong." Other anchors consisted of the phrases "not at all full" and "extremely full" or "a large amount" and "nothing at all" or "very pleasant" and "not at all pleasant" to assess fullness, prospective consumption, and meal likes or dislikes. In addition to the VAS, participants marked a checklist of the types of foods they would like to eat, independent of availability. Food items were listed that varied in fat and carbohydrate content as well as in categories of sweet or savory. This assessment was intended to provide a measure of the subjects' motivation to eat certain types of foods that differed in basic flavor and macronutrient composition at each time postprandially. The use and value of these scales for assessing motivation to eat and food preference were reported previously (11, 12).

Biochemical measures

Blood was drawn before (ie, fasting sample) and at specific time points after consumption of each test meal (ie, 20, 40, 60, 90, 120, 180, 240, 300, and 360 min). Blood samples were collected in EDTA-coated evacuated tubes and immediately cooled in ice and transferred to a tabletop centrifuge for separation of plasma and red blood cells. Plasma was obtained by spinning samples at $2000 \times g$ for 15 min at 23 °C. Aliquots (22 mL) of plasma were extracted onto Sep-Pak cartridges (Waters Corporation, Milford, MA) containing octadecylsilysilica and frozen at -70 °C for determination of cholecystokinin concentrations by radioimmunoassay. Another portion (2 mL) of plasma was stored in microcentrifuge tubes and frozen at -20 °C for subsequent analysis of glucose, insulin, and triacylglycerol concentrations.

Plasma cholecystokinin concentrations were measured by radioimmunoassay with the use of the highly specific and selective antibody Ab-92128 (a gift from Jens Rehfeld, Rigshospitalet, Copenhagen) (13). Briefly, according to the method of Rehfeld, plasma was eluted from Sep-Pak cartridges and evaporated to dryness by vacuum centrifuge at 1725 rpm for 14 h at ambient temperature (22–25 °C) (SpeedVac Concentrator SVC200H, Savant Instruments, Farmingdale, NY). Samples were incubated with [125]I Bolton-Hunter-labeled sulfated cholecystokinin 8 (Amersham, Arlington Heights, IL) for 4 d at 4 °C. Free and bound radiolabeled isotopes were separated by addition of 0.5 mL 6% charcoal by weight (Sigma, St Louis) suspended in assay buffer without albumin and with outdated human plasma (Sacramento Blood Foundation, CA). Plasma insulin was measured by radioimmunoassay

according to the basic method described by Yalow and Berson (14) modified by using a 0.05-mol phosphate/L buffer containing 0.4% human serum albumin by weight and the precipitation method described by Desbuquois and Aurbach (15), with the use of polyethylene glycol to separate free and antibody-bound insulin. Plasma glucose and triacylglycerols were analyzed in the University of California, Davis, Clinical Nutrition Research Unit analytic core laboratory, according to approved protocols.

Study design and experimental protocol

The study used a randomized crossover design in which all meals were tested in all subjects, randomly, ≥1 wk apart. The subjects were instructed to keep detailed 24-h food records 3 d before and the day before a scheduled test session. On the day of the study session, the subjects arrived at the laboratory between 0700 and 0800 after they had fasted overnight. Each subject was scheduled to come to the study center at the same time on the same week or weekend day within 4 wk. No more than 4 subjects were tested per day. An intravenous catheter was placed in each subject's nondominant arm by a registered nurse. After the initial fasting blood draw, the subjects rested for a few minutes, acquainted themselves with their dining area, and then filled out their first set of VAS questions assessing hunger, fullness, desire to eat, and prospective consumption. After filling out the VAS, the subjects were given 1 of the 3 test meals to consume in 20 min. Blood was sampled and VAS booklets were completed after meal ingestion at 20, 40, 60, 90, 120 (2 h), 180 (3 h), 240 (4 h), 300 (5 h), and 360 min (6 h). At the end of the test session, the catheters were removed and the subjects were offered a selection of foods from a tray containing preweighed foods to be consumed as they desired before leaving the study site. The foods offered on the tray included bananas, oranges, apples, cookies, pretzels, chips, nuts, bagels, granola bars, cheese, juice, and soda. Any foods or portions thereof consumed from the tray were recorded on the subjects' test day food-intake records. In addition, the subjects were required to record all foods consumed after leaving the study site for the remainder of the day on the same food-intake record form. After the final test meal study day, the subjects were interviewed about the study.

Data analysis

To determine the subjective satiety response to the 3 test meals varying in fat, carbohydrate, and fiber content, data from the visual analogue rating scales, the food preferences check list, and the subject-recorded scale-weighed food records were analyzed by repeated-measures analysis of variance with test meal, time, and sex as main factors and subject as the blocking variable. Substrate metabolites and hormones were analyzed by repeated-measures analysis of variance as well. Data analyzed from the laboratory measurements for insulin, glucose, and triacylglycerol concentrations were first converted to increments above baseline to account for relative baseline variability among subjects. Data from cholecystokinin analysis were log transformed before statistical analysis. Significant differences among treatment means (adjusted) were analyzed by pairwise t test and Tukey's honestly significant difference test for appropriate comparisons. A relation between the subjective satiety response (VAS) and the biological satiety response (cholecystokinin) was tested by using linear regression analysis. Results were considered significant at $P < 0.05$. All data were analyzed with the PC-SAS GLM procedure
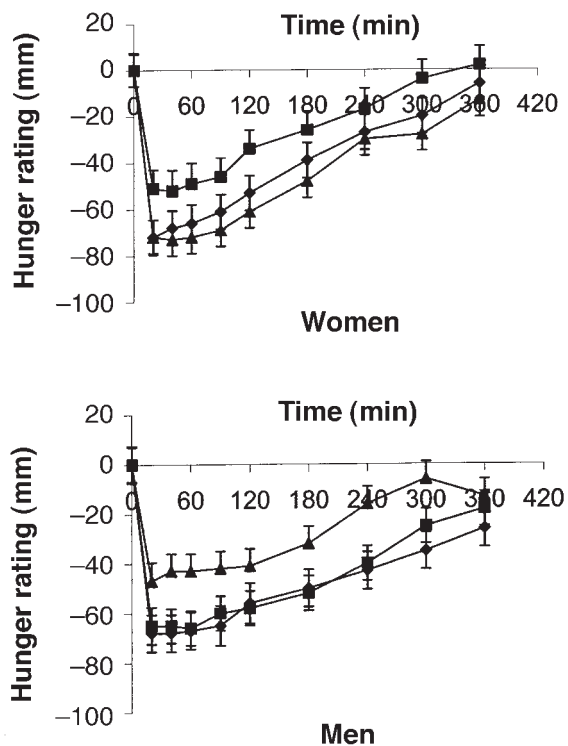
FIGURE 1. Mean (± SEM) hunger ratings on a visual analogue scale by the women ($n = 8$) and men ($n = 7$) at 0 min (fasting, baseline assessment) and then 20, 40, 60, 90, 120 (2 h), 180 (3 h), 240 (4 h), 300 (5 h), and 360 (6 h) min after the start of test meal ingestion. Meal-related suppression of hunger is represented by negative ratings. In the women, the response to the low-fiber, low-fat meal (■) was significantly less than the response to the high-fiber, low-fat (◆) or the low-fiber, high-fat (▲) meal, $P < 0.05$. In the men, the response to the low-fiber, high-fat meal was less than the response to the other 2 meals.

(SAS version 6; SAS Institute Inc, Cary, NC). Results are displayed as least-square means ± SEMs unless noted otherwise.

RESULTS

Subject characteristics

The mean (± SD) ages of the men and women were 31 ± 3.4 and 39 ± 2.2 y, respectively. The average body mass indexes of the men and women were 25.5 ± 0.53 and 23.9 ± 0.72, respectively. The subjects complied with the requirements of the study, including maintaining consistent body weight (± 1 kg) throughout the experimental period.

Food records and background diets

Collection of weekly food records provided information about the subjects' background diets as well as their consistency in food intake and feeding patterns during the study. Nutrient and statistical analysis of the food records indicated that energy intake differed between men and women, at 10.26 ± 0.29 MJ and 8.95 ± 0.40 MJ, respectively ($P < 0.01$); however, energy intake did not differ within each sex group throughout the experimental period. Macronutrient composition, expressed as percentage of energy and dietary fiber intake/4.2 MJ, was not different between sex groups and remained consistent throughout the study. In

general, the subjects consumed ≈30% of energy from fat, 55% from carbohydrate, and 15% from protein. Dietary fiber intake was ≈6.4 ± 0.9 g/4.2 MJ. Sodium and cholesterol intakes/4.2 MJ were also not different among subjects.

Subjective satiety measures

Visual analogue scales were used to evaluate the subjective satiety response to each of the test meals. In all subjects there was an overall significant test meal effect for ratings of hunger ($P < 0.0001$), fullness ($P < 0.03$), desire to eat ($P < 0.0009$), and the amount of food subjects thought they could eat ($P < 0.0001$) (data not shown). The HFB-LF meal was rated as having the greatest suppressive effect on hunger, desire to eat, and feelings of fullness, the LFB-LF meal had the least suppressive effect, and the LFB-HF meal had an intermediate effect. With respect to prospective consumption of food, the least amount of food was projected to be consumed after the HFB-LF test meal, followed by the LFB-LF meal and then the LFB-HF test meal.

In addition to a significant effect by test meal, a significant time effect ($P < 0.0001$) was observed for each of the variables tested by VAS (data not shown). All the test meals significantly suppressed hunger and the desire to eat immediately after consumption. Depending on the test meal consumed, feelings of hunger returned to levels not different from baseline at different time points during the 6-h experimental period. Hunger ratings no longer differed significantly from baseline ≥ 1 h earlier (4-h compared with 5-h time point) after eating the LFB-LF meal than after eating either the HFB-LF or LFB-HF meals. Changes in feelings of fullness followed a similar pattern in response. Over the 6-h experimental period, prospective consumption increased to levels that did not differ from baseline ratings after the LFB-LF (5-h time point) and the LFB-HF (4-h time point) meals, but the ratings after the HFB-LF meal remained significantly different from baseline ratings at the last time point measured (6 h, $P < 0.03$).

Sex-by-meal interaction was significant for each of the VAS measures ($P < 0.0001$) and indicated that among the women the HFB-LF and LFB-HF meals were more satisfying than was the LFB-LF meal and that among the men the HFB-LF and LFB-LF meals were more satisfying than was the LFB-HF meal. Only the data for hunger are presented in a graph showing the change in hunger over time along with the relative difference in hunger response after each meal by sex (**Figure 1**). Similar patterns of response were observed with fullness and desire to eat. These data are presented in **Table 2** as the means over time for each sex. These data further support the consistency in response of men and women to the respective meals. The sex-by-meal interaction on prospective consumption indicated that men could eat the least amount of food after the HFB-LF meal, followed by the LFB-LF meal and then the LFB-HF meal. Women, like men, indicated suppressed prospective consumption after the HFB-LF meal, but unlike men, women showed similar levels of prospective consumption after the LFB-LF and the LFB-HF meals.

To determine the types of foods desired by the subjects, a checklist of foods was provided for completion after VAS scoring. Foods were randomly listed but could be grouped into 4 main categories: sweet, savory, high in fat, and low in fat. Statistical analysis indicated no specific test meal effect. In general, men were ready to consume the different food types sooner than were the women.

Food-intake measures

To assess short-term compensatory adjustments in food intake, on the day of each test meal, foods consumed after the 6-h postmeal

TABLE 2
Measures of subjective satiety in subjects after consumption of a test breakfast[1]

	Fullness	Hunger	Desire to eat	Amount of food[2]
Women				
HFB-LF meal	46.5 ± 2.9^b	-44.3 ± 2.5^b	-40.5 ± 2.3^b	-43.8 ± 2.3^b
LFB-LF meal	33.5 ± 3.2^a	-22.8 ± 2.8^a	-21.6 ± 2.6^a	-30.3 ± 2.6^a
LFB-HF meal	48.8 ± 2.9^b	-45.5 ± 2.5^b	-46.8 ± 2.3^b	-28.7 ± 2.3^a
Men				
HFB-LF meal	47.9 ± 3.1^b	-46.6 ± 2.7^b	-47.3 ± 2.5^b	-42.8 ± 2.5^b
LFB-LF meal	45.5 ± 2.9^b	-44.5 ± 2.5^b	-47.9 ± 2.3^b	-38.0 ± 2.3^b
LFB-HF meal	35.1 ± 2.9^a	-28.9 ± 2.5^a	-30.3 ± 2.3^a	-23.1 ± 2.2^a

[1] $\overline{x} \pm$ SEM over time for measurements taken 20, 40, 60, 90, 120 (2 h), 180 (3 h), 240 (4 h), 300 (5 h), and 360 (6 h) min after the start of test meal ingestion. $n = 8$ F, 7 M. HFB-LF, high-fiber, low-fat; LFB-LF, low-fiber, low-fat; LFB-HF, low-fiber, high-fat. For all measures, the effects due to the test meal, time, and the interaction between sex and meal were significant ($P < 0.05$). Values in the same row with different superscripts are significantly different, $P < 0.05$.

[2] Indicates the consumption projected if food were available.

testing period that were not part of the test meal were recorded on food-record forms and analyzed for energy and macronutrient intake. No significant differences were detected in energy or macronutrient intake relative to test meal condition (**Figure 2**). In general, the subjects compensated appropriately for the energy content of the test meals so that their total daily intake on test days was similar to their usual average daily energy intake as indicated from food records before the test day. Macronutrient composition followed the same pattern as that described for energy intake. Dietary fiber intake increased on the days when subjects consumed the HFB-LF meal because of the contribution of the fiber

in the test meal. No adjustment in fiber intake was made to account for the extra fiber consumed during the HFB-LF test meal.

Biochemical measures

Fasting concentrations of cholecystokinin did not differ among treatment groups. In contrast, the postprandial cholecystokinin response to the test meals differing in fat and fiber content differed significantly by test meal ($P < 0.0002$) and time ($P < 0.0001$). The HFB-LF and LFB-HF meals elicited a similar cholecystokinin response (5.82 ± 1.04 and 5.69 ± 1.04 pmol/L, respectively), which was significantly greater than the cholecystokinin response elicited by the LFB-LF meal (4.49 ± 1.05 pmol/L). A significant meal-by-sex interaction was also noted ($P < 0.0002$). The cholecystokinin response in the women (**Figure 3**) illustrates the similarity in cholecystokinin response after the HFB-LF and LFB-HF meals, whereas the response to the LFB-LF meal was blunted relative to the response to the other 2 test meals ($P < 0.0001$). In contrast, the cholecystokinin response in men did not differ significantly among the test meals (Figure 3).

The glucose response to the test meals differed by meal ($P < 0.005$) and time ($P < 0.0001$), as did the insulin response (meal, $P < 0.03$; time, $P < 0.0001$) and triacylglycerol response (meal, $P < 0.03$; time, $P < 0.0001$) (**Figures 4** and **5**). Examination of differences at each time point indicated that the glucose response after the LFB-HF meal was significantly lower than after the LFB-LF meal at 20, 40, 60, 90, and 120 min after the meal. Overall, the HFB-LF meal resulted in glucose values that were intermediate between those of the other 2 meals and were significantly higher than those of the high-fat meal at 20 and 60 min after the meal (Figure 4). The LFB-LF meal resulted in the highest insulin response; for the LFB-HF meal at 60, 90, and 120 min and for the HFB-LF meal at 90 and 120 min after the meal, insulin concentrations were significantly lower than after the LFB-LF meal (Figure 4).

Evaluation of the triacylglycerol response showed that the LFB-HF meal produced the highest increase in plasma triacylglycerol concentrations (Figure 5). At 120 min, response to the high-fat meal was significantly higher than response to the 2 low-fat meals, and at 180 and 240 min, response to the high-fat meal was still significantly higher than response to the LFB-LF meal. Responses to the HFB-LF meal were typically intermediate between the other test meals; however, at 300 min the increase in triacylglycerol
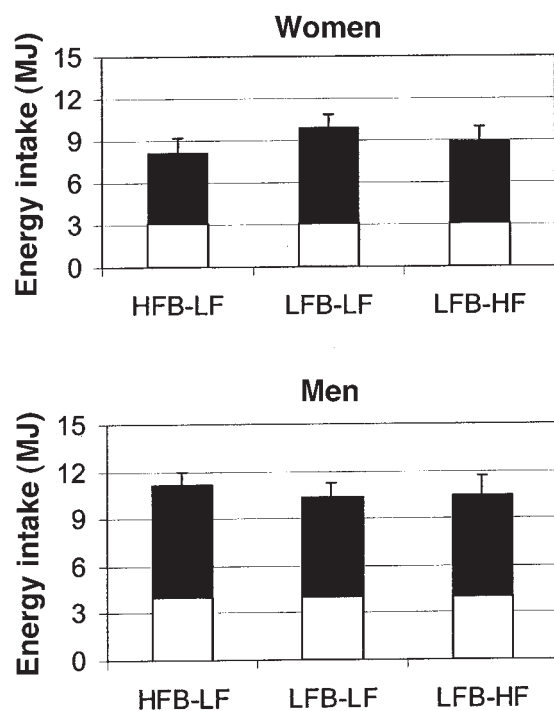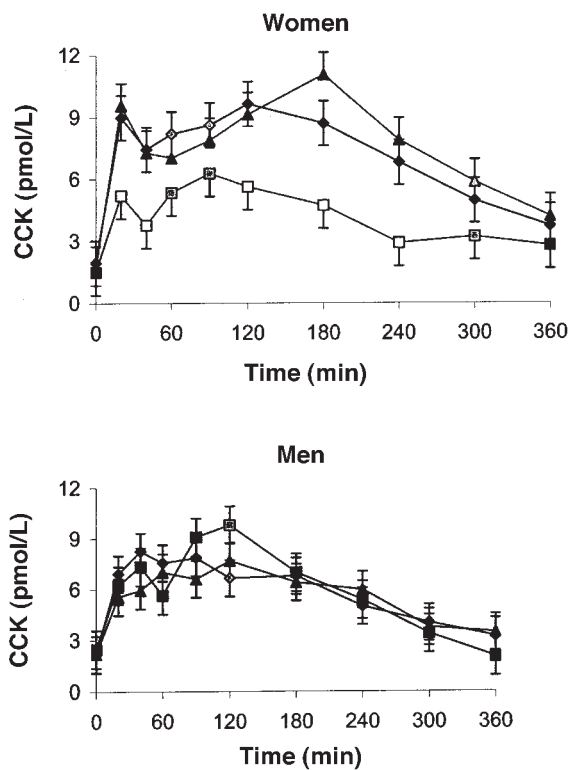

FIGURE 2. Mean ($\pm$ SEM) energy intakes of the women ($n = 8$) and men ($n = 7$) on the test day, by test condition: high-fiber, low-fat (HFB-LF) meal; low-fiber, low-fat (LFB-LF) meal; or low-fiber, high-fat (LFB-HF) meal. □, energy consumed from the test breakfast; ■, energy consumed from other foods on the test day.
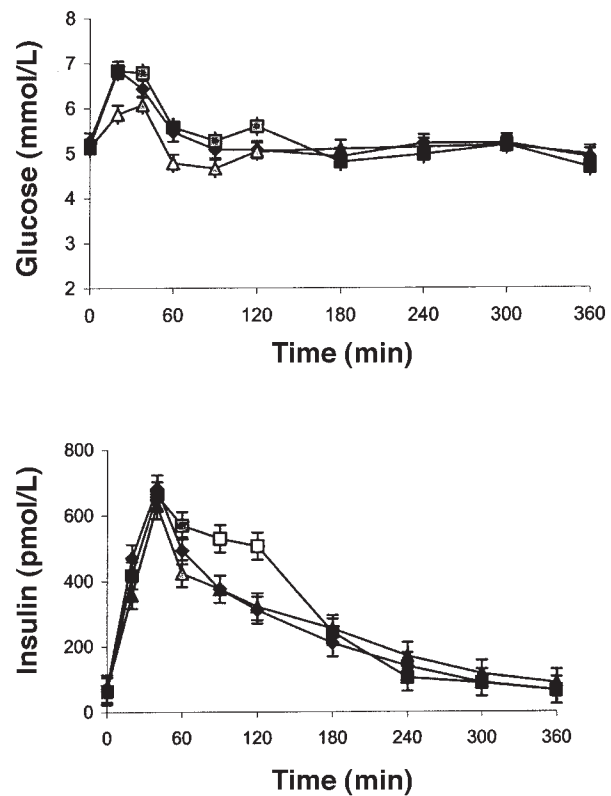
FIGURE 3. Mean (± SEM) plasma cholecystokinin (CCK) concentrations in the women (*n* = 8) and men (*n* = 7) over the 6-h period after consumption of the test breakfast. All the breakfast meals induced a significant increase in plasma CCK concentrations from baseline, *P* < 0.05. In the women, the CCK response to the low-fiber, low-fat meal (■) was significantly different from the responses to the high-fiber, low-fat (◆) and low-fiber, high-fat (▲) meals (*P* < 0.05). In the men, the CCK response did not differ significantly among the test meals. Unfilled symbols indicate that the test meal differed significantly from the other 2 test meals at that time point. Two test meals at a time point with gray filled symbols indicate that these treatments differed significantly from each other at that time point.

FIGURE 4. Mean (± SEM) plasma glucose and insulin concentrations in the men and women (*n* = 15) after consumption of the test breakfasts: ■, low fiber, low fat; ◆, high fiber, low fat; and ▲, low fiber, high fat. All the breakfast meals induced a significant increase in glucose and insulin concentrations from baseline, *P* < 0.05. Unfilled symbols indicate that the test meal differed significantly from the other 2 test meals at that time point. Two test meals at a time point with gray filled symbols indicate that these treatments differed significantly from each other at that time point.
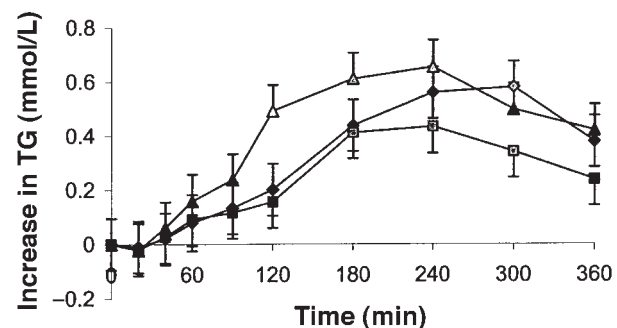
response was significantly higher than that for the LFB-LF meal. Examination of the triacylglycerol response curves show that responses to the LFB-HF and HFB-LF meals did not differ in peak triacylglycerol concentrations, but the high-fiber meal shifted the response curve to the right so that peak plasma triacylglycerol concentrations occurred later in the experimental period.

Relation between cholecystokinin and subjective satiety measures

Statistical evaluation of the subjective measures of satiety (ie, VAS) and the biochemical measure of satiety (ie, cholecystokinin) indicates a highly significant relation between measures of hunger and satiety and plasma cholecystokinin response (*P* < 0.0001). For every 1% increase in cholecystokinin, hunger, desire to eat, and the amount that a subject wanted to eat declined by an average of 0.45 on the subjective rating scales. Ratings of fullness increased by 0.50 for every 1% increase in cholecystokinin. A significant meal-by-cholecystokinin interaction was also observed for ratings of hunger (*P* < 0.0001), desire to eat (*P* < 0.0001), and prospective consumption (ie, amount) (*P* < 0.0003). The HFB-LF meal produced the greatest change in subjective satiety measures/1%

FIGURE 5. Mean (± SEM) increments in plasma triacylglycerol (TG) concentrations in men and women (*n* = 15) after consumption of the test breakfasts: ■, low fiber, low fat; and ◆, high fiber, low fat; and ▲, low fiber, high fat. All the breakfast meals induced significant increases in TG concentrations from baseline, *P* < 0.05. Fasting concentrations of TG were 1.04 ± 0.09 mmol/L, 0.98 ± 0.09 mmol/L, and 0.90 ± 0.09 mmol/L, for the 3 meals, respectively. Unfilled symbols indicate that the test meal differed significantly from the other 2 test meals at that time point. Two test meals at a time point with gray filled symbols indicate that these treatments differed significantly from each other at that time point.

change in cholecystokinin [regression coefficients $\pm$ SEE for hunger (-0.73 ± 0.07), desire to eat (-0.74 ± 0.08), and prospective consumption (-0.65 ± 0.07)] compared with either the LFB-LF or LFB-HF meals [regression coefficients $\pm$ SEE for hunger (LFB-LF: -0.37 ± 0.07, LFB-HF: -0.28 ± 0.07), desire to eat (LFB-LF: -0.39 ± 0.07, LFB-HF: -0.33 ± 0.07), and prospective consumption (LFB-LF: -0.30 ± 0.06, LFB-HF: -0.35 ± 0.06)].

DISCUSSION

Results from the present study show that adding either fat or a source of fiber to a low-fiber, low-fat test meal enhances the subjective satiety response to the meal and the release of cholecystokinin, a hormonal mediator of satiety.

In animal models, fat has been shown to have a potent inhibitory effect on feeding behavior when infused into the small intestine (16–18). This effect of fat is independent of energy load. In rats infused with equal energy loads, as the proportion of energy from fat increases, the period between meals (intermeal interval) is lengthened in a dose-dependent manner (16). In addition, when a fixed amount of fat is infused into the intestine at a slower rate for a longer period, the inhibitory effect of fat on feeding is prolonged (6). This effect of fat is specific to the upper one-third of the small intestine, because fat infusion into the ileum, hepatic or portal vein, or vena cava does not produce the same inhibitory effect on feeding (16, 17, 19). These data indicate that a fat-sensitive mediator of satiety exists in the small intestine and is responsible for providing a signal to the brain about the fat content of the diet so that appropriate adjustments in food intake and feeding behavior occur. Several studies have suggested that cholecystokinin is a primary mediator of fat-induced satiety (8). Cholecystokinin is located in intestinal mucosal cells of the upper one- to two-thirds of the small intestine. It is released on ingestion of a meal, particularly in response to the fat content of the meal. Exogenous administration of cholecystokinin inhibits food intake, and cholecystokinin receptor antagonism increases food intake, reverses the inhibitory effects of exogenous cholecystokinin, and has been shown to reverse the inhibitory effects of intestinal fat infusion on food intake and feeding behavior (19, 20–27). This study was designed to focus primarily on subjective satiety during the immediate 6-h postmeal period. These measurements provide a subjective assessment of the subjects' response to the meal rather than a measure of food intake or feeding behavior directly. Subjects adjusted their food intake in the period after the meal to compensate for the energy consumed in the test meals, as would be expected for nonrestricted eaters, and hence total food intake did not differ in this short-term period. Future research might focus on whether dietary patterns designed to enhance cholecystokinin release and subjective satiety will influence overall food-intake patterns and affect long-term energy balance.

The effect of fiber on feeding behavior is less well defined, in part because the action of fiber may be indirect. Foods high in fiber typically have low energy density, and in some cases the bulk associated with fiber is also associated with lower palatability (28). Another route by which fiber may affect feeding behavior is through its effects on alimentary function. Viscous polysaccharides delay gastric emptying and slow absorption from the small intestine (1, 2). Adding a viscous polysaccharide to an enteral formula increases feedback from distal regions of the small intestine because a longer length of the small intestine is involved with absorption (29). Bourdon et al (9) reported that adding barley to a test meal prolonged the time that cholecystokinin concentrations were elevated above fasting concentrations. Consumption of bean flakes, another source of viscous polysaccharide, doubles the cholecystokinin response to the test meal (10). These bean flakes have been associated with increased feelings of fullness and decreased desire to eat after a meal (30). Thus, the properties of some fibers to prolong exposure of meal contents, and especially dietary fat, to the intestinal mucosa may contribute to the enhanced measure of subjective satiety during the postmeal period. This effect of fiber on satiety may be mediated, in part, through prolonged release of cholecystokinin.

In the present experimental design, we tested whether adding sources of fiber to a low-fat, low-fiber meal, which might slow fat absorption, would have the same effect on subjective satiety as would adding fat to the meal, which would increase the fat-to-carbohydrate ratio. In the same subjects, the correlation between the subjective response and the concentrations of circulating cholecystokinin was determined. The relevance of peripheral cholecystokinin as a mechanism for regulating food intake is controversial. Reports both in the animal and human literature using exogenous cholecystokinin or antagonists of cholecystokinin have shown data that argue in support of and against peripheral cholecystokinin as a mechanism for food-intake regulation. However, adequate tools to measure endogenous cholecystokinin in the plasma after typical meal-induced stimulation recently became available. Much of the earlier research on endogenous release of cholecystokinin used fat loads or other types of stimulants that are not typical of normal eating patterns. Although this measure of plasma cholecystokinin alone does not tell us about the peripheral mechanism by which cholecystokinin may work, it can provide important information on the potential role of cholecystokinin in regulating food intake in response to dietary stimuli. Our findings show that in the women the HFB-LF and LFB-HF diets produced a similar satiety response, which was stronger than the response produced by the LFB-LF test meal. The subjective satiety was significantly correlated to the cholecystokinin response. These results suggest that the presence of fat in the small intestine is an important factor in meal-induced subjective satiety in women and that cholecystokinin may be a key mediator of the effect. In men the overall pattern of meal-induced subjective satiety and cholecystokinin increase was the same as in women; however, the relative effectiveness of the 3 test meals varied significantly from the response in women. The 2 meals that were low in fat had a stronger subjective satiety effect than did the high-fat test meal, and the 3 meals did not differ in their cholecystokinin response. This response in men is consistent with findings reported by Rolls et al (31, 32), where adjustments in energy intake and changes in fullness and hunger were greatest with the least energy-dense preload with the greatest volume.

Few studies have investigated differences between men and women in the effect of fat or fiber on satiety. Rolls et al (31, 32) suggested that individuals consume a constant weight of food rather than a constant quantity of energy; however, these studies were conducted in male subjects. Because of the higher fat content of the LFB-HF test meal, the solid food weight was less than the solid food weight of either the HFB-LF or the LFB-LF test meals. Although the weight of the 3 test meals was equalized with water, the ratio of solid to water weight differed among meals. The results suggest that both the macronutrient composition of the diet and the weight-to-volume ratio of the diet can affect meal-induced satiety; however, the relative importance of these mechanisms may

differ in men and women. Further research is needed to gain a better understanding of the sex-specific differences in meal-related subjective satiety as well as in the physiologic indicators of satiety such as cholecystokinin.

In addition to measuring meal-related satiety, the present experimental design enabled us to compare the effect of the test meals on postprandial glycemia and insulinemia. The 2 low-fat test meals, which differed in fiber content, resulted in similar glucose responses, but the insulin response to the meal with high fiber was lower and more comparable to the high-fat test meal. Adding fat to the LFB-LF meal reduces the energy from digestible carbohydrate in the meal, which undoubtedly contributes to the lower glucose and insulin response. Several lines of evidence have suggested that both fat and fiber, especially viscous polysaccharides, may be useful in the diets of non-insulin-dependent diabetic patients for reducing the glucose and insulin response to foods (33, 34). Both fat and fiber enhance or prolong cholecystokinin release after a meal. Cholecystokinin delays gastric emptying, and in patients with type 2 diabetes, the rise in cholecystokinin after a meal is associated with reductions in plasma glucose and insulin concentrations (35–38). In the present study, when data from all subjects were pooled, the test meal that produced the highest insulin response also produced the lowest cholecystokinin response. This observation is consistent with the report by Liddle et al (38) showing that cholecystokinin has a physiologic role in reducing hyperglycemia. Ludwig et al (39) reported that meals with a high glycemic index promote excessive food intake in teenage boys; however, the subjective satiety response or cholecystokinin response to the low–, medium–, or high– glycemic index meals was not reported. In another report, the glycemic and insulin responses to carbohydrate foods were inversely proportional to the cholecystokinin response and satiety (40). Hence, foods or meals that augment the cholecystokinin response may be associated with improved glycemia as well as greater satiety.

The addition of fat to the LFB-LF test meal significantly enhanced the alimentary triacylglycerol response. Dubois et al (41) reported that increasing the amount of fat in a test meal results in an increase in the alimentary triacylglycerol response, consistent with the present findings. Interestingly, the addition of fiber to the low-fat meal in the present study resulted in a triacylglycerol response that was intermediate and not different from either the LFB-LF or the LFB-HF meal except at one time point (120 min). In addition, the peak of triacylglycerol response after the fiber-enriched meal was shifted to a later time point than the peak after the high-fat meal. These results support the concept that a diet high in viscous polysaccharides prolongs the presence of alimentary lipoproteins in the plasma, perhaps by slowing the rate of fat digestion and absorption.

In summary, these results show that addition of fiber to a meal can increase subjective measures of satiety. Fiber, in addition to its known effects on volume in the gastrointestinal tract, may exert an effect on satiety in a manner analogous to that of fat, that is, by enhancing the release of cholecystokinin. Further research is needed to understand the long-term effects of fiber on the control of food intake and energy balance and to determine the role that sex has in the mechanisms for controlling food intake.

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