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Appetite regulation – does it exist?

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ABSTRACT

Appetite regulation and feeding behaviour are critical for survival. Through appetite regulation the proper amounts of fat, carbohydrate and protein are provided through specific signals, as has been demonstrated both in rodents and in man. Although feeding is necessary to provide energy, it also leads to severe perturbations in the homeostasis of the body. To help the body to maintain homeostasis various pre-meal events occur, such as the cephalic phase secretion of pancreatic juice, the production of satiety signals and the production of heat. The latter probably involves the action of uncoupling proteins present in the intestine. The diet-induced thermogenesis is hence important for achieving energy balance in the body. The increasing prevalence of obesity in the Western world is suggested to be a consequence of the overflow of tasty high-fat and sweet food items, which after ingestion override the original rules that we were once constructed for.
Keywords: diet-induced thermogenesis, leptin, NPY, opiates, uncouling protein

Introduction

Animals and humans eat for a variety of reasons, the most obvious being energy deficiency. Other reasons for eating involve palatability/reward, stress, social setting and in the case of humans the availability of food at little or no cost. The various situations involve different signals and molecular mechanisms (1,2) .

Energy deficiency feeding

Historically, the first studies of appetite regulation had as a working model that feeding was initiated by food deprivation or food restriction. The underlying concept was that the body continually sensed the amount of energy available; hence a deprivation of food would trigger the onset of feeding. According to *Mayers'* glucostatic theory a decline in blood glucose would trigger the start of a meal (3). In an analogous way a lipostatic model was proposed, stating that appetite regulation was closely related to the amount of fat stored in the adipose tissue, a depletion of adipose tissue stimulating food intake (4). These theories are still valid today, the molecular mechanisms being continuously identified.

In the case of energy deficiency feeding one important candidate apperars to be neuropeptide Y (NPY). NPY is a potent appetite-stimulating signal, produced in the arcuate nucleus of the hypothalamus (5). When injected into rat NPY promotes food intake in satiated rats. Moreover, in a macronutrient choice between carbohydrate, protein and fat, NPY has been found to stimulate carbohydrate intake (6). The ability of NPY to specifically stimulate carbohydrate intake may be important to re-establish energy balance after an overnight fast, the storage of carbohydrate being highly limited. That NPY is important for feeding behaviour in a state of energy deficiency has been suggested by several groups demonstrating increased levels of NPY mRNA following food deprivation or food restriction (7). In addition to an appetite-stimulating effect NPY also suppresses energy expenditure in brown adipose tissue. Moreover, NPY has been found to divert the ingested glucose to white adipose tissue, where it is converted to triacylglycerol, NPY hence promoting a gain in body weight. Other energy-consuming activities, such as intense running or lactation, have also been found to increase the endogenous production of NPY levels in the hypothalamus in rat (8), supporting the role of NPY in re-establishing energy balance during energy deficiency.

Taste feeding

Humans and animals overeat as a result of readily available palatable food, leading to a positive energy balance. This overeating hence occurs even if the animal or human being is already in energy balance. The taste signals hence override the energy balance system of the body and work through different mechanisms.

One important component in the taste/reward feeding system is the endogenous opiate system, as suggested several years ago (9). Hence, opioids have been found to increase food intake in satiated rats, and if given a choice the animals prefer high-fat food to low-fat food (10). Also sweet food is preferred to non-sweet food under the influence of opiate agonists (11). That opiates are more important in fed rats than in food-restricted animals was demonstrated by studying the influence of naloxone, an opiate antagonist, on fed and fasted rats (10). In such experiments it was found that naloxone had no or only a minor effect during consumption of various carbohydrate items in chronically food-restricted rats, whereas in satiated rats the opiate influence was more important. The endogenous production of opiate peptides has also been shown to be decreased in situations of food restriction and increased during the consumption of energy-rich and tasty food like fat and sucrose (12). Moreover, repeated injections of opiate agonists caused a steadily increased food intake, which might indicate a state of "dependence". The significance of these findings is that reward/palatability eating creates a "self-perpetuating" eating pattern, whereas food restriction leads to a loss of reward eating.

When do we stop eating?

Does the body defend itself against overeating or are overweight and obesity a physiological adaptation to a wealth-fare situation as occurs in the Western world with the steadily increased prevalence of obesity?

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In fact, the body has powerful defence mechanisms against overeating, the primary mechanisms residing in the gastro-intestinal tract. These defence mechanisms may be seen as strategies to minimise the homeostatic pertubations during feeding. We must realise that to the body homeostasis *all meals are disturbing events.* One strategy is the digestive secretion occurring during the cephalic phase, which begins at the sight or smell of food. This secretion is dependent on the taste of the food as well as on the familiarity with the food. *Sarles* et al. (13) found that a familiar French breakfast caused a significantly higher pancreatic flow in a group of French patients compared to an unfamiliar meat-containing English breakfast! In further studies aversive taste stimuli lead to a low pancreatic response. This is an important message to "forbid" potential feeding situations, where children are "forced" to eat food that they dislike.

Another strategy to minimise the homeostatic disturbance following feeding is the production of satiety signals, mostly peptides, that restrict feeding (Figure 1). These signals reside primarily in the gastro-intestinal tract, like the cholecystokinin (CCK) and *glucagon-like peptide,* and cause satiety, as demonstrated both in animals and in man. Hereby, CCK acts mainly to inhibit gastric emptying (14), while glucagon-like peptide has a central appetite-decreasing effect (15). In addition, signals residing outside the gastro-intestinal tract assist in restricting food intake. One important candidate molecule is *leptin*, produced in the adipose tissue (16), which reduces feeding. The mechanism of action for leptin involves a class I cytokine receptor for leptin, localised in the brain. It has also been demonstrated that leptin counteracts the appetite-stimulating effect of NPY (17), NPY-leptin hence forming an important system for regulating energy balance. The importance of leptin for appetite regulation in man has been clearly demonstrated in two severely obese children, with total lack of leptin, due to a genetic mutation (18). These children are being treated with recombinant leptin, leading to a reduced body weight.

Most obese patients do not lack leptin; instead the levels of leptin have been found to be elevated (19). This phenomenon has given birth to the expression "leptin resistence", which suggests that the system somehow is resistant to the effects of leptin. The mechanism of action for this resistance is not known, but may be due to the failure of action of a couple of leptin-dependent anorectic peptides, such as cocaine- and amphetamine-regulated transcript (CART), melanocyte stimulating hormone (MSH) and CCK.

Leptin: MCWRPLCRFLWLWSYLSYVQAVPIHKVQDDTKTLIKTIVTRINDISHTQSVSARQRVTGLDFIPGLHPILSLSKMDQ TLAVYQQILTSLPSQNVLQIAHDLENLRDLLHLLAFSKSCSLPQTRGLQKPESLDGVLEASLYSTEVVALSRLQGSLQDILQQ LDLSPEC

NPY: MLGNKRLGLSGLTLALSLLVCLGALAEAYPSKPDNPGEDAPAEDMARYYSALRHYINLITRQRYGKRSSPETLISDLL MRESTENVPRTRLEDPAMW

Glucagon-like peptide 1: HDEFERHAEGTFTSDVSSYLEGQAAKEFIAWLVKGR

CCK (8): DYMGWMDF

CCK (33): KAPSGRMSIVKNLQNLPSHRISDRDYMGWMDF

Met-enkefalin: YGGFM

Leu-enkefalin: YGGFL

Beta-endorfin: YGGFMTSEKSQPTLVTLFKNAIIKNAYKKGE

Dynorfin: YGGFLRRIRPKLKWDNQ

Enterostatin: APGPR

Figure 1. Amino acid sequences of a couple of appetite-regulating peptides. Amino acids are here noted by the one-letter code. CCK (8) and CCK (33) indicate number of amino acids.

The body also produces signals that affect the taste feeding. One such molecule is *enterostatin*, which has been found to restrict fat intake in experimental animal models (20,21). The mechanism of action suggests a target protein of 53 kDa, which specifically binds enterostatin, opiate peptides (*met-enkephaline and β-casomorphine*) acting as competitive inhibitors for this binding (22).

A third strategy to maintain homeostasis during feeding is the production of heat. Every feeding event leads to a rise in body temperature, a process named diet-induced thermogenesis. This rise in body temperature occurs steadily during a meal and declines rapidly after the meal has ended. According to the theory of thermostatic regulation of feeding (23), Figure 2, the rise in body temperature acts to restrict feeding, feeding being stopped to avoid hyperthermia, a critical temperature being 39.3°C in mouse (24). The rise in temperature has several favourable effects in attaining homeostasis, since digestion and absorption of food products is accelerated as well as the passage of food through the intestine (2).

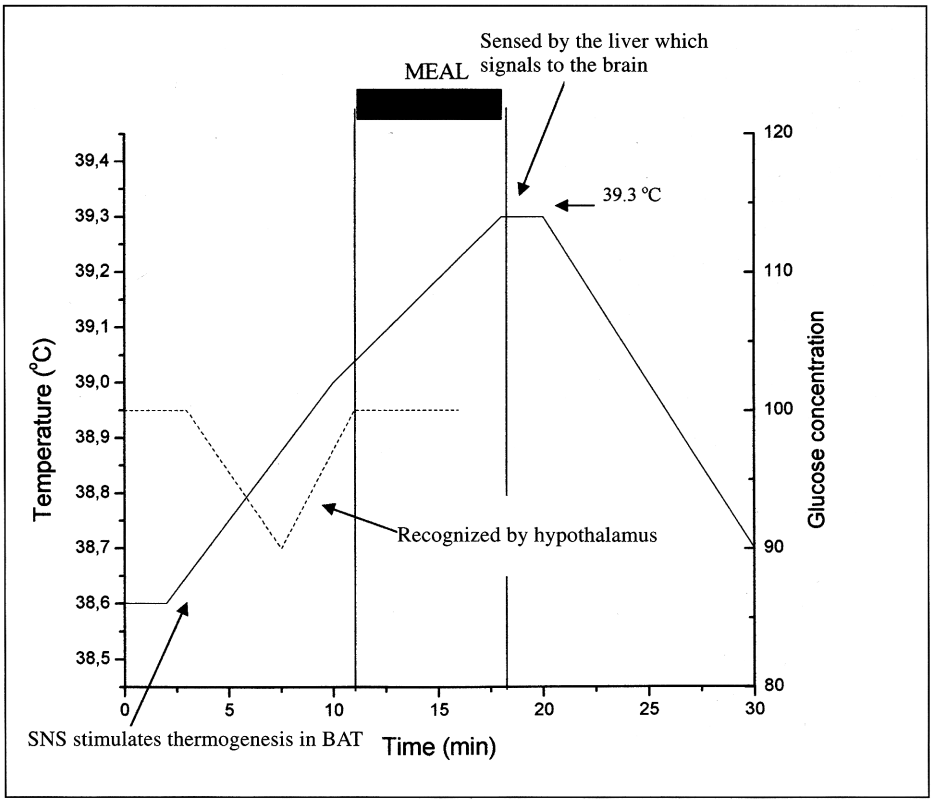

Figure 2. According to the thermostatic theory for regulation of food intake is arrested at a certain critical temperature to avoid hyperthermia, feeding being an important metabolic activity producing heat (23).

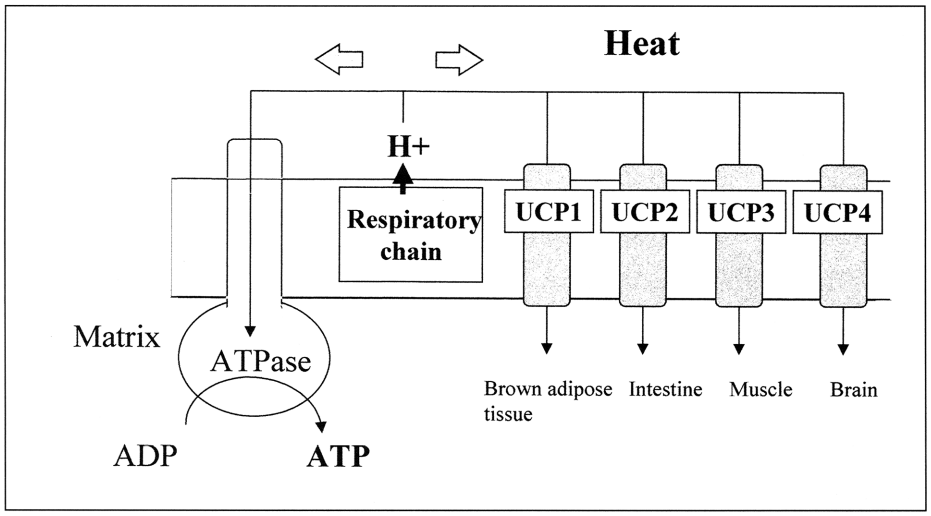

Figure 3. Uncoupling proteins produce heat by uncoupling respiratory chain from ATP-synthesis. There are now four different proteins, UCP1-4. In the intestine UCP2 is present in high amounts and may contribute to the diet-induced thermogenesis.

Heat production through uncoupling proteins

The production of heat occurs through a rise in metabolic activity. This is seen following the various processes occurring during feeding, i.e. chewing, swallowing, digestion, absorption and metabolism of food products. Another stimulus for metabolic activity is mitochondrial uncoupling due to the presence of a recently discovered family of uncoupling proteins in the intestine, named *uncoupling protein 2* (25), Figure 3. These proteins uncouple the electron transport chain in the inner mitochondrial membrane from ATP synthesis, creating heat instead of chemical energy. The regulation of these proteins and their expression is being investigated; in the intestine enterostatin has been shown to cause an upregulation of uncoupling protein 2, which could be an important appetite restricting effect. Leptin has in a similar way been demonstrated to cause an upregulation of uncoupling protein 2 in the adipose tissue (26), whereas NPY has been demonstrated to have the opposite effect. This suggests that uncoupling proteins may be important target molecules in appetite regulation.

Conclusions

In conclusion, a couple of strategies assist the body during a meal to restrict feeding and allow the body to reach energy balance as soon as possible after food taking. In spite of these restricting signals there is an increasing prevalence of obesity in the affluent society. This increased prevalence of obesity is probably due to the surplus of highly tasty and energy-rich food items, which we were originally shaped to be rewarded by and which we cannot resist.

The present situation is hence completely new in evolution, defence mechanisms being insufficient in most people. Education and information is so far the only remedy that works, judging from the inverse relationship found between body weight and education, from school to university (27). Women seem more ready to learn than men (28)! "The doctor entertains the patient, while Nature heals the patient", was a saying attributed to the French philosopher *Jean-Jacques Rousseau.* In today's situation we need both the doctor and the dietician to entertain and heal the patient. Nature does not manage!

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