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Metabolic aspects of satiety

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The simple view of satiety is that it occurs when the combined strength of signals from gastrointestinal and liver receptors reaches a threshold. However, this does not allow for long-term balancing of feed intake with requirements, as in order to match food intake with requirements feeding must terminate long before the animal knows how much of the various nutrients have been absorbed. Therefore, some way(s) of predicting nutrient availability is required. Learned associations between the organoleptic properties of a food and its eventual nutritive values is one mechanism. Another is the learned association between the gastrointestinal effects and eventual yield of nutrients, while another is learned associations between the early metabolic effects of the nutrients absorbed from a meal on liver and brain, and eventual nutrient yield. It is not anticipated that the total of all these mechanisms could be accurate, so that feedbacks from the regulated stores of nutrients are required in addition to the previously mentioned immediate effects of a meal on feeding. Therefore, satiety is induced and feeding ceases at a point at which the total of all the signals, from both direct physical and chemical stimuli and from learned associations, reach a satiating level. It is the purpose of the present review to consider the components of this complex that are generated within the body directly and indirectly as a result of eating.

In searching for satiety signals we are looking for changes in the body that go in one direction during a meal, may continue in that direction for some time after the meal, but eventually return to the premeal level. There are many metabolites and hormones which exhibit such changes and several will be examined in turn, some more cursorily than others in view of the brevity of the present review.

GLUCOSE

One of the original 'metabolic' theories of intake control postulated that animals eat in order to maintain a relative constancy of blood glucose concentration and the classical glucostatic theory of food intake control envisages central nervous sensitivity to glucose. While this has since been broadened to encompass energy utilization or availability, the fact that glucose is the major source of energy in many animals has meant that it continues to be viewed as a major contributor to satiety.

Plasma glucose rises during a meal and peaks shortly after the meal ends (Louis-Sylvestre & Le Magnen, 1980) and could be a direct cause of satiation. Preventing the fall in blood glucose concentration which normally occurs just before a meal, in rats, maintained satiety so that animals which would have otherwise started to eat 12 min later actually waited 318 min before starting to eat (Campfield *et al.* 1985). Glucose introduced into the stomach has a much greater effect on the size of a subsequent meal than the same amount of the unabsorbable analogue of glucose, 3-O-methylglucose (Booth, 1972*a*), showing that the metabolic effect of glucose is more important than the osmotic effect; fructose, which is used by the liver, was as effective as glucose in suppressing

feeding (Booth, 1972*b*); galactose was ineffective as it is utilized very inefficiently by the liver. These results demonstrate a post-absorptive effect of glucose on feeding in which the liver and the central nervous system (CNS) have been particularly implicated as sensors.

Liver. The importance of the liver was confirmed by infusion of glucose into the hepatic portal vein which depressed food intake to a much greater extent than infusion into the jugular vein (e.g. Novin *et al*. 1974). This effect is blocked by vagotomy (Martin *et al*. 1978). In the last decade a considerable amount of work has been done to elucidate the mechanism by which the liver senses the availability of energy-yielding substrates and this has been reviewed by Forbes (1988). In summary, infusion of substances which are oxidizable in the liver (or which mobilize oxidizable substrates) depress food intake while those which are not oxidized, even though they may be metabolized, do not affect feeding. Blocking the sodium pump by injection of ouabain intraperitoneally prevents oxidation in the liver and results in increased food intake (Langhans & Scharrer, 1987). Ouabain also suppresses the decrease in vagal firing rate when glucose is infused into the hepatic portal vein (Niijima, 1981). This evidence supports the hypothesis that changes in the polarization of the hepatocyte membrane affects the firing rate in vagal afferent fibres. These pass via the hepatic plexus to the coeliac ganglion and, thence, to the CNS via the splanchnic nerves. Information is first integrated in the nucleus tractus solitarius in the hind-brain before being relayed to the hypothalamus.

Several authors claim to have refuted the idea that the liver plays an important role in the control of food intake as they have been unable to influence feeding by manipulations of the type mentioned previously. Bellinger (Williams & Bellinger, 1986), in particular, has failed to show effects of portal vein infusions of glucose in dogs, but the animals had been fasted for 23 h so that their metabolism was not that of a fully *ad lib*.-fed animal. The accumulated evidence is persuasive that, under many conditions, the liver plays an important role in satiety.

As stated previously, in order to be fully effective signals from the liver have to become associated with the type of food being eaten. Langhans *et al*. (1989) presented a novel diet to liver-denervated rats immediately after surgery and found that they ate more on days 1–4 after the operation than sham-operated rats; with no negative feedbacks from liver it took the animals several days to realize the nutritive value of new food. Tordoff & Friedman (1986) also demonstrated the importance of the learned component based on work in which rats were given infusions of glucose paired with one flavour of food and infusions of saline (9 g sodium chloride/l) paired with another flavour. In rats with jugular catheters there was no subsequent preference for either flavour whereas the animals with portal vein catheters, in which glucose infusion depressed intake, subsequently showed preference for the flavour which had been paired with glucose infusion. Thus, not only was infusion of glucose at physiological rates not aversive, it actually formed the basis for the acquisition of a learned food preference. It is not surprising then that experiments which have not given animals chance to associate the organoleptic characteristics of the food with the metabolic effects of the infusions are amongst those in which there was a lack of effect of hepatic portal infusion of glucose.

CNS. It is known that the area postrema and the nucleus of the solitary tract in the hind-brain are sensitive to reduced glucose availability (Grill, 1986) and that receptors in the fore- and hind-brain appear to be linked with those in the liver (Shimizu *et al*. 1983); presumably there is an integrated system for monitoring energy status with multiple

inputs and built-in redundancies analogous to systems for controlling other vital functions of the body, such as the circulation.

A shortage of glucose availability to the brain stimulates food intake whereas an increased supply of glucose given into the cerebroventricles does not depress intake (Parrott & Baldwin, 1978; Ritter & Edwards, 1986). This suggests that the brain can act in an emergency to alleviate an energy shortage by inducing feeding but does not directly play a part in preventing excessive intake; for this purpose it depends on information relayed from other parts of the body, particularly the liver. Glucoprivation causes activation of the sympathetic nervous system leading to release of catecholamines, glucocorticoids, growth hormone and glucagon, as well as inhibition of insulin secretion, all of which mobilize glucose and protect the brain.

AMINO ACIDS

Amino acids are absorbed during the digestion of protein and when infused into the hepatic circulation can depress intake. Most of the effects of amino acids on the liver can be ascribed to their oxidation, however, and it is not likely that there are specific receptors for each amino acid. This is not to deny, however, the ability of animals to sense a deficiency or excess of amino acids and modify their diet selection accordingly.

TRIACYLGLYCEROLS, GLYCEROL AND FREE FATTY ACIDS

There is an increase in triacylglycerol levels in blood during meals of a high-fat diet and intravenous infusion of fat emulsion depresses intake, an effect that is not accompanied by changes in plasma glucose or insulin concentrations (Woods *et al.* 1984). The liver is an important site of fat metabolism in mammals and especially in birds where Lacy *et al.* (1986) found that cockerels of an egg-laying strain were sensitive to fat infused into the hepatic portal vein, but not into the jugular vein, while in broilers there was no effect, irrespective of site of infusion. In a converse manner to the infusion of triacylglycerol, reducing the availability of dietary fat for oxidation in the liver of the rat by insulin treatment stimulated intake at a subsequent meal (Friedman & Ramirez, 1987).

The continuous turnover of adipose tissue involves the release of fatty acids, glycerol and ketones. Glycerol levels in blood do not increase during a meal so that any involvement in the control of intake is more likely to be as a long-term signal of adiposity, added to the immediate signals of the nutrient value of food being eaten or recently eaten. Wirtshafter & Davis (1977) showed that exogenous glycerol depressed intake and suggested that glycerol might be a factor linking adiposity with intake as adipose tissue is continually releasing fatty acids and glycerol. However, it might simply be oxidation in the liver that is responsible for the intake-depressing effect of exogenous glycerol. The effect of glycerol on feeding was prevented when a high-protein diet was given, which would reduce the rate of glycerol oxidation in the liver.

Intravenous infusion of long-chain fatty acids depresses feed intake in sheep (Vandermeerschendoize & Paquay, 1984) and in the rat the intake-depressing effects of fatty acids are blocked by substances which block fatty acid oxidation. Inhibition of fatty acid oxidation with mercaptoacetate increased intake of a diet containing 180 g fat/kg but had no effect when the diet contained only 30 g fat/kg (Scharrer & Langhans, 1986). Presumably rats on the medium-fat diet were accustomed to obtaining a significant

proportion of their energy from fat so that when this source was denied them they ate more food, whereas in the low-fat diet fatty acids provided such a small proportion of their energy that there was no need to eat significantly more when fatty acid oxidation was inhibited. Vagal section prevented the effect of mercaptoacetate on the medium-fat diet (Langhans & Scharrer, 1986), further strengthening the belief that fatty acids can play a significant role in satiation via the liver.

INSULIN

The metabolites referred to previously are mostly products of the digestion of a meal and their potential for controlling feeding are fairly obvious. In addition, they have many effects on the secretion of hormones which might, therefore, be indirectly involved in satiety.

Insulin secretion rises during a meal and continues during the absorption of the products of digestion of the meal. It is, therefore, in a position to act as a satiety hormone and short infusions of insulin hasten the termination of feeding. This satiety seems to be a pleasant sensation because when the insulin was paired with a flavour, rats subsequently preferred that flavour (Oetting & Vanderweele, 1985). Infusion of insulin at physiological levels into the third ventricle depresses intake (Plata-Salaman & Oomura, 1986) and the natural rise in insulin secretion which accompanies fattening has been implicated in the reduction in intake in fat animals.

In contrast to these observations, chronic treatment with insulin increases the rate of fat deposition and stimulates food intake. It seems as if insulin depresses intake in the presence of high rate of supply of nutrients but stimulates intake when the availability of nutrients is insufficient to match the increased demand created by insulin treatment; there was only a 40% reduction in intake when glucose alone was infused intravenously at 170% of the normal rate of utilization, but a 70% reduction when insulin was also administered (Even & Nicolaidis, 1986); insulin alone stimulated intake.

GLUCAGON

The concentration of glucagon increases during feeding and the rapidity of this increased secretion suggests that it is induced by the autonomic nervous system or gut hormones, or both, rather than by changes in blood glucose concentration. Exogenous glucagon depresses feeding. Very small amounts (25 ng) given directly into the cerebral ventricles depressed intake (Inokuchi *et al.* 1984), but it seems unlikely that changes in glucagon secretion can be sensed by the brain as there is little change in circulating glucagon concentration during and between meals, the fluctuations being absorbed by the liver (Langhans *et al.* 1984).

Section of the vagus nerves close to the liver blocks the effect of glucagon given into the portal vein of rats (Weatherford & Ritter, 1986), but Strubbe *et al.* (1989) found that glucagon had the same effect on intake whether given into the general circulation or into the hepatic portal vein and claimed that this refuted the idea that the satiating effect of glucagon was primarily via the liver. Further doubts were cast by Langhans *et al.* (1987) on the physiological nature of doses of glucagon which depressed feeding when they found that the minimal dose given intraperitoneally (480 μg/kg) elevated blood levels of glucagon by thirty–seventyfold, i.e. a grossly unphysiological amount.

GUT PEPTIDES

The secretion of several gut hormones is increased during feeding and subsequently as digesta pass through the stomach and duodenum. Of these cholecystokinin (CCK) is perhaps the most studied as a satiety signal, but others, such as bombesin and gastrin have also been implicated. As these are discussed in some detail in the present Symposium by Rayner (1992) and Read (1992) they will not be further covered here.

CATECHOLAMINES

Adrenaline secretion increases during feeding, both from the adrenal medulla and from sympathetic nerve endings in the liver, and this may act as a satiety signal, perhaps by its influence on glucose metabolism. α- and β-receptor blockers prevented the intake-depressing effects of exogenous adrenaline (Langhans *et al.* 1985) but there were no effects on spontaneous feeding. The intake-depressing effects of adrenaline infused into the hepatic portal vein of the rat are blocked by abdominal vagotomy, but not by hepatic vagotomy (Tordoff & Novin, 1982), showing that it is not principally the liver which is mediating the intake-depressing effects of adrenaline. It can be concluded that the status of peripheral catecholamines as regulators of feeding behaviour in response to metabolic signals is uncertain.

OTHER 'HORMONES'

Numerous other hormones and metabolites have been found to depress food intake, to be present in increased amounts during or after feeding, or both, and, therefore, to be potential satiety agents. Amongst these are bombesin, calcitonin, satietin, vasopressin and adipocyte satiety factor.

CONCLUSIONS

Attempts to understand what causes animals to stop eating have often involved injection of putative satiety factors into parts of the digestive or vascular systems with observation of food intakes during and after the injection period. In a 'well-designed' experiment each animal is given each treatment only once before it is given control and other treatments in a Latin-square design. Thus, the animals are not given the opportunity to learn to associate the effects of the injection with any characteristic of the food and are denied an important route of control which is normally open to them, i.e. learned associations between the organoleptic properties of the food, its eventual visceral effects and yields of metabolites. It is postulated that many such experiments have underestimated the satiating effects of metabolites and some may even have shown no effects of a factor which is, under 'natural' circumstances, actually quite important.

To suppress feeding completely (cause satiety?) it is necessary to infuse not just a supply of energy, but also fat and protein (Nicolaidis & Rowland, 1976), and it is abundantly clear that satiety is not induced by a single mediator acting on a single group of receptors in a single target organ. A simple explanation of how different signals might be integrated is given by the theory of additivity of negative and positive feedback signals in which the total effect on the CNS of all the various signals coming from mouth, gut, liver etc. are added together; once the total signal exceeds a threshold then feeding

ceases. Experimental evidence includes the approximate additivity of effects of infusion of short-chain fatty acids and inflation of a balloon in the rumen (sheep, Adams & Forbes, 1981; cows, Mbanya *et al.* 1989), of rumen infusion of acetate and hepatic portal infusion of propionate (Adams & Forbes, 1981), of glucagon and CCK in rats (Le Sauter & Geary, 1987), and of insulin and CCK given into the cerebral ventricles (Figelwicz *et al.* 1986).

A more realistic theory relies not just on the direct effects of stimulation of receptors but on learned associations between the organoleptic properties of the food(s), the subsequent effects on receptors in the gastrointestinal tract, and the eventual yield of nutrients. This comes into the realm of Booth's (1992) paper.

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