

## The effect of meal composition on the degree of satiation following a test meal and possible mechanisms involved

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1. Possible links between metabolism and satiation were investigated using volunteer subjects given test meals based on milk solids. Satisfaction was rated by the subjects on a six-point scale and the course of metabolism was followed by measurement of the respiratory quotient (RQ).

2. The time-course of satiation was the same for a high-carbohydrate, a high-fat and a high-protein meal, in spite of the very different time-course of metabolism. The degree of satiation was reduced by added sodium chloride, without affecting the RQ rise. On the other hand, calcium chloride produced a suppression of the RQ rise without altering the satiation.

3. It is proposed that the results indicate that the primary receptors responsible for post-prandial satiation lie within the gut wall and that there is probably a number of receptor types. Likely candidates for these receptors are the gut hormone-secreting cells.

4. Although very-low-protein meals produce less satiation than meals containing 220 g protein/kg dry weight, there is no additional satiation obtained by increasing the protein level further. This is not inconsistent with the possibility of a protein hunger separate from an energy hunger.

Information that would help in managing hunger would be useful in several situations. Although there are many models of how the sensations relating to hunger and satiation may be relayed to the higher centres of the central nervous system, there remains a dearth of information on the effect of food composition on these sensations. Many of these models allow predictions of effects of food composition on subjective sensations of hunger and satiation, other than the factors currently recognized.

A central role for glucose, arising principally from carbohydrates, was first proposed by Mayer (1955), who indicated that lateral hypothalamic glucose receptors are responsible for the onset of hunger when blood glucose levels fall. This model has been the subject of intense study and has been well reviewed by Le Magnen (1985). In more recent years there has been more emphasis on the liver as a key organ in the generation of feedback signals, again with glucose as the important metabolite (e.g. Russek, 1970). The liver is the first organ in a position to monitor the total amounts of nutrients being absorbed, except those nutrients that flow into the lymphatic drainage of the gut. On the other hand, other studies have challenged this (e.g. Louis-Sylvestre *et al.* 1980). This is discussed by Novin (1983). Thus it may be possible that nutrients taken up by the portal circulation, i.e. carbohydrate and protein, may be more effective in producing satiation than nutrients, such as fat, that are taken up by the lymphatic system.

In addition, it is asserted that there is a separate protein appetite. Rats will independently regulate the intake of total food energy and protein if given a choice of low- and high-protein diets, whereas lesion of the ventromedial nucleus of the hypothalamus causes an increase in total energy intake without affecting protein intake (Anderson *et al.* 1979). Under the action of some anorectic drugs, and given the same free choice, the intake of proteins is increased or decreased independently of changes in total energy intake (Wurtman & Wurtman, 1979). Compensatory changes in protein intake have been described after gastric preloads or intestinal infusions of amino acids (Booth, 1972; Novin

*et al.* 1979). Furthermore, Almquist (1954) has pointed out a correlation between the concentration of plasma amino acids and food intake. Thus protein may be an essential component of a satisfying meal, and may have a superior effect in producing satiation compared with other nutrients. For this reason, and since all realistic long-term diets must contain at least a modest amount of protein, all test diets reported here contained some protein. In addition, a high-protein diet was tested for its ability to produce satiation.

Gastric distension, e.g. by isotonic saline (9 g sodium chloride/l) has been shown to depress the food intake of dogs (Share *et al.* 1952), rats and monkeys (Deutsch & Gonzalez, 1980). The intestine is also sensitive to the presence of osmotically active substances (Haupt, 1983). Thus it might be expected that a more osmotically active meal may be more satisfying.

Gut receptors producing a series of neuropeptides, notably cholecystokinin (CCK), have been implicated in the genesis of satiation (Bray, 1975; Smith & Gibbs, 1975). Endocrine cells are recognized in many parts of the gut (Koopmans, 1981). These secretory cells are capable of responding to the contents of the gut lumen before foodstuffs enter the bloodstream (Fujita & Kobayashi, 1981). CCK, when given peripherally, influences behaviour and has strong satiety effects. These effects were first characterized by Gibbs *et al.* (1973) and have subsequently been confirmed in many species using a variety of models. However, observations by a number of other authors suggest that CCK in particular and intestinal hormones in general may be of little or no significance in eating behaviour in the rat (Deutsch & Hardy, 1977; Koopmans, 1981; Kraly, 1981; Bernstein & Goehler, 1983; Swerdlow *et al.* 1983). Given the possibilities of the role of gut peptides in satiation, manipulation of the local environment (e.g. by varying the electrolyte composition) may well alter the responsiveness of these neuroreceptor cells and thus alter the satiation response, although the direction of the effect cannot readily be predicted. Thus for a second reason, addition of electrolytes may be expected to alter the satiation response to a meal.

Accordingly, in these experiments the compositions of the test meals have been altered by varying the ratios of fat, carbohydrate and protein or by adding electrolytes to the meals. We have simultaneously measured subjective hunger in our subjects and have followed the metabolism of some of the test meals by the non-invasive techniques of expired gas analysis. In these experiments, we have taken measurements during a period following ingestion of the meal until hunger returns. It was expected that the results may produce further insights into mechanisms of hunger and clinically useful information.

#### METHODS

In the experiments described, subjects were given a test meal based on milk solids to produce a meal that contained a range of nutrients found in normal meals and was capable of producing satiation of hunger. The absence of fibre and solids had been found in preliminary experiments to produce larger respiratory quotient (RQ) rises than were found with solid meals and meals containing added fibre. Thus changes in the rise in RQ may be measured more precisely than with other meals. Furthermore, in a second series of preliminary experiments, pure carbohydrate meals containing either glucose or lactose were found to be substantially less satisfying than meals containing some protein in the form of skim milk. For this reason, all meals in this series were designed to have a minimum of protein.

The forty-two subjects were of both sexes, all Caucasian, aged from 19 to 50 years, and had body mass indices (weight (kg)/height (m)<sup>2</sup>) in the range 19–31. Experiments were performed at 09.00 or 14.00 hours. Individuals who did not normally eat a meal before the

Table 1. *Hunger scale used in the experiments*

Score	Normal feeling or response
-1	The very thought of food makes me ill
0	Not interested in food; would normally refuse food
1	I would accept a small amount of food if offered, but would leave most
2	I would be happy to eat, but would not feel distressed if I only had very little
3	I am ready for a meal; I would normally search for food in the house but if unavailable I would restrain myself
4	I want food badly; I am unable to work; I would stop work to get food

test period were excluded from the study. Subjects were asked to miss the meal before the test and consequently were hungry. They rated their hunger on a six point hunger scale ranging from -1 to 4 (see Table 1), and in Expt 2, expired gases were analysed by a Beckman metabolic measuring cart II (MMC II). They were then given a test meal mixed with water (approximately 0.2 litres) and measurements of RQ and satiation were taken at half-hourly intervals for up to 4 h. In each case the subject acted as his or her own control, being tested again at the same time of day and under as similar conditions as possible on a subsequent day, usually 1 week later. Details of the protocols of each series of experiments are given in Tables 2, 3, 4 and 5. The MMC II was calibrated as instructed by Beckman with standard calibration gases supplied by Commonwealth Industrial Gases (Australia), Victoria Australia. The MMC II provides continuous processing of the data, and includes an RQ in the output.

Subjects were volunteers and were free to withdraw if they desired. Two subjects did withdraw. The results from these subjects were not included as they were incomplete. Subjects were told as much as possible about the experiment before the experiment while still allowing the test meals to be given in an order unknown to them. After the tests they were informed of the findings as fully as possible.

## RESULTS

In Expt 1 the time course of satiation following a high-carbohydrate, high-fat or high-protein meal was compared. The details of the protocol are set out in Tables 2 and 3 and the results are shown in Fig. 1. There was no significant difference between the different meals in the degree of satiation at any point.

To study satiation further, in Expt 2 the course of metabolism of the test meal was also followed. In the case of a high-carbohydrate meal, this is conveniently measured by the rise in RQ. Thus the high-carbohydrate meal was given and the RQ was measured using the metabolic cart. In Expt 2 the effect of adding NaCl to the test meal was tested. The protocol is described in Tables 2 and 4, and the results appear in Fig. 2. The RQ rise observed was not significantly different at any point, but the average hunger score was lower at 1.5, 2 and 2.5 h. This indicated that the subjects were more hungry and were hungry again sooner when NaCl was added to the test meal. In this experiment it was not possible to disguise the composition of all the meals as the NaCl could be readily tasted in the meal. For this reason, in Expt 3 the satisfaction rating experiment was repeated with the NaCl being taken separately but simultaneously in a gelatine capsule, but without repeating the measurements of RQ. The control capsule contained an identical weight of lactose. The details of the protocol are given in Tables 2 and 5, and the results of this experiment appear in Fig. 3.

Table 2. *Protocol of experiments*

Phase 1	
Pre-test:	Satiation ratings Measure RQ
Treatment:	Consume test meal 1, 2 or 3
Post-test:	Satiation ratings and RQ measurements at 0.5 h intervals for up to 4 h Subject working at desk carrying out normal study or classroom activities Subject free to move around between measurements and permitted water <i>ad lib</i> .
Gap of 1 week	
Phase 2	
Pre-test:	Satiation ratings Measure RQ
Treatment:	Consume test meal; use a different meal
Post-test:	Subject conditions as for phase 1 Satiation ratings and RQ measurements at 0.5 h intervals for up to 4 h
Gap of 1 week	
Phase 3	
Pre-test:	Satiation ratings Measure RQ
Treatment:	Consume test meal; use third meal type
Post-test:	Subject conditions for phase 1 Satiation ratings and RQ measurements at 0.5 h intervals for up to 4 h
Independent variable:	Type of meal consumed
Dependent variables:	1. Degree of satiation measured by self-report scale in Table 1 2. RQ
Extraneous variables:	Order of meal effects controlled by counterbalancing the orders between the subjects
Time of day effects:	Controlled by taking all measurements at the same time of day a week apart for each phase
Initial degree of hunger:	Controlled by measuring at comparable times 1 week apart for each phase. Its success was assessed by a pre-test measure for each phase
Knowledge of type of food:	Controlled by ensuring that the subject did not know the food composition of any container

RQ, respiratory quotient.

Table 3. *Expt 1. Composition of test meals (g/kg body-weight)*

Meal...	High-carbohydrate	High-protein	High-fat
Lactose	0.45	—	—
Skim milk	0.45	0.90	—
Full-cream milk powder	—	—	0.65
Chocolate- or strawberry-flavoured Quik (g)	15	15	15

The experimental protocol is as described in Table 2, except that no respiratory quotient readings were taken. Satiation scores were recorded for 4 h each time. Subjects chose one of a set of three cups containing different preweighed solid mixture as described and the same flavouring agent in all three. Neither the experimenter nor the subjects knew which container contained which mixture. The subject then dissolved the mixture in water and drank it. Each experiment lasted 4 h.

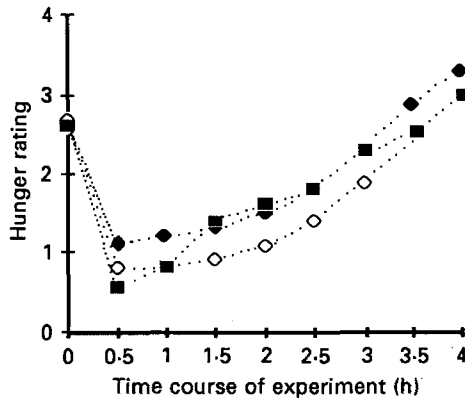


Fig. 1. Comparison of the time courses of satiation with a high-fat (■), a high-carbohydrate (◆), and a high-protein meal (◇). The meal compositions and the protocol are detailed in Tables 2 and 3. Fourteen subjects took part in the experiment. There was no significant difference between any two curves (Kruskal-Wallis test).

Table 4. *Expt 2. Composition of test meals (per kg body-weight)*

Meal...	Control	With sodium chloride	With calcium carbonate
Skim milk (g)	0.29	0.29	0.29
Lactose (g)	0.29	0.29	0.29
NaCl (mg)	—	24	—
CaCO <sub>3</sub> (mg)	—	—	24

The experimental protocol is as described in Table 2. Subjects were given pre-weighed mixtures by the experimenter who was aware of the nature of the test meal.

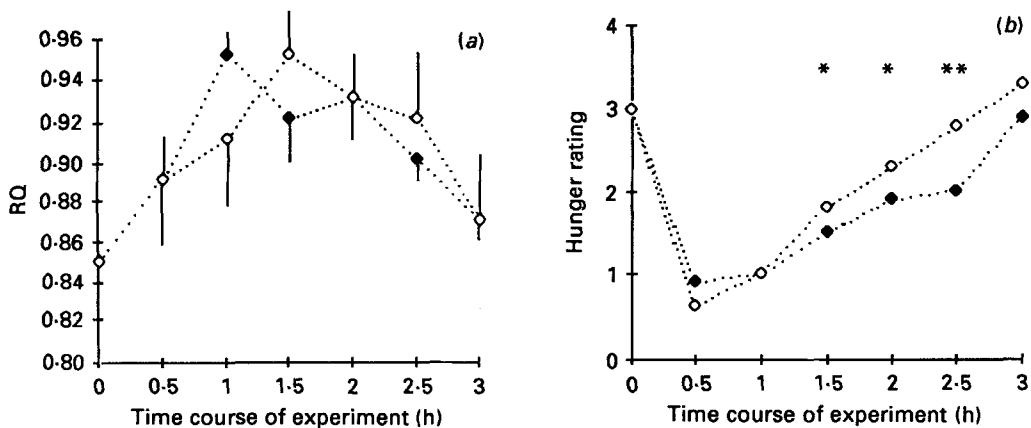


Fig. 2. The effect of extra sodium chloride on (a) the rise in respiratory quotient (RQ) and (b) the hunger rating. (◆), Control meal; (◇), meal with sodium chloride. The protocol is detailed in Table 3. Seven subjects participated in the experiment. There was no significant difference between the RQ readings at any time (Student's *t* test). The satiation ratings are significantly different where indicated: \*  $P < 0.05$ , \*\*  $P < 0.01$  (Wilcoxon matched-pair test). Values are means with their standard errors represented by vertical bars. (The satiation readings do not have errors indicated as it is not appropriate.)

Table 5. *Expt 3. Composition of test meals (per kg body-weight)*

Meal...	Control	With sodium chloride
Skim milk (g)	25	25
Lactose (g)	25	25
NaCl (g) (in a capsule)	—	1
Lactose (g) (in a capsule)	1	—

The experimental protocol is as described in Table 2, except that no respiratory quotient measurements were taken. Subjects were all given the same mixture of milk solids in a cup and a gelatin capsule containing a white powder as detailed. As the capsules were made up by a third person, neither subject nor experimenter knew the contents of the capsule. The milk solids were mixed with water (0.2 litres) in the cup to make a drink. The capsule was swallowed with the drink.

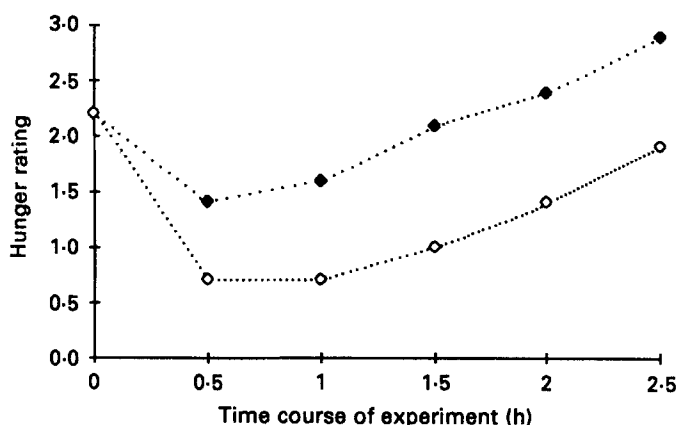


Fig. 3. The effect of additional sodium chloride following a test meal. Conditions are as described in Table 4. ( $\diamond$ ), Control meal; ( $\blacklozenge$ ), meal with NaCl. Fifteen subjects were involved in the experiment. The differences were significant at all times after zero time (Wilcoxon matched pair test;  $P < 0.01$ ).

It can be seen that hunger was again increased by NaCl and the subjects returned to their initial state of hunger sooner.

In the second series of experiments calcium was also tested. Ca in the soluble form of calcium chloride coagulated the milk proteins, so reprecipitated calcium carbonate was used, which was expected to dissolve in the hydrochloric acid of the stomach. The effect of the Ca is shown in Fig. 4. Since this powder is tasteless and cannot be readily detected in the milk solid mixture, the experiment could be performed without the subject knowing the nature of the test meals. There was no effect of Ca on the satiation but the RQ rise was considerably reduced.

#### DISCUSSION

The scale of hunger and satiation used in the present study was designed with the co-operation of the first four subjects. A scale that had readily identifiable (to the subjects) values that were intermediate between very hungry and not hungry was sought, with the expectation that the scale would only have rank order validity. The scale thus obtained was found to be readily accepted and was used by the subsequent subjects. Furthermore, the sets of scores obtained on repeat measurements under identical conditions were found to

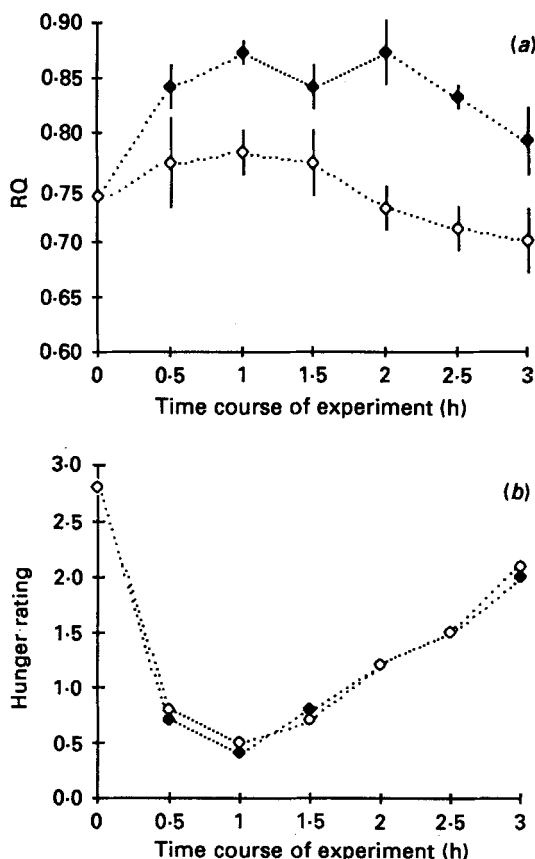


Fig. 4. The effect of added calcium carbonate on (a) the rise in respiratory quotient (RQ) following a meal and (b) the satiety. The protocol and meal composition are described in Tables 2 and 3. ( $\blacklozenge$ ), Control meal; ( $\diamond$ ), with  $\text{CaCO}_3$ . Six subjects participated in the experiments. The RQ readings were significantly different at all times after zero time ( $P < 0.01$ , Student's  $t$  test). Values are means with their standard errors represented by vertical bars. No significant difference was found at any point for the satiety scores (Kruskal-Wallis test).

be identical or to differ by only one point, provided that the subjects had not done anything greatly different on the day before the test session (results not shown). To achieve this, it was found a great advantage to test subjects in the middle or at the end of the working week. In the comparisons shown, each subject acts as his or her own control, to allow for any variation in the subjective meaning of the scores. The tests of significance used were non-parametric tests.

The fact that a high-fat meal was almost as satisfying as a high-carbohydrate meal is in line with common experience, but is inconsistent with any model such as the glucostatic model of Mayer (1955) that assumes that the meal has to be absorbed to satisfy hunger. Fat is absorbed more slowly than carbohydrate, and the majority of the fat would be expected to be still in the intestine and incompletely digested at the time of maximum satisfaction and at the time of return of readiness to eat a meal. The only plausible explanation is that the chemoreceptors are in the gut itself. In addition, these chemoreceptors must be sensitive to a wide variety of chemically different molecules, which suggests that a group of sensory cell types may be involved rather than one. For that reason, it seems unreasonable to

suppose that a single chemical, such as CCK, may have a pivotal role in the feedback from the gut to the central nervous system.

The suggestion that food is sensed within the gastrointestinal lumen itself is further supported by later observations. In the experiments with NaCl and CaCO<sub>3</sub>, the satisfaction following the meal and the metabolism of the meal can apparently be uncoupled by both these electrolytes but in different ways. It is noteworthy that either salt could produce a change in response, because if either of these salts were equilibrated with the total body pool of salts the rise in concentration of sodium or calcium ions or the associated anions would be barely detectable. It seems more likely that these salts should have an effect before equilibration, for example in the lumen of the gastrointestinal tract, or perhaps in the hepatic portal circulation.

As discussed earlier, osmotically active substances may inhibit gastric emptying and could therefore affect the subjective sensation of satiation. Thus, the osmotically active NaCl might be expected to increase satiation. In fact, the reverse is true. Furthermore, the action of NaCl is most evident when the RQ rise is most pronounced. This suggests that NaCl acts after the meal is present in the stomach, in fact when it is in the duodenum. The only plausible explanation is that receptors in the lumen, and probably the duodenal lumen, are stimulated by food molecules and that the concentration of NaCl in the lumen alters this response.

Moreover, one difference between the high-fat and the high-carbohydrate meal was that the osmotically active sugar lactose was replaced by the osmotically inert milk fat. In spite of the major differences between the two meals in osmolarity, there is no difference between them in the time course of satisfaction. It follows that in this case there was little satiation arising from gastric or intestinal swelling arising from the presence of osmotically active substances.

Other salts have been tested in preliminary experiments. Potassium chloride appears to mimic NaCl and magnesium sulphate has a more complex effect, altering both satiation and metabolism in the manner of NaCl and CaCO<sub>3</sub> respectively. Accordingly, there is no reason to assume that the salts tested were in any way unique.

The possibility of a separate protein hunger deserves further comment. In preliminary tests (results not shown), it was found that meals consisting of pure glucose or pure lactose were very unsatisfying and nauseating, compared with the meals containing the same amount of food energy and about 220 g protein/kg dry weight. It was for this reason that pure sugar meals were not used. On the other hand, when subjects were given high-protein meals (about 450 g protein/kg dry weight) no further satiation was obtained. Thus it would appear that at this level of intake protein is treated simply as an energy source. In contrast, Hill & Blundell (1986) found that at high concentrations protein was still more satisfying than carbohydrate. The reasons for the differences are not obvious.

The lack of evidence for significant involvement of glucoreceptors or the liver does not necessarily lead to the conclusion that these are of no consequence in man. A more cautious interpretation would be that these systems may be important as additional controls and may well be expected to be triggered in the context of other meals. For this reason more extensive testing of the effects of variation in meal composition may be of value.

The deliberate alteration of an appetite stimulant such as salt may well be useful in a variety of clinical situations. In addition, the fact that hunger may be modified from the gut lumen, probably by altering the responsiveness of a set of chemoreceptors, raises the possibility of using pharmacological blockade by agents that will only reach low concentrations in the body, or even using agents linked to a solid support so that they are not absorbed at all. Considering that most current anorectics have significant side effects, such approaches may be very useful.

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