

The effects of specific nutrients on the regulation of feeding behaviour in human subjects

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Regulation of short-term energy intake involves the balance of positive drives to eat arising from the sight, smell and palatability of food with negative feedback signals from learned associations, gastrointestinal and metabolic signals. The stomach and small intestine are major sites in the feedback inhibition of food intake and subsequent period of appetite suppression. The present paper reviews the evidence that not only does the nature of the regulatory signal suppressing food intake depend on the type and energy content of nutrient consumed, but also the specific chemical composition of the nutrients and the site at which they are delivered. It is evident that feedback inhibition of feeding can be modulated by the particular chemical structure of nutrients (e.g. specific sugar or triacylglycerol structures). These differences in response are likely to be a consequence of differences in physical properties of particular nutrients depending on their chemical structure, and may also result from different receptor affinities for specific dietary structures. Moreover, the site of administration of nutrients can also profoundly affect the size and nature of the subsequent feeding response, suggesting that feed-forward interactions occur between the taste of foods and gastrointestinal stimulation.

Appetite: Gastrointestinal function: Macronutrients

Excess energy intake relative to expenditure will lead to weight gain and ultimately obesity. While high-fat diets usually lead to excess energy consumption due to their energy density and high palatability (Prentice & Poppit, 1996), the epidemiological evidence that fat *per se* is the major cause of obesity is far from clear (Seidell, 1998; Willett, 1998). The underlying mechanisms by which different dietary components affect the regulation of energy balance are not well understood. It is not clear whether the specific properties of diets determine changes in appetite or body weight through different actions on the oxidation of fuels, or whether changes in dietary composition simply result in changes in the energy density of the diet (Frayn, 1995). Frayn (1995) also highlights that macronutrient balances cannot be considered independently, and that manipulation of the level of one macronutrient in the diet will influence the systems regulating the storage or utilization of the other macronutrients. There have been several recent reviews covering the regulation of appetite by different macronutrients and relating these macronutrients to the subsequent oxidation of fuels (Langhans, 1996; Friedman, 1997). The present paper will review the more immediate physiological regulatory processes associated with the

ingestion of dietary components in human subjects which may also influence the regulation of feeding behaviour, particularly in the short term.

The mechanisms regulating short-term human feeding behaviour are numerous and complex. They involve the integration of positive drives to initiate and continue feeding from sensory cues such as the sight, smell and palatability of food with negative feedback signals arising from learned associations, gastrointestinal and metabolic signals (Blundell & Greenough, 1994). Short-term regulation of food intake can be thought to represent a balance between positive (hedonic) and negative (satiety) motivations to continue eating during a meal and the subsequent suppression of the drive to eat following meal cessation (satiety). The impact of specific dietary components on the regulation of short-term feeding behaviour has not been extensively studied in human subjects. Our current understanding suggests that different macronutrients can affect feeding behaviour by having an impact at each of the sites mentioned earlier. Thus, the relative balance between the positive drives to eat and the negative feedback consequences of particular dietary components will define the feeding behaviour responses to a particular meal.

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The three major macronutrients (carbohydrate, fat and protein) represent a very diverse group of molecules ranging widely in physical and chemical properties. Simple sugars have molecular masses of approximately 180 kDa, while proteins range in molecular mass (kDa) from 5000 to several million. Carbohydrates and proteins are hydrophilic, while fats are lipophilic. Carbohydrates and proteins are generally solid at room temperature, while fats range from liquid to solid depending on their chemical composition. All these factors can have profound implications for the assimilation of ingested foods of particular macronutrient composition.

It is perhaps not surprising, given the wide variety of chemical and physical properties of the components of our diet, that there will be an enormous range of possible post-ingestive responses to these components. We are only beginning to recognize these differences and the possible implications that they have for our understanding of the regulation of human feeding behaviour. The aim of the present paper is to review our current knowledge concerning the effects of specific nutrients, and different forms of the same nutrient, on the physiological and psychological factors governing food intake.

Oral preload studies

Most of the studies utilizing oral preloads to investigate short-term modulation of feeding behaviour have focused on carbohydrates. The term carbohydrates covers a very wide range of compounds, ranging from simple mono- and disaccharides through to very large complex carbohydrate molecules. Since most of the carbohydrates which are available for absorption by the small intestine are broken down to the simple mono- or disaccharides, many of the studies investigating the appetite responses to carbohydrates have been carried out using these simple sugars.

A robust reduction in feeding can be observed when sugars are ingested as a preload. Consumption of glucose- or sucrose-containing drinks results in a reduction in intake from subsequent meals when compared with non-energy artificially-sweetened or plain water drinks (Booth *et al.* 1970a; Rogers *et al.* 1988; Birch *et al.* 1989; Lavin *et al.* 1997). Similarly, the addition of carbohydrate to a preload food decreases subsequent intake when compared with preloads containing artificial sweeteners or left plain (Rogers & Blundell, 1989a; Rogers *et al.* 1990; Blundell *et al.* 1994). Moreover, the reduction in energy intake following the ingestion of these preloads is frequently found to be similar to the energy value of the carbohydrate, indicating that carbohydrate energy can be accurately detected and compensated for by adjustments in further intake (Birch *et al.* 1989; Rogers & Blundell, 1989a,b; Blundell *et al.* 1994; Lavin *et al.* 1997). This compensation for relatively small carbohydrate preloads (628–1674 kJ) is usually seen within the next meal or subsequent meals during the remainder of the day, indicating that carbohydrate has a strong effect on appetite in the short term. Significantly, however, several studies have found no change in appetite or food intake following carbohydrate preloads, or have even found a stimulation of intake (Spitzer & Rodin, 1987). The wide variety of methodologies and carbohydrate preloads used in different studies is a likely

explanation for the differences in findings (for a comprehensive review of the methodologies used, see Reid & Hetherington, 1997). Importantly, for the present discussion, it is apparent that a wide variety of sugar molecules have been utilized: glucose, fructose, maltodextrin, sucrose, maltose. As will be discussed later in the present review, it is now clear that different carbohydrates (even simple sugars) cannot be considered similar in their physiological properties, and hence cannot be expected to have similar effects in studies of food intake or appetite.

Several studies have compared the satiating effectiveness of equienergetic preloads of different macronutrients. Protein is generally reported to be the most satiating of the macronutrients in short-term feeding studies (Booth *et al.* 1970b; Hill & Blundell, 1986, 1989; Rolls *et al.* 1988). However, it is very difficult to covertly manipulate the protein content of meals which may lead to large differences in cognitive, orosensory and expectancy factors associated with the different preloads. When an attempt is made to mask the taste and texture of the preload (Geliebter, 1979; Driver, 1988) no differences in short-term feeding behaviour have been observed between macronutrients. Addition of carbohydrate to a preload has been shown to lead to a greater suppression of appetite and food intake in the short term compared with unsupplemented or fat-supplemented preloads (Cotton *et al.* 1994; Rolls *et al.* 1994). Furthermore, Green *et al.* (1994) demonstrated that *ad libitum* intake of high-carbohydrate low-fat snacks was less than that of equally palatable high-fat low-carbohydrate snacks, suggesting that the high-carbohydrate snacks were more satiating. Despite the difference in energy intake from the snacks, subsequent *ad libitum* food intake was similar in both conditions. Thus, total energy intake over the day was lower when high-carbohydrate snacks were consumed. Other studies, however, have demonstrated that fat and carbohydrate produce similar reductions in subsequent food intake when given orally (Foltin *et al.* 1990, 1992; Rolls *et al.* 1991).

Gastrointestinal nutrient infusion

Direct gastric or intestinal infusions of nutrients allow the role of specific areas of the gastrointestinal tract in the control of feeding to be investigated. Furthermore, subjects receive no cues regarding the taste or palatability of the nutrients infused. However, results should be treated with a certain degree of caution regarding their generalizability, as this type of study, while revealing many of the physiological processes associated with the control of feeding, cannot be thought of as a normal feeding situation.

Macronutrient infusions

It is very difficult to assess the feeding responses following gastric or intestinal infusions of purified protein solutions as these become solid before a moderate energy density can be reached. Our one previous attempt only allowed an energy density of 1.66 kJ/ml, which failed to show any differences between protein, carbohydrate and saline on appetite or food intake (at an infusion rate of 3 ml/min for 210 min; N Khan and J Francis, unpublished results). Comparing the effects

of gastric or intestinal infusion of fat and carbohydrate, studies conducted to date show no indication of a higher satiating potency of carbohydrates in human subjects (Shide *et al.* 1995; Cecil *et al.* 1998a,b). The most recent reports have suggested that fat may be more satiating than carbohydrate when given directly into the small intestine (Cook *et al.* 1997; Andrews *et al.* 1998). The most striking difference between direct gastrointestinal infusion and oral preloads is the stimulation of the taste receptors in studies using oral preloads. Thus, even despite care to match oral preloads for taste and palatability, it seems that oral preloads can be subtly distinguished and may influence the outcome of preload studies. These differences may be too subtle for measurement by standard techniques of visual analogue rating.

Levels of control

The differences in response depending on the site of administration of nutrients can be highlighted from studies comparing appetite and physiological regulation of the same nutrients given via different routes. Cecil *et al.* (1998b) have shown that oral consumption of a high-fat soup had a more marked effect on suppression of appetite than when the same meal was infused into the stomach; both these routes of administration were more effective than intestinal infusion. Furthermore, two gastric infusion conditions were compared, the first in which subjects were not aware of the nature of the infusion that they were receiving and the second in which they were told what the infusion comprised. Knowledge of the nature of the infusion resulted in a greater suppression of appetite, highlighting the importance of cognitive information concerning food in the modulation of appetite responses. A second study of similar design compared the satiating effectiveness of high-fat and high-carbohydrate soups on feeding behaviour when administered orally or intragastrically. Again oral administration resulted in greater suppression of appetite than gastric infusion for both high-fat and high-carbohydrate infusions; additionally there were differences in the appetite responses to the two soups when delivered orally (fat produced a greater suppression of appetite in this study) but not when delivered intragastrically.

These studies highlight the importance of cognitive information in the modulation of appetite responses to nutrients in human subjects. Following ingestion of a normal meal, a combination of signals will be elicited to bring about an integrated signal which we recognize as satiety. It can be demonstrated from laboratory-based studies that modulation of signals associated with the ingestion of food (oral and gastric stimulation) occurs by the presence of nutrients in the small intestine. In several of our recent studies we have observed no effects on appetite ratings during upper-small-intestinal nutrient infusions given at physiological rates (Castiglione *et al.* 1998; Cecil *et al.* 1998b; French *et al.* 1998). However, where meal intake was measured towards the end of the infusion period, intake was markedly influenced by the nature of the infusion (Castiglione *et al.* 1998; French *et al.* 1998). We interpret these findings as support for the hypothesis that intestinal nutrient stimulation modulates other signals of satiety (in

this case the taste and gastric distension elicited by ingestion of the test meal). Similar modulation of gastric distension has been observed by combining the distension of the stomach with an inflatable bag with duodenal infusion of nutrients. Both maltodextrin and lipid infusions into the upper small intestine led to an increase in the sensation of meal-like fullness (as opposed to uncomfortable distension) when compared with saline (9 g NaCl/l) infusion (Feinle *et al.* 1997). Furthermore, this effect can be partially reversed by the administration of the cholecystokinin receptor antagonist loxiglumide (Feinle *et al.* 1996). Gutzwiller *et al.* (1996) have also shown that combination of intestinal fat infusion with a milk shake preload induces a greater suppression of intake than either preload or infusion alone. These observations may be important in the normal satiety responses to a meal, as it has been demonstrated that the early gastric emptying rate of a liquid meal, especially during the period while food is still being ingested, is quicker than the normal emptying rate in rats (Kaplan *et al.* 1992). Thus, a moderate proportion of the meal may be expected to interact with the upper intestinal mucosa within the first few minutes of a meal.

Are all sugars or fats the same?

It is difficult to make appropriate comparisons between many of the previously described studies due to the wide variety of different carbohydrates and fats which have been used as preloads. We are now coming to understand that all sugars or fats cannot be considered to be equal in their physiological effects and in their ability to modulate feeding behaviour.

Generally, it has been thought that the gastric emptying rate of energy-dense foods is regulated by the osmotic and energy properties of the food (Hunt & Knox, 1968; Barker *et al.* 1974; McHugh & Moran, 1979; McHugh *et al.* 1982; Brenner *et al.* 1983). However, the observation that fructose empties from the stomach more rapidly than equienergetic and equiosmotic glucose solutions (Elias *et al.* 1968; Moran & McHugh, 1981; Guss *et al.* 1994) has suggested that the feedback regulation of gastric emptying is related to the sugar molecule itself. Furthermore, intestinal stimulation of insulin release is also markedly different following glucose and fructose ingestion in human subjects (Macdonald *et al.* 1978). This finding is not surprising considering the highly specific sugar transporter systems which have now been identified (Levin, 1994). Similar sugar-molecule-specific regulation of gastric emptying has recently been shown for the common disaccharide sucrose and the partial breakdown product of starch, maltose (JH Lavin, SJ French and NW Read, unpublished results). Despite the markedly faster emptying of sucrose, the appetite responses were similar, which may suggest that the feedback mechanisms regulating gastric emptying and appetite responses are different.

Similarly, fats cannot be considered to be equal in their physiological regulation of human feeding behaviour. It has been suggested from the studies in animals that different fatty acids may modulate the feeding response differently. Again differences can be noted in the effects depending on the site of administration of the fatty acids. Maggio & Koopmans (1982) reported no differences in the potency of

fatty acids in the range C₆ to C₁₈ in rats when infused into the stomach. Conversely, when infused into the small intestine, it has been reported that the potency of medium-chain-length fatty acids increases as the chain length increases (McCaffery *et al.* 1994). Furthermore, within the C₁₈ fatty acids, large differences in potency have been demonstrated in sham-fed rats depending on the degree of unsaturation of the fatty acid (Lewis *et al.* 1990). We have recently shown a similar effect due to direct intestinal infusion of oils containing different proportions of the C₁₈ fatty acids in human subjects (Fig. 1). Similar to the data of Lewis *et al.* (1990), we have found that of the C₁₈ fatty acids tested, linoleic acid was the most potent inhibitor of food intake. Taken together, these findings indicate that the mechanisms detecting the composition of the ingested nutrients are highly specialized, and are able to discriminate between factors as subtle as the degree of unsaturation of a fatty acid.

Several possible mechanisms exist which may explain the findings reported earlier. As mentioned previously, the chemical composition of different fatty acids has a profound effect on the physical characteristics of the triacylglycerol molecule, for example there is an inverse relationship between the degree of unsaturation of the fatty acids and the melting point (Table 1). The degree of unsaturation is also likely to affect the ease of emulsification of the triacylglycerol both *in vitro* and in the digestive tract. These factors will markedly affect the ease of digestion and absorption of fatty acids (Small, 1991), and therefore

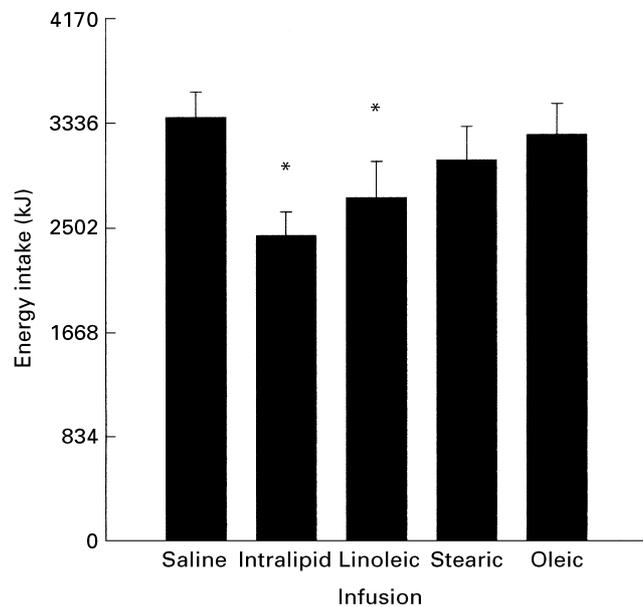


Fig. 1. The effect of upper intestinal infusion of C₁₈ fatty acid-enriched oils on food intake. Infusions were given for 100 min at a rate of 1 ml (8.3 kJ)/min (200 ml/l emulsions). At 90 min after the start of the infusion, subjects were given a liquid meal (strawberry drinking yoghurt) and were instructed to eat to comfortable fullness; the infusion continued throughout ingestion of the meal. Values are means with their standard errors represented by vertical bars. Mean values were significantly different from those for saline (9 g NaCl/l) infusion: * $P < 0.05$. (From French *et al.* 1998.)

Table 1. The effect of increasing unsaturation of component fatty acids on the melting point of pure long-chain triacylglycerols

Fatty acid	Structure	Melting point of triacylglycerol (°)
Stearic acid	18:0	67.9
Oleic acid	18:1	16.0
Linoleic acid	18:2	-5.0
Linolenic acid	18:3	-11.0

influence the rate of interaction between fatty acids and putative mechanisms regulating feeding behaviour. Chemical signals from the upper small intestine have been shown to be sensitive to the composition of the long-chain fatty acids. Particularly relevant to the suppression of food intake is that cholecystokinin, a peptide hormone thought to be involved in the normal feedback regulation of food intake (Ballinger *et al.* 1995), has been shown to be more potently stimulated by linoleic acid-containing oils than by other oils (Beardshall *et al.* 1989). Apolipoprotein A-IV is also differentially released in response to different fatty acids, in rats, with an order of potency similar to the satiety effects observed by the oils in the present study (Kalogeris *et al.* 1996). Apolipoprotein A-IV has been shown to reduce meal size in rats and its inhibition stimulates intake (Fujimoto *et al.* 1992, 1993).

An intriguing possibility concerning the action of fatty acids in the regulation of physiological feedback has arisen recently from patch clamping studies of rat taste-receptor cells. Previously it was thought that fats are not tasted but rather they are 'felt' by the mouth, and that their main effects on palatability are to modulate the tastes of other dietary components (Elizalde & Sclafani, 1990; Ramirez, 1992). Gilbertson *et al.* (1997) have shown, however, that different fatty acids can indeed be discriminated by taste receptors on the tongue in rats. Measurement of K⁺ currents (affecting the membrane potential of taste-receptor cells) shows that they are markedly inhibited by linoleic and linolenic acids ($P < 0.01$) but not by stearic or oleic acids (Fig. 2). These findings closely parallel the human food intake data. The same ion channel has now also been identified in other tissues, including the duodenum (Gilbertson *et al.* 1998), suggesting that similar signalling from the small intestine in response to fatty acids may occur. The full significance of this work for human subjects is not yet clear, as rats possess a greater amount of lingual lipase (*EC* 3.1.1.3), and thus can digest more dietary triacylglycerols in the mouth. However, it has been demonstrated that stimulation of the human tongue with full-fat soft cheese increases the serum lipid response to an intragastric load of triacylglycerol when compared with non-fat soft cheese or no stimulation (Fig. 3; Mattes, 1996). Subjects were not informed of the nature of the cheese nor were they able to distinguish between the cheese samples in sensory tests, suggesting that a specific chemosensory or tactile mechanism from the mouth mediated this change. This finding is analogous to previous reports of cephalic modulation of digestive processes by food in the mouth (Helman, 1988; Teff & Engelman, 1996).

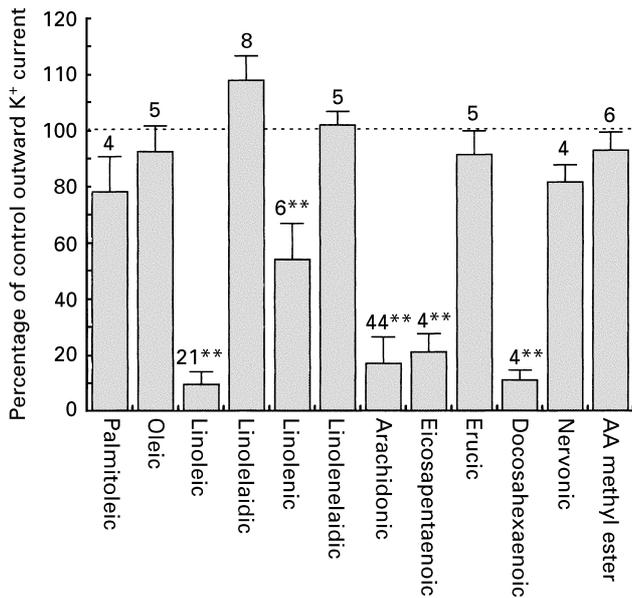


Fig. 2. Effect of oral administration of free fatty acids on suppression of steady-state outward potassium ion current from taste-receptor cells in the rat. AA methyl ester, arachidonic acid methyl ester. The values shown indicate the number of taste receptor cells tested. Values are means and standard deviations represented by vertical bars. Mean values were significantly suppressed by the free fatty acid: ** $P < 0.01$. (From Gilbertson *et al.* 1997; reproduced with the permission of the American Physiological Society.)

Summary and conclusions

The findings presented in the present review show that subtle differences exist in the feeding behaviour response to dietary components. Furthermore, the responses vary according to the site of interaction of dietary components with the gastrointestinal tract. It is apparent that not only can feedback interactions occur to modulate the nature of the feeding behaviour response, but also feed-forward interactions can be demonstrated which appear to play an important role in the modulation of human feeding behaviour. The physiological responses to dietary components depend not only on the energy content and specific macronutrient composition, but also the particular structure of the sugars, fats, or proteins contained therein. These factors probably influence the feeding behaviour response due to a combination of effects. First, the chemical structure influences the physical properties of molecules, affecting the rate of digestion and absorption, and thereby influencing the timing and extent of interaction with receptive areas of the gut. Second, differential receptor affinities for particular dietary components may exist, indicating that particular molecules may directly influence the feeding response to a greater extent than others. Currently, our understanding of the nature of these interactions is very limited. Further study in this area will increase our understanding of the mechanisms by which dietary components are recognized, and may also provide useful strategies for manipulation of the diet to enhance satiety.

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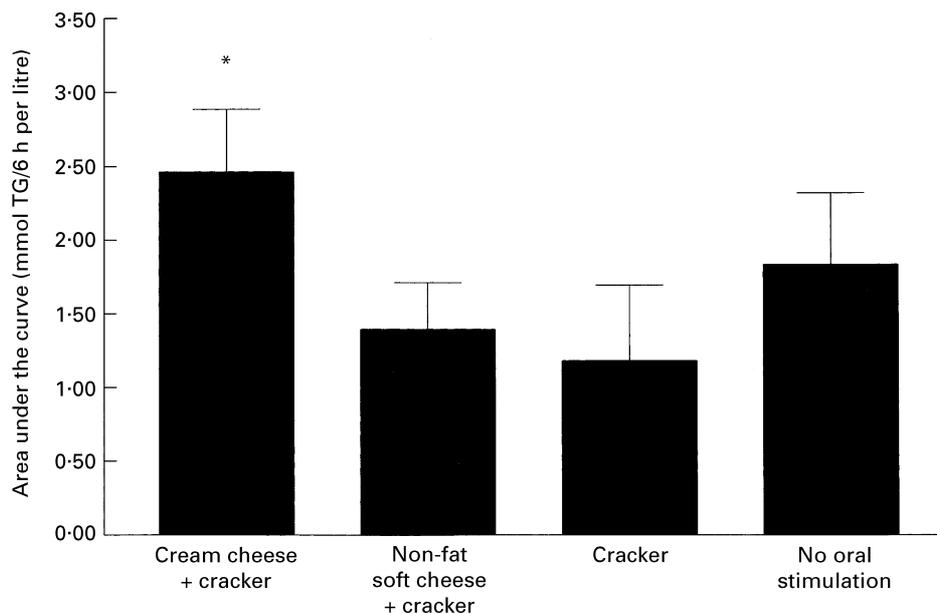


Fig. 3. Area under the curve for plasma triacylglycerol (TG) concentration during the 6 h after lipid load ingestion and various forms of lipid stimulation. Values are means with their standard errors represented by vertical bars. Mean value was significantly different from those for all other treatments: * $p < 0.05$. (From Mattes, 1996; reproduced with the permission of the American Society for Clinical Nutrition.)

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