

## Adaptation to high-fat diets: effects on eating behaviour and plasma cholecystokinin

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Twelve male subjects took part in a study to investigate the effects of overfeeding a high-fat diet (19.17 MJ/d; 58% energy from fat) for 2 weeks on plasma cholecystokinin (CCK) levels, food intake, and subjective feelings of hunger and fullness. Before and after the diet, subjects completed a 2-week weighed dietary inventory, formal measurements of food intake from a pre-selected appetizing evening meal were carried out, and blood samples were taken after a standard breakfast for measurement of CCK. Hunger and fullness were rated on visual analogue scales before and after each of these meals and at evening meals during the diet period. Following the high-fat diet there was a small non-significant increase in food intake from the pre-selected meal (6919 (SE 615) kJ *v.* 6405 (SE 540) kJ;  $P = 0.1$ ) and a significant increase in the average daily food consumption measured from the diaries (10.25 (SE 0.49) MJ/d *v.* 9.59 (SE 0.62) MJ/d;  $P = 0.05$ ). Corresponding trends of increasing feelings of hunger and declining fullness also occurred over the study period. Plasma CCK responses to the standard breakfast were raised following the diet (1285 (SE 153) *v.* 897 (SE 78) pM min; 3 h integrated CCK production post *v.* pre diet;  $P < 0.01$ ) with the major differences observed at 90 and 120 min following the meal. These results suggest that the increase in food intake may be related to a down-regulation in putative CCK receptors responsible for food intake. Elevated CCK levels might suggest a corresponding down-regulation in CCK receptors responsible for feedback inhibition of CCK release.

### Cholecystokinin: Fat: Food intake

Previous studies have shown that gastric emptying of a fatty meal is accelerated after a 2-week period on a high-fat diet (Cunningham *et al.* 1991), suggesting down-regulation of the nutrient responsive mechanisms that inhibit gastric emptying. Recent studies from our laboratory suggest that nutrient receptors in the small intestine may control food intake (Welch *et al.* 1988). The infusion of lipid solutions into the jejunum of human volunteers can reduce hunger sensations before a meal, induce earlier feelings of satiety during ingestion of a meal and reduce energy intake. Moreover, a breakfast rich in fat induces a reduction in energy intake at lunch compared with a similar breakfast which contains much less fat even though the amounts of each type of breakfast remaining in the stomach at lunchtime are similar (Sepple & Read, 1990). If nutrient receptor mechanisms controlling gastric emptying can be down-regulated, it seems reasonable to propose that nutrient receptor mechanisms controlling eating behaviour may be down-regulated in the same way, resulting in an adaptive increase in energy intake.

Cholecystokinin (CCK) has been implicated in the nutrient regulation of both gastric emptying (Moran & McHugh, 1982) and food intake (Kissileff *et al.* 1981; Wolkowitz *et al.* 1990). Thus, lower production of CCK or decreased sensitivity to released CCK may be

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involved in both the acceleration of gastric emptying and possible increases in food intake in subjects eating a diet rich in fat.

The aims of the present study were therefore to investigate, in normal volunteers, the effect of eating a diet rich in fat for 2 weeks on food intake and associated subjective feelings, and on CCK responses to a standard meal.

## METHODS

### *Subjects*

Twelve healthy, non-obese male subjects (age 21–40 years) took part in the present study. None of the subjects had any history of major gastrointestinal disease or surgery, nor were they taking any drugs which could influence gastrointestinal motility. Each subject gave written informed consent for the studies to be carried out and the protocols were approved by the Local Research Ethics Committee, Northern General Hospital, Sheffield.

### *Protocol*

The study lasted 6 weeks and was divided into three periods (Fig. 1). For the first 2 weeks of the study subjects were required to fill in detailed weighed records of all food and drink consumed. Subjects were given a set of accurate electronic scales (Soehnle-Waagen GMBH and Co., Murrhardt/Württ, Germany) and were instructed to be as accurate and descriptive as possible in their recording. During this time, subjects' alcohol intake was restricted to no more than 4 units in any day. A formal assessment of food intake was conducted on the last day of this period, and on the following morning a standard breakfast (see Table 2) was given and postprandial plasma CCK responses were measured.

This was followed by a 2-week period during which subjects consumed a high-fat diet (19.17 MJ/d; 58% energy from fat; Table 1). Each subject was given pre-packed breakfast and lunch meals every day for the 2-week diet period and the subjects were required to come into the department at approximately 17.00 hours for the evening meal. Subjects were instructed to eat and drink everything that they were given and nothing else. Alcohol was not permitted during this period. Subjects recorded their subjective sensations on a questionnaire before and after each evening meal.

Measurements of food intake and plasma CCK responses to a standard meal were again conducted immediately after the diet. On the day following the 2-week diet subjects were asked to eat the same breakfast and lunch as for the initial food-intake day (as reported in their food diaries) and they were given the same evening meal as for the first study; the protocol was the same as before. On the next day, subjects returned in the fasted state and plasma CCK responses to a standard breakfast were again measured.

Finally, for the last 2 weeks of the study, subjects again carried out a weighed dietary intake inventory identical to that of the first 2-week period.

### *Measurement of food intake*

Subjects were asked to eat their normal breakfast and lunch and not to consume any afternoon snacks. These meals were entered into their diaries. At approximately 17.00 hours subjects were given a visual analogue scaled questionnaire containing a range of questions concerning their feelings of hunger, fullness and desire to eat, along with general questions regarding their well-being. These latter questions were given not only to determine that subjects were feeling well and contented but also to distract subjects so that they were not conscious that their feelings of hunger and fullness were our main concern.

Each subject was then presented with the meal that he had selected from a menu upon recruitment to the study. The food was prepared in excess of what was considered to be a

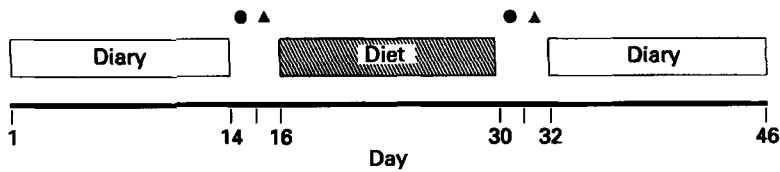


Fig. 1. Outline of the study design used in (●) the food intake study and (▲) the cholecystokinin study. For details, see p. 180.

Table 1. *Standard diet consumed by subjects during a high-fat diet study period*

**Breakfast (3799.6 kJ; 36.4 g fat)**

50 g Cornflakes  
200 ml Full-fat milk  
90 g White bread  
30 g Butter  
50 g Jam

**Lunch. The following lunches were given on alternate days:**

**Day 1 (6892.8 kJ; 129 g fat)**

120 g White bread  
40 g Butter  
100 g Tuna (in brine)  
100 g Mayonnaise  
60 g Cucumber  
125 g Low-fat fruit yoghurt  
30 g Double cream  
100 g Apple

**Day 2 (6433 kJ; 128.5 g fat)**

120 g White bread  
40 g Butter  
100 g Mayonnaise  
65 g Tomato  
30 g Cucumber  
30 g Lettuce  
125 g Low-fat fruit yoghurt  
30 g Double cream  
100 g Apple

**Dinner. \* Subjects were fed on 4-d rota for their evening meals as follows:**

**Day 1 (8713.6 kJ; 145.2 g fat)**

630 g Shepherds pie (incorporating 100 g butter)  
200 g Cauliflower  
100 g Green beans  
25 g Meringue  
200 g Tinned peaches  
62 g Double cream

**Day 2 (8701.1 kJ; 145.3 g fat)**

550 g Chicken supreme (incorporating 100 g butter)  
300 g Cooked white rice  
35 g Jelly  
62 g Double cream

**Day 3 (7954.1 kJ; 123.5 g fat)**

750 g Fish pie (incorporating 100 g butter)  
200 g Cauliflower  
100 g Peas  
25 g Meringue  
200 g Tinned pineapple  
62 g Double cream

**Day 4 (9493.2 kJ; 126.7 g fat)**

970 g Lasagne (incorporating 100 g butter)  
200 g Tinned peaches  
62 g Double cream

Full-fat milk was used for all sauces. In addition to the above, subjects were given 60 ml concentrated low-energy orange squash per day and an extra 50 ml milk for use in either a cup of tea or coffee with breakfast and lunch.

normal meal size and was weighed before it was given to the subjects. Each subject also chose a non-alcoholic drink (fruit juice or squash) which was also presented in excess. Subjects were then asked to eat and drink to comfort and the time taken for the subjects to complete their meal was recorded. Further questionnaires were administered at intervals of 10 min for 50 min after presentation of the meal.

Food and drink remaining following completion of the meal were reweighed and the energy intake from the meal was calculated. The mean rates of eating and drinking throughout the meal were also calculated.

Table 2. *Breakfast consumed by subjects before plasma cholecystokinin measurement*

	Quantity	Fat (g)	kJ
Quarter pounder beefburger J. Sainsbury Ltd.)	1	17.3	966
Baked beans (HP Healthy Choice)	120 g	0.6	282
Grilled back bacon (J. Sainsbury Ltd.)	45 g	15.2	766
Tinned tomatoes (Napolina Ltd., Surrey)	120 g	—	61
White bread (J. Sainsbury Ltd.)	60 g	0.8	643
Butter (J. Sainsbury Ltd.)	10 g	8.1	308
Orange juice (Longlife, J. Sainsbury Ltd.)	300 ml	—	454
Total		42	3480

#### *Measurement of plasma CCK responses to a standard breakfast*

Subjects were instructed not to consume any alcohol or spicy food on the evening following food intake measurement and to refrain from eating or drinking after 21.00 hours until they returned to the department on the following morning.

Subjects returned at 09.00 hours to undergo measurements of plasma CCK following a standard breakfast. An intravenous indwelling catheter was placed in an arm vein. A basal blood sample was taken and subjects were also given an initial questionnaire of the same type described above. They were then presented with a standard breakfast, different from that given during the diet period (Table 2), and the time taken to eat the meal was again noted. Blood samples were taken at intervals of 10 min for the first 30 min and at intervals of 30 min thereafter. Questionnaires were administered at intervals of 15 min throughout the study. Blood samples were immediately centrifuged at 0° and the plasma taken off and frozen at -20° for later measurement of CCK concentration. The study continued for at least 4 h or until the subject's hunger levels returned to preprandial levels (as determined by the questionnaire scales) if this was longer. Subjects were asked to record any further food or drink consumed for the rest of this day.

#### *CCK bioassay*

Frozen plasma samples were thawed and extracted onto Sep-Pak C-18 cartridges (Waters Association, Milford, MA, USA) previously washed with 5 ml methanol and 5 ml distilled water.

Plasma CCK concentrations were measured using a bioassay technique (Liddle *et al.* 1984). Resuspended plasma samples were incubated in triplicate with a dispersed suspension of rat pancreatic acinar cells (Peiken *et al.* 1978). Amylase (EC 3.2.1.1) production was detected spectrophotometrically and results were compared with a standard curve of CCK-8 concentrations (CCK-8 was a gift from the Squibb Institute). Results were expressed in pM CCK-8 equivalents.

The detection limit of the assay was 1–2 pmol/l and the intra-assay variances were 11%. The inter-assay variance of stripped plasma to which 30 pM CCK was added was 17%. This assay has previously been shown to have negligible cross-reactivity with gastrin (compared with CCK-8, the relative potencies of gastrin I and II were 0.00046 and 0.0025 to 1 respectively (Liddle *et al.* 1984)).

Total CCK production over a 3 h period was calculated by determining the area under

the profile (integrated CCK response) using Calcomp Drawing Board computer software (Calcomp, Anaheim, CA, USA), and this was expressed in units of pm min.

#### *Subjective scores*

From the visual analogue scales profiles of hunger and fullness were created and values for the time when subjects reported that they wanted another meal were determined.

#### *Statistical analysis*

Differences in body weight and meal intake variables (e.g. energy intake, rate of eating) from the laboratory test meal and energy intake measured from food intake diaries, before and after the diet, were tested for significance using Student's paired *t* test. Data from questionnaire responses, CCK release and day-by-day energy intake measured from intake diaries were analysed with two-way repeated measures analysis of variance (ANOVA), using time and pre- or post diet as fixed factors. *Post hoc* comparisons of means were tested for significance using Student's paired *t* test. In all comparisons,  $P < 0.05$  was taken to indicate significance.

### RESULTS

#### *Body weight*

There was a significant increase in the body weight of the subjects following the high-fat diet (76.1 (SE 2.4) v. 74.2 (SE 2.4) kg; post- v. pre-diet weight;  $P < 0.01$ ).

#### *Food intake from preselected meal*

Following the high-fat diet there was a small non-significant increase in food intake from the pre-selected meal (6405 (SE 540) v. 6919 (SE 615) kJ; pre- v. post-diet energy intake;  $P = 0.1$ ). Subjects drank significantly more (397.2 (SE 47.5) v. 582.0 (SE 61.7) g; amount drunk pre v. post diet;  $P < 0.01$ ) and at a faster rate (24.7 (SE 2.8) v. 37.8 (SE 4.7) g/min; rate of drinking pre v. post diet;  $P < 0.05$ ) following the high-fat diet (Table 3).

#### *Food consumption over the 2-week pre- and post-diet periods*

There was a significant increase in the average daily energy consumption over the 2 weeks following the diet compared with pre-diet levels (10.25 (SE 0.49) MJ/d v. 9.59 (SE 0.62) MJ/d; post- v. pre-diet energy intake;  $P = 0.05$ ). Inspection of the day-by-day fluctuations in the group's mean energy intake before and after the diet suggests that subjects continued to eat more at the end of the 2-week post-diet period than the average of the 2 week pre-diet period (Fig. 2); however, ANOVA revealed no effect of diet on these day-by-day changes ( $F_{1,20} 0.84$ ,  $P > 0.05$ ) and it can be seen from Fig. 2 that, although energy intakes were above the mean pre-diet level, they fell within the range of the pre-diet daily means.

#### *Subjective ratings*

Feeding of the high-fat diet for weeks did not lead to any significant changes in either the mean hunger ( $F_{1,311} 0.31$ ,  $P > 0.05$ ) or mean fullness ( $F_{1,312} 0.00$ ,  $P > 0.05$ ) profiles following ingestion of the standard breakfast (Table 2) used to determine plasma CCK levels. There were also no differences in the times at which subjects reported that they would want to eat another meal (156 (SE 17.9) v. 143 (SE 25.3) min; time following breakfast that subjects reported wanting to eat another meal;  $P > 0.1$ ) following this breakfast.

ANOVA revealed a significant interaction between time and condition (pre or post diet) on subjects' questionnaire responses to the question 'how much food do you think you could eat?' ( $F_{5,110} 2.98$ ,  $P < 0.05$ ), and *post-hoc* Student's *t* tests showed that subjects reported that they thought they could eat more food following the diet before being

Table 3. *Effect of a 2-week high-fat diet on the amounts of food and drink consumed by healthy male subjects from a pre-selected appetizing meal†*  
(Mean values with their standard errors for twelve subjects)

	Pre-diet		Post-diet	
	Mean	SE	Mean	SE
Amount eaten (g)	769.0	68.9	773.6	60.6
Amount drunk (g)	397.2	47.5	582.0**	61.7
Time taken to eat meal (min)	16.3	1.4	14.8	1.1
Total energy intake (kJ)	6405	540	6920	615
Rate of eating (g/min)	48.9	4.8	53.2	4.1
Rate of drinking (g/min)	24.7	2.8	37.8**	4.7

Mean values were significantly different from those of the pre-diet period: \*\*  $P < 0.01$  (Student's  $t$  test).

† For details, see pp. 180–181.

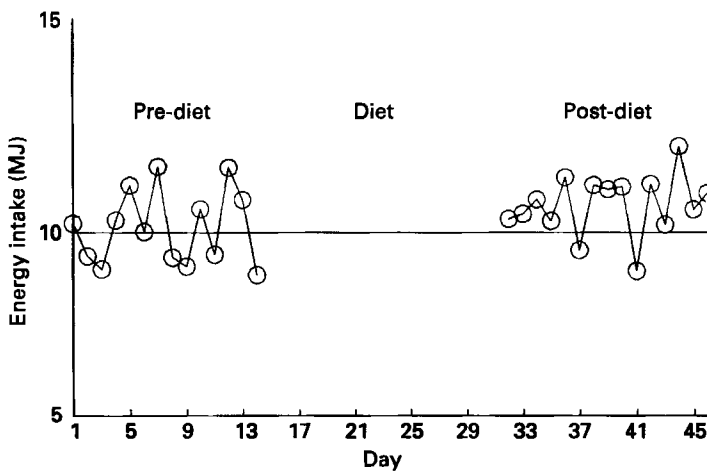


Fig. 2. Mean daily energy intake by twelve healthy male subjects, before and after a 2-week period on a high-fat diet. For details see pp. 180–181. The horizontal line represents the mean of the 2-week pre-diet period.

presented with the laboratory test meal (Fig. 3). There was also a trend towards a similar interaction between time and condition to the question 'I feel hungry' ( $F_{5,110} 2.07$ ,  $P < 0.08$ ; Fig. 3). Subjects also reported feeling more full following the high-fat diet ( $F_{1,22} 5.75$ ,  $P < 0.05$ ). A *post-hoc* probe of this effect using Student's paired  $t$  test showed that subjects reported feeling more full 10 min following presentation of the meal (Fig. 3). Over the 2-week diet period of consumption of the high-fat diet there was a trend toward increasing feelings of hunger before the evening meals and decreasing feelings of fullness both before and after the meals (Fig. 4).

#### Plasma CCK levels

The mean total plasma CCK released in response to the standard breakfast was raised following the high-fat diet (1285.0 (SE 153) v. 896.7 (SE 78.2)  $\mu\text{M min}$ ; 3 h integrated CCK production post v. pre diet;  $P < 0.01$ ). ANOVA (one-tailed) revealed a significant effect of condition on plasma CCK release from a standard meal ( $F_{1,22} 2.98$ ,  $P < 0.05$ ). The profile was similar to the pre-diet profile for the first 30 min of the study, it then increased above

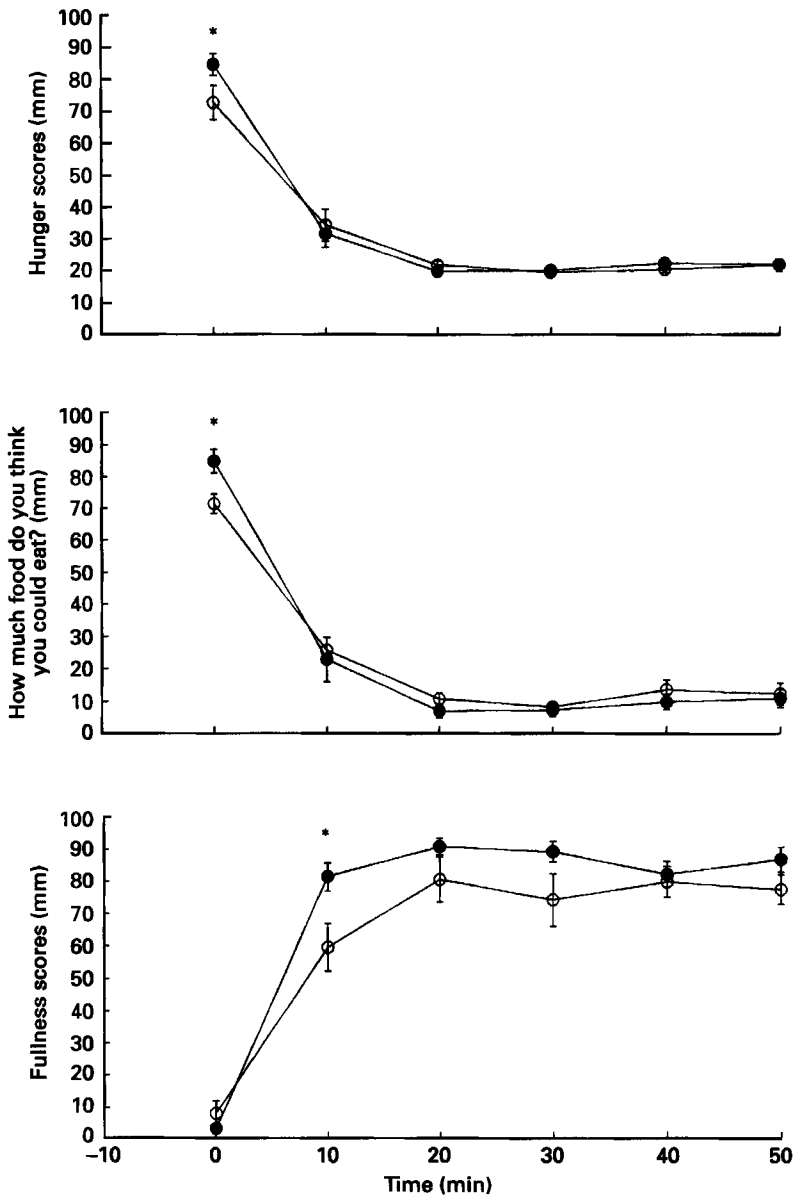


Fig. 3. Visual analogue ratings from questionnaires given to healthy male subjects during a pre-selected appetizing meal before (○) and after (●) a 2-week period on a high-fat diet. Values are means for twelve subjects with their standard errors represented by vertical bars. \* Mean values before and after the high-fat diet were significantly different,  $P < 0.05$ . For details, see pp. 180–183.

pre-diet levels and remained elevated above these levels for a further 90 min. *Post-hoc* Student's *t* tests showed that CCK levels were significantly elevated compared with pre-diet levels at 90 and 120 min following the meal (Fig. 5).

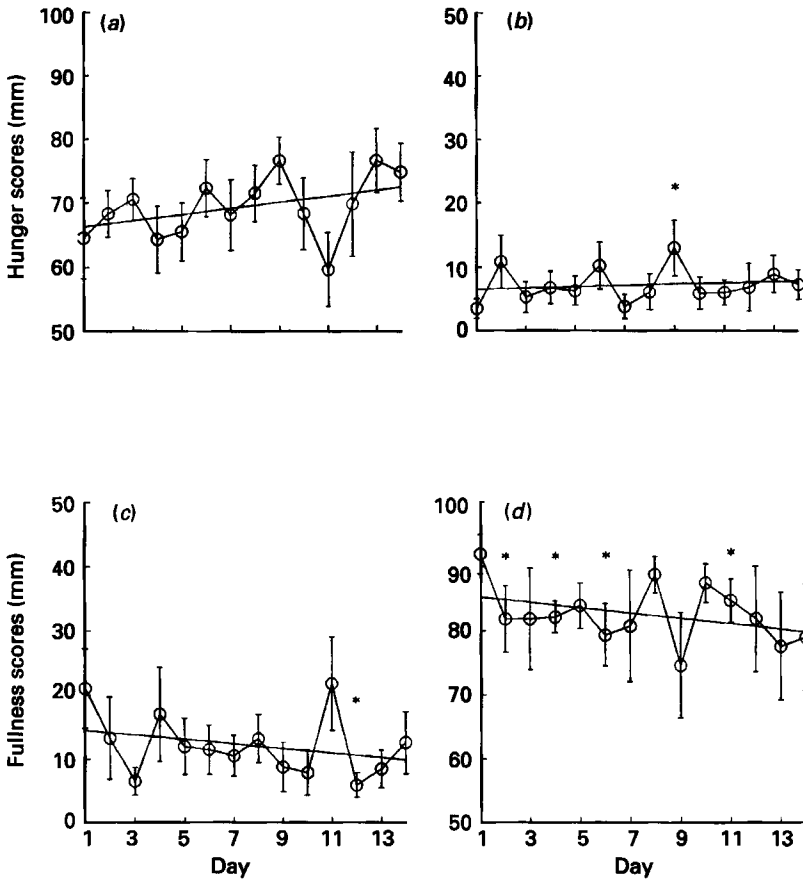


Fig. 4. Changes in visual analogue rated feelings of hunger (top) and fullness (bottom) measured before (a, c) and after (b, d) evening meals given to healthy male subjects during a 2-week period on a high-fat diet. Values are means for twelve subjects with their standard errors represented by vertical bars. The line through the points shows the best line of fit. \* Mean values were significantly different from those of day 1,  $P < 0.05$ . For details, see pp. 180–183.

#### DISCUSSION

The results of the present study show that overfeeding human volunteers on a high-fat diet for 2 weeks results in a significant increase in energy intake of about 660 kJ (160 kcal)/d for the subsequent 2-week period. Although this adaptive increase in energy intake is relatively small, if continued it could, in susceptible subjects, lead to energy storage and the development of obesity. Inspection of the temporal relationship of this effect does not reveal any decline in energy intake 2 weeks after completion of the high-fat diet. Diary records of food intake suffer problems in accuracy of recording and subject's motivation, creating the risk that a decline in motivation could have led to a spurious reduction in food intake which would have become more apparent as the study progressed. The fact that we observed a sustained increase in food intake towards the end of the study is more likely to be due to an adaptive response to the high-fat diet and if any lack of motivation had occurred the true response may have been much higher.

In contrast to the diary records, measuring the food intake from a single meal does not appear to be sufficiently sensitive to reveal an adaptive overconsumption. Although we saw



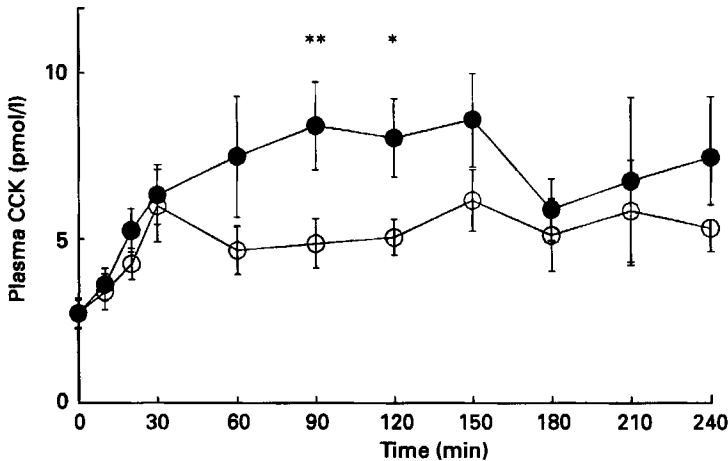


Fig. 5. Plasma cholecystikinin (CCK) response to a standard breakfast given to healthy male subjects before (○) and after (●) a 2-week period on a high-fat diet. Values are means for twelve subjects with their standard errors represented by vertical bars. Mean values for the pre- and post-diet measurements were significantly different: \*  $P < 0.05$ , \*\*  $P < 0.01$ . For details, see pp. 180–183.

a small increase in food intake following the high-fat diet, this did not achieve statistical significance. The results are similar to those of a previous study from our laboratory (Cunningham *et al.* 1991), in which we were unable to demonstrate any significant difference in food intake from a standard evening meal following periods on a high- or a low-fat diet, although in that study we suspected that our results may have been influenced by fasting the subjects from their morning breakfast. The large increase in liquid intake in the post-diet test is likely to have been due to a marked change in the weather. There was a dramatic increase in temperature while four of the subjects were consuming the high-fat diet which could account for the increased liquid intake at the second test period. This may also have affected these subjects' food intake at the second test period and could have reduced the effectiveness of the high-fat diet in increasing food intake.

Corroborative evidence for altered food intake was afforded by analysis of visual analogue ratings throughout the study. At the laboratory test of food intake, ANOVA revealed a significant interaction between the pre- and post-diet conditions and time for the question 'how much food do you think you could eat?' so that subjects initially scored higher to this question before meal presentation and then scored slightly lower to this question after meal presentation. There was also a trend towards a similar effect when subjects were asked how hungry they felt. Conversely, following the diet, subjects felt significantly more full 10 min after commencing eating. These apparently divergent findings may be reconciled by the slightly faster rate of eating of this meal following the diet (Table 3). This increase in the rate of eating could explain both the direction of the interaction between diet and time described above and the higher fullness scores 10 min after the meal. In addition, there was a trend towards increasing feelings of hunger and declining feelings of fullness at the evening meals given in the department over the 2-week diet period.

Plasma CCK is released into the bloodstream following the interaction between fat and protein components of a meal and duodenal receptors (Liddle *et al.* 1984). Thus if feeding a high-fat diet accelerated gastric emptying (Cunningham *et al.* 1991) and increased energy intake by down-regulating nutrient receptors in the small intestine, then we would expect plasma CCK responses to be reduced. The increases in the plasma CCK response to a

standard breakfast following the high-fat diet are more compatible with the hypothesis that it was not the nutrient receptors but the CCK receptors which had been desensitized by the period of exposure to large amounts of fat. This could not only explain the acceleration in gastric emptying and increase in energy intake, but could also explain the higher plasma CCK profiles following a standard meal. Studies using specific CCK receptor antagonists have shown that blockade or down-regulation of CCK receptors leads to an increase in plasma CCK possibly by decreasing negative feedback on release (Liddle *et al.* 1989; Meyer *et al.* 1989; Cantor *et al.* 1992). The release of CCK is believed to be inhibited by trypsin secreted from the pancreatic acinar cell by the action of CCK in humans (Owyang *et al.* 1986; Calam *et al.* 1987). Thus down-regulation of pancreatic receptors for CCK would reduce trypsin secretion which would in turn reduce the feedback inhibition of CCK release. The result would be an increase in plasma CCK profiles. These conclusions match those from studies in obese humans and rats. We have previously suggested that the higher CCK production in obese subjects may have been due to adaptive desensitization of CCK receptors due to overeating (French *et al.* 1993*a*) while others have proposed that the lower sensitivity to the satiating effects of exogenous CCK in obese rats (McLaughlin & Baile, 1980) was a consequence of increased meal size (Baile *et al.* 1986).

An alternative explanation for the increased energy intake following the high-fat diet is the increased body weight of subjects leading to increased energy expenditure. In the present study, however, most of the additional energy consumed during the diet was eaten as fat and subjects were asked not to increase their activity levels, therefore it is likely that weight gain was predominantly in the form of fat deposition which would be metabolically inert. However, without body composition or energy expenditure measurements, which were not taken during the present study, this cannot be stated for certain. Additionally, a possible alternative explanation for the enhanced CCK response to a standard breakfast following the high-fat diet evokes the adaptive acceleration in gastric emptying (Cunningham *et al.* 1991). In support of this possibility, we have previously shown a close inverse correlation between the half-time for gastric emptying and the integrated CCK response to a meal, compatible with a limitation of CCK release by the delivery of food into the duodenum (French *et al.* 1993*b*). However, in those studies the increase in CCK in the first 30 min after the meal was greater in those with the more rapid gastric emptying whereas this index was identical before and after the high-fat meal. Moreover, obese subjects had elevated CCK responses with no change in gastric emptying (French *et al.* 1993*a*). These observations suggest that the elevated CCK response to a standard meal after a high-fat meal are more likely to be related to a down-regulation of CCK receptors.

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