MiniReview

How Palatable Food Disrupts Appetite Regulation

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Abstract: Appetite regulation is part of a feedback system that controls the energy balance, involving a complex interplay of hunger and satiety signals, produced in the hypothalamus as well as in peripheral organs. Hunger signals may be generated in peripheral organs (e.g. ghrelin) but most of them are expressed in the hypothalamus (neuropeptide Y, orexins, agouti-related peptide, melanin concentrating hormone, endogenous opiates and dopamine) and are expressed during situations of energy deficiency. Some satiety signals, such as cholecystokinin, glucagon-like peptide 1, peptide YY and enterostatin are released from the digestive tract in response to food intake. Others, such as leptin and insulin, are mobilized in response to perturbations in the nutritional state. Still others are generated in neurones of the hypothalamus (α-melanocyte-stimulating hormone and serotonin). Satiety signals act by inhibiting the expression of hunger signals and/or by blunting their effect. Palatable food, i.e. food rich in fat and sugar, up-regulates the expression of hunger signals and satiety signals, at the same time blunting the response to satiety signals and activating the reward system. Hence, palatable food offsets normal appetite regulation, which may explain the increasing problem of obesity worldwide.

Today obesity is the greatest threat to public health in the developed world. It is a silent killer in many disorders, such as heart disease, hypertension and diabetes that are the consequences of obesity (Taubes 1998). Genetic factors are certainly important for the development of obesity. This is true for a large number of mutations, for instance those occurring in the melanocortin receptor gene (Yeo et al. 2003). Hence, it has been found that mutations in the melanocortin receptor gene result in a distinct obesity syndrome that is inherited in a co-dominant manner (Farooqi et al. 2003). Various other mutations are associated with obesity as illustrated by leptin gene deficiency (Montague et al. 1997) or leptin receptor gene deficiency (Clement et al. 1998). Although such mutations verify the importance of genetic factors, they do not explain obesity world-wide (Frooguel et al. 2000).

The most important cause of obesity is probably over-eating (coupled with inactivity). Over-eating is stimulated by the ready availability of food rich in fat and sugar. Appetite regulation and the understanding of the rewarding effect of food, in particular energy-rich food (fat and sugar), has become of great scientific interest. Much knowledge has been provided by techniques of molecular biology, which have identified a large number of genes and gene products responsible for sensations of hunger and satiety. On one hand food intake appears to be a highly regulated process, considering the irregularity in the number and composition of meals from one day to the next, and the energy balance and stability in body weight over longer periods of time. On the other hand obesity in the world is increasing, suggesting that there is a fundamental weakness in the regulation of appetite and in the control of energy homeostasis. The aim of this article is to review the mechanisms underlying appetite regulation and the influence of highly palatable food on this process. This review draws from previous overviews on the control of hedonic eating (Saper et al. 2002; Cummings & Schwartz 2003; Zigman & Elmquist 2003; Gale et al. 2004).

General aspects of hunger and satiety

The regulation of food intake is based on an intricate feedback system, which is influenced not only by the availability of nutrients but also by various environmental and psychological factors. It is a complex system, as has been described in a number of recent reviews (Schwartz et al. 2000; Blundell & Gillett 2001). Basically however, food intake is controlled by hunger and satiety signals. The signals are generated in peripheral organs, such as the digestive tract and adipose tissue, and in the brain itself. Certain neurones in the hypothalamus are the targets of these signals. The fairly recent identification of hunger- and satiety peptides as well as their receptors has renewed the interest in appetite regulation with special focus on the identification of tools that might be useful in the pharmacological treatment of eating disorders, from anorexia to over-eating and obesity.
Hunger signals and the drive to eat

The identification of appetite regulating signals started with the realization that satiety peptides signals are of paramount importance in appetite control (to terminate food intake). It has since become clear that the sensation of hunger, the drive to seek food, is the central event in appetite regulation, satiety signals inhibiting the effect of hunger signals. Quite a few hunger peptides have been identified, among these neuropeptide Y, ghrelin, the orexins and agouti-related peptide, and the melanin-concentrating hormone.

Neuropeptide Y is a 36 amino acid peptide with sequence homologies with pancreatic polypeptide and peptide YY. It is abundantly expressed in both the central and peripheral nervous system (Allen et al. 1983), a great density of neuropeptide Y neurones being observed in the arcuate nucleus, projecting to the paraventricular nucleus. Injection of neuropeptide Y into the paraventricular hypothalamus stimulates food intake in the rat, carbohydrates in particular (Stanley & Leibowitz 1985). Upon intracerebroventricular injection neuropeptide Y suppresses energy expenditure from brown adipose tissue (Billington et al. 1994). A physiological role of neuropeptide Y is suggested by the fact that it is released from the hypothalamus in situations of fasting and in situations of increased energy demands, such as exercise and lactation. Long-term infusion of neuropeptide Y into the lateral ventricle of mice produces hyperphagia, insulin resistance, and obesity (Raposinho et al. 2001). Raised neuropeptide Y mRNA levels in specific hypothalamic nuclei, including the arcuate nucleus and the paraventricular nucleus are found in animals with hyperphagia and obesity (Gao et al. 2002). Upon fasting the neuropeptide Y knockout mouse has a lower food intake than wild-type mice, nut normal body weight (Bannon et al. 2000), supporting a role for neuropeptide Y in mediating energy intake and energy homeostasis. Both leptin and insulin inhibit the expression of neuropeptide Y and its receptor (Schwartz et al. 1991; Erickson et al. 1996), which can be interpreted to mean that hunger elicited by neuropeptide Y is controlled by leptin and insulin.

High-fat diets have been found to either reduce the expression of neuropeptide Y in neurones of the arcuate nucleus (Giraudo et al. 1994; Lin et al. 2000) or to stimulate neuropeptide Y expression (Huang et al. 2004). The reason for the conflicting data is not clear, but the type of fat ingested is probably important, saturated fat producing an upregulation of neuropeptide Y expression in contrast to polyunsaturated fat (Huang et al. 2004). A sucrose-containing diet has been found to stimulate the expression of hypothalamic neuropeptide Y, and to cause hyperglycaemia, hyperinsulinaemia and an increased body weight (Kaga et al. 2001). Since neuropeptide Y stimulates food intake an upregulation of hypothalamic neuropeptide Y by saturated fat or by sucrose may be one reason for the hyperphagia induced by palatable food.

Ghrelin is a meal initiator, circulating levels being elevated during fasting and suppressed following a meal (Tschop et al. 2000; Dornonville de la Cour et al. 2001; Wren et al. 2001 & 2002). It is produced in the stomach by endocrine cells (A-like cells) in the oxyntic glands and secreted into the blood stream (Dornonville de la Cour et al. 2001). The pre-prandial rise in ghrelin is not proportional to the ingested caloric load during the previous meal (Callahan et al. 2004). Ghrelin receptors occur in the arcuate nucleus, where they activate neuropeptide Y neurones (Tschop et al. 2002). It has also been shown that ghrelin releases neuropeptide Y from hypothalamic explants in vitro, suggesting that it may be a mediator of the ghrelin effect (Wren et al. 2002). A role of endogenous ghrelin in appetite regulation is suggested by an increased ghrelin expression in the stomach following fasting and a decrease in circulating ghrelin after intake of a regular chow meal (Dornonville de la Cour et al. 2001; Kim et al. 2003). The suppression of plasma levels of ghrelin following a meal may be an effect of nutrients in blood. The most striking effect of long-term ghrelin treatment is the increased body weight and accumulation of fat (Tschop et al. 2000). That ghrelin may be involved in the defense against human obesity is suggested by the observation of decreased blood levels of ghrelin in obese subjects, as demonstrated in obese Pima Indians who were found to have 33% lower fasting plasma ghrelin than lean subjects (Tschop et al. 2001). Ghrelin has been shown to increase food intake in humans (Wren et al. 2001), demonstrated after a 270 min. infusion of ghrelin, during which a standard free-choice buffet was served.

Ghrelin expression in the mouse stomach is decreased in response to a high-fat diet (Moesgaard et al. 2004), an effect that may serve to restrain the hyperphagia induced by high-fat diets. The effect of sucrose on ghrelin expression is not known.

The orexins are two homologous peptides A and B, identified as ligands for two orphan receptors, belonging to the G-protein coupled receptor family (Sakurai et al. 1998). The two peptides derive from the same 130 amino acid precursor, prepro-orexin, that is cleaved into orexin A and B. They are produced in neurones of the lateral and posterior hypothalamus, which project widely in the brain. Intracerebroventricular injection of orexin A or B promptly stimulates food intake (Sakurai et al. 1998). There is a close interaction between neuropeptide Y, orexin and leptin, the expression of orexins being increased by neuropeptide Y and suppressed by leptin (Niimi et al. 2001). Orexin neurones are activated by fasting (Diano et al. 2003).

Orexin gene expression is stimulated by high plasma triglyceride levels, obtained either through high-fat consumption or through Intralipid infusion (Wortley et al. 2003). The effect of sucrose on orexin expression is not known.

Agouti-related peptide is a neuropeptide, synthesized and secreted by neuropeptide Y neurones in the arcuate nucleus (Korner et al. 2001). Agouti-related peptide stimulates appetite and causes obesity as first described in the yellow agouti mouse having an overexpression of agouti protein (Kleibig et al. 1995). Agouti-related peptide interacts with the melanocortin receptor, acting as a competitive antagonist to α-
melanocyte-stimulating hormone (α-MSH), which is an inhibitor of food intake. Administration of agouti-related peptide to hypothalamic explants stimulated the release of neuropeptide Y, suggesting that orexigenic behaviour can be enforced via a positive feedback loop (Dhillon et al. 2002).

Mice on a high-fat diet have higher agouti-related peptide mRNA expression in the bed nucleus of the stria terminalis and in the ventral part of the lateral sepalal nucleus than mice on a low-fat diet suggesting that agouti-related peptide may be involved in fat-evoked hyperphagia (Huang et al. 2003). The effect of sucrose on agouti-related peptide expression is not known.

Melanin-concentrating hormone is a proteolytic cleavage product of the melanin-concentrating hormone preprohormone of 165 residues, giving rise also to two other peptides, neuropeptide E-I and neuropeptide G-E (Shi 2004). Melanin-concentrating hormone-expressing neurones in the brain have a restricted localization to the lateral hypothalamic area and zona incerta (Zamir et al. 1986; Bittencourt et al. 1992) with projections to the nucleus of the solitary tract. Cumulative evidence suggests that melanin-concentrating hormone plays an important role in maintaining energy homeostasis by regulating food intake and energy expenditure (Shi 2004). Intracerebroventricular injection of melanin-concentrating hormone stimulates food intake in rats (Rossi et al. 1997; Shearman et al. 2003) and long-term infusion of melanin-concentrating hormone induces hyperphagia and body weight gain (Ito et al. 2003). The expression of melanin-concentrating hormone is upregulated by food deprivation (Qu et al. 1996; Herve & Fellmann 1997). It is also upregulated in the leptin-deficient ob/ob mouse, suggesting that leptin controls the expression of melanin-concentrating hormone (Segal-Lieberman et al. 2003). In addition to being present in the hypothalamus, melanin-concentrating hormone is also present in peripheral tissues and in blood (Sun et al. 2004). There is a positive correlation between serum melanin-concentrating hormone levels and body mass index and fat mass (Gavrla et al. 2005), in line with the view that circulating melanin-concentrating hormone acts as a hunger signal.

**Satiety signals and the termination of feeding**

The sensation of satiety (meal termination) reflects the suppression of hunger signals and/or the mobilization of satiety signals in response to a meal. Many of these latter signals derive from the pancreas and gastrointestinal tract, transmitting information from the periphery (via the vagus or via the circulation) to the brain. Other circulating satiety signals (nutrient metabolites) are generated in the liver, entering the brain from the blood (e.g. glucose and ketone bodies).

**Meal-initiated satiety signals from the digestive tract: cholecystokinin, glucagon-like peptide 1 and peptide YY.**

Gastrointestinal satiety peptides are released from the intestine in response to food. While all of these peptides reduce food intake in experimental animals, some of them, like cholecystokinin, glucagon-like peptide 1 and peptide YY, have been shown to reduce food intake also in man (Gutwiller et al. 2000).

**Cholecystokinin** was the first peptide hormone to be associated with meal-evoked satiety (Smith & Gibbs 1975). Cholecystokinin is released in response to nutrients in the duodenum and acts by stimulating vagal afferents, which carry cholecystokinin-1 receptors (Moran et al. 1997). Cholecystokinin is thought to act as a neurotransmitter or neuromodulator in various parts of the brain, for instance in the nucleus tractus solitarius and in the medial basal hypothalamus. Following intracerebroventricular injection of cholecystokinin food intake is reduced, whereas injection of a cholecystokinin-1-receptor antagonist stimulates food intake (Corp et al. 1997). One important effect of cholecystokinin is to suppress the neuropeptide Y expression in the dorsomedial hypothalamus (Bi et al. 2001). Rats lacking the cholecystokinin-1 receptor, the Otsuka Long-Evans Tokushima Fatty (OLETF) rats, have a five-fold elevation of neuropeptide Y expression in this region, which could explain their hyperphagia and obesity. Thus, cholecystokinin seems to be important within the brain to regulate hunger and satiety.

There is no data on the expression of cholecystokinin in the upper small intestine after high-fat or sucrose diets. The satiety response to circulating cholecystokinin is blunted in rats maintained on a high-fat diet compared to rats maintained on a low-fat diet (Covasa et al. 2000). Also, inhibition of gastric emptying by cholecystokinin is markedly attenuated in rats maintained on a high fat diet. The attenuation of cholecystokinin-induced inhibition of food intake and gastric emptying is thought to reflect a reduced vagal cholecystokinin responsiveness, measured as a decreased Fos expression in nuclei of the solitary tract and area postrema, where the vagal sensory fibers terminate (Covasa et al. 2000). There is also a blunted satiety response to cholecystokinin during hyperglycemia (Lam et al. 1998).

**Glucagon-like peptide 1** is a gut hormone derived from the processing of proglucagon in intestinal L cells. In addition to stimulating insulin release, glucagon-like peptide 1 also reduces food intake after intracerebroventricular administration (Turton et al. 1996). The glucagon-like peptide receptor knock-out mouse did not display obesity or increased food intake, possibly because other satiety systems were activated (Gallwitz & Schmidt 1997). Glucagon-like peptide 1 is of particular interest because it inhibits food intake also in man (Naslund et al. 1999). The mechanism behind the glucagon-like peptide 1-induced inhibition of food intake is probably a combined effect of gastric dilation and an increase in the level of circulating serotonin, associated with satiety (Owji et al. 2002). In dogs fed a high-fat diet the fasting plasma glucagon-like peptide 1 concentration was 2.5 times higher than in controls (van Citters et al. 2002). Additionally, expression of the glucagon-like peptide 1 receptor in the whole pancreas was increased 2.3 times in the fat-fed animals. This suggests that glucagon-
like peptide 1 may provide a defence against hyperphagia induced by high-fat food. The effect of sucrose on glucagon-like peptide 1 expression is not known.

Peptide YY is released from the intestinal L cells to reduce food intake in rodents as well as in man (Batterham et al. 2002). It acts to inhibit the electrical activity of neuropeptide Y neurones in the arcuate nucleus (Batterham et al. 2002). It has been suggested that peptide YY serves as a circulating factor mediating satiety following ingestion of a meal (Batterham et al. 2002). Peptide YY is active as a satiety signal with both high-fat and low-fat diets (Challis et al. 2004) and hence may provide a defence against fat-induced hyperphagia. Whether peptide YY acts as a satiety signal with sucrose-enriched food is unknown. Endogenous post-prandial levels of peptide YY were significantly lower in obese subjects compared to a lean group. Peptide YY infusion also caused a significant decrease in the cumulative 24 hr caloric intake in both obese and lean subjects, suggesting that obese subjects were sensitive to the peptide YY action (Batterham et al. 2003).

Adiposity related satiety signals: insulin, leptin and pro-opiomelanocortin (POMC)-derived peptides. Inter-meal and long-term signalling constitutes a complementary regulatory system that probably acts synergistically to short-term signals.

The ability of insulin to reduce food intake at first appeared a paradox, insulin being a hormone that promotes storage of energy in liver and adipose tissue. The paradox was resolved, when it was found that insulin induced satiety by acting on receptors in the brain, whereas the anabolic actions of insulin occurred peripherally (Woods et al. 2000). There is evidence that insulin passes the blood-brain barrier intact and in a regulated receptor-mediated fashion (Woods et al. 2003). When blood insulin is raised following a meal, the passage of insulin into the brain is thought to reflect this increase (Baskin et al. 1999). After fasting the penetration of insulin into the brain is greatly reduced with the consequence that a larger meal can be eaten before insulin evokes satiety (Strubbe et al. 1988).

High-fat diets induce insulin resistance, which from the point of view of appetite regulation means suppressed satiety (Kim et al. 2004). That insulin indeed inhibits the intake of high-fat food is clear from the use of non-peptide insulin mimetics, which when given intracerebroventricular were shown to reduce over-eating and prevent obesity in rats maintained on high-fat diet (Air et al. 2002). Intracerebroventricular injection of insulin has been shown to reduce sucrose intake in rats, that have been stimulated to eat sucrose by treatment with the opiate κ receptor agonist U50, 488 (Sipols et al. 2002). However, sucrose-rich diets are known to cause the classical signs of insulin resistance, with increased food intake, adiposity, hyperinsulinemia and hypertriglyceridaemia (Davidoff et al. 2004), indicating that the defence against over-eating afforded by insulin is overridden at some point. Also the passage of insulin through the blood brain barrier is decreased after a high-fat meal compared to a low-fat meal, hence leading to a reduced satiety (Gerozissis et al. 1997).

Leptin has emerged as a major suppressor of appetite and is therefore viewed as an anti-obesity hormone (Friedman & Halaas 1998; Leibel 2002; Loos & Bouchard 2003). This view is based on the finding that total deficiency of leptin or its receptor leads to hyperphagia and obesity in mice and man (Campfield et al. 1995; Montague et al. 1997). Leptin is a 16-kDa protein produced in adipose tissue and secreted into the blood. Leptin has its own receptor with signalling properties similar to the interleukin-6 receptor, localized to the arcuate nucleus (Tartaglia et al. 1995). Leptin is thought to pass the blood-brain barrier to reach its receptor, reducing food intake and increasing thermogenesis (Friedman & Halaas 1998). The main role of leptin is to control the expression and activity of various other appetite controlling peptides. One target for leptin is the arcuate nucleus, which harbours neuropeptide Y neurones that carry receptors for both leptin and insulin (Erickson et al. 1996). Fasting or weight loss lead to low blood leptin levels, which in turn cause the hypothalamic neuropeptide Y expression to rise, thereby stimulating food intake (Blundell & Gillett 2001).

High-fat diet causes increased leptin expression and an increased body weight (20%) compared with standard diet as illustrated in rodents (Moraes et al. 2003). This suggests that leptin is involved in the feedback control of fat intake. High-fat diets result in an inability to respond to leptin (Moraes et al. 2003). This phenomenon will be discussed below under the name of leptin resistance. Leptin has also been found to inhibit the response to sweet taste (Kawai et al. 2000), suggesting that the intake of sweet food might be regulated by leptin. A high-sucrose meal was found to increase adipose tissue leptin mRNA levels by at least 5 times within 3 hr, suggesting a feedback control of leptin to regulate sucrose intake (Polson & Thompson 2003). The enhanced preference for sweet substances found in the db/db mice lacking the leptin receptor could hence be explained by a defect leptin suppression of the reward induced by the sweet taste (Shigemura et al. 2004). In a comparison between dietary sucrose and coconut fat (rich in saturated fatty acids) in ob/ob mice, lacking leptin, it was found that the body weight gain was greater in sucrose-fed ob/ob mice than in fat-fed mice (Platt et al. 1990). Further experiments are needed to establish a role of leptin in promoting satiety with intake of palatable food.

Pro-opiomelanocorticotropin is a prohormone produced by specific neurones in the arcuate nucleus that seem to operate under leptin control. Approximately 40% of the pro-opiomelanocorticotropin neurones carry leptin receptors (Cheung et al. 1997). The pro-opiomelanocorticotropin neurones generate α-melanocyte-stimulating hormone, which is released from terminals in the paraventricular nucleus and lateral hypothalamus (Tritos & Maratos-Flier 1999). α-melanocyte-stimulating hormone suppresses food intake, acting through the melanocortin-4 receptor in neurones of the arcuate nucleus. The leptin-induced activation of the melanocortin receptor seems to be critical for the regulation of food intake, since interruption at any point in this chain...
of events causes overeating (Yeo et al. 1998). Leptin stimulates the pro-opiomelanocorticotropin neurons, while inhibiting the neuropeptide Y neurones (Williams et al. 1999). Hence, the arcuate nucleus of the hypothalamus controls food intake, acting through neuropeptide Y neurones to stimulate and through pro-opiomelanocorticotropin neurones (α-melanocyte-stimulating hormone) to inhibit food intake. Patients with a defect of the pro-opiomelanocorticotropin gene product due to mutations were found to display red hair, early-onset obesity, and congenital hypocortisolism (Krude et al. 2003; Farooqi & O’Rahilly 2004). Also, inherited abnormalities in the synthesis and processing of pro-opiomelanocorticotropin and defects in the action of pro-opiomelanocorticotropin-derived peptides could help to explain obesity (Coll et al. 2004).

With a high-fat diet pro-opiomelanocorticotropin-derived peptides appear to be important to enable the individual to resist overeating. This conclusion is based on studies of pro-opiomelanocorticotropin-deficient mice, which respond to a high-fat diet with hyperphagia and obesity (Challis et al. 2004). The importance of pro-opiomelanocorticotropin-derived peptides in appetite regulation is supported by studies of mice on a high-fat diet for 13 weeks; they became obese concomitantly with a reduction of pro-opiomelanocorticotropin mRNA expression in the arcuate nucleus (Huang et al. 2004). Pro-opiomelanocorticotropin mRNA in these animals was upregulated by a diet rich in n-3 polyunsaturated fat, emphasising the fact that the type of dietary fat matters in the regulation of hypothalamic neuropeptide expression (Huang et al. 2004).

During the processing of the pro-opiomelanocorticotropin molecule, endorphins are also produced, which stimulate rather than inhibit appetite. Mice lacking β-endorphin but not the other pro-opiomelanocorticotropin-derived peptides were orexigenic, suggesting that endorphins are important in normal appetite regulation and that the different pro-opiomelanocorticotropin-derived peptides interact in a complex manner in the regulation of energy homeostasis (Appleyard et al. 2003).

Table 1.
Peptides involved in appetite control.

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<tr>
<th>Peptides</th>
<th>Fat</th>
<th>Sucrose</th>
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<tr>
<td>Hunger peptides</td>
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<td>Hypothalamus: NPY, AgRP, orexins, MCH</td>
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<tr>
<td>Stomach: Ghrelin</td>
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<td>Satiety peptides</td>
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<tr>
<td>Hypothalamus: α-MSH</td>
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<td>Gut: CCK, enterostatin, GLP-1, PYY</td>
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<td>Pancreas: Insulin</td>
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<td>Adipose tissue: Leptin</td>
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<tr>
<td>Hunger peptides are released in the circulation or upregulated (hypothalamus) in response to food deprivation. Satiety peptides are released into the circulation or upregulated (hypothalamus) in response to food intake. NPY – neuropeptide Y, AgRP – agouti-related peptide, MCH – melanin-concentrating hormones, MSH – melanocyte-stimulating hormone, CCK – cholecystokinin, GLP – glucagon-like peptide 1, PYY – peptide YY.</td>
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Palatable food and appetite regulation
As stated above, palatable food, i.e. food rich in fat and sugar, will increase food intake, i.e. the activity and expression of signals controlling appetite will be balanced in favor of prolonged eating (table 2). Palatable food activates the reward system, thereby affecting ingestive behaviour. Typical of “reward eating” is that the driving force is gratification rather than energy deficit (Pelchat 2002). From an evolutionary point of view it makes sense that food rich in fat and sugar is attractive, because such food can be rapidly converted into energy (Nesse & Berridge 1997). Long-term overconsumption of palatable food has been compared to drug addiction (Berridge 1996; Gosnell 2000). The behaviour induced by stimulating the reward system is to “come back for more” (Kelley et al. 2002). Accordingly, free access to palatable food may lead to over-eating, characterized by prolongation of the meal because the normally induced sensation of satiety is overridden. Another parallel between palatable food and addictive drugs is the phenomenon of adaptation (Koob & Le Moal 1997). Addictive drugs are known to start a series of adaptations leading to a shift in homeostatic set points. Overconsumption of palatable food gradually shifts the set point for energy balance and body weight (Levine et al. 2003).

There are two main explanations for compulsive overeating of palatable food. One is the activation of the reward system, represented by endogenous opioids, dopamine and serotonin. The other is the phenomenon of “resistance”, i.e. an impaired ability to respond to food intake with a signaling cascade that leads to satiety.

Table 2.
Effects of diets rich in fat or sucrose on the expression of hunger and satiety peptides.

<table>
<thead>
<tr>
<th>Peptides</th>
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<th>Sucrose</th>
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<tr>
<td>Hunger peptides</td>
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<td>Hypothalamus:</td>
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<td>NPY</td>
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<td>Orexins</td>
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<td>AgRP</td>
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<td>Galanin</td>
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<td>MCH</td>
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<td>Stomach:</td>
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<td>Ghrelin</td>
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<td>Satiety peptides</td>
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<td>Hypothalamus:</td>
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<td>α-MSH</td>
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<td>Gut:</td>
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<td>CCK</td>
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<td>GLP-1</td>
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<td>PYY</td>
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<td>Enterostatin</td>
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<td>Insulin</td>
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<td>Adipose tissue:</td>
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<td>Leptin</td>
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↑ upregulated, ↓ downregulated, – not investigated, * saturated fat. For abbreviations, see table 1.
Activation of the reward system by palatable food

The reward system. In recent years the mechanisms underlying reward and motivation have been outlined (Kelley 2004). Nucleus accumbens is a brain region that appears to play a crucial role in behaviour related to natural reinforcers, such as ingestion of food and mating. The nucleus accumbens is also a site for the rewarding and reinforcing properties of addictive drugs. The nucleus accumbens receives information from the brain stem in response to taste and gastrointestinal sensations from the food ingested through a direct connection with the nucleus of the solitary tract. There is also a connection between the nucleus accumbens and the lateral hypothalamus, being important for energy homeostasis. Although there are many neurotransmitter systems within this region, studies on the rewarding effects of food has focused on three signal systems, involving endogenous opioids, dopamine and serotonin.

The opioid system. Since the discovery of the endogenous opioid peptides and their receptors nearly 30 years ago there has been a need to understand the role of these compounds in the brain (Pert & Snyder 1973; Lord et al. 1977). Initially, interest was focused on pain and pain relief but lately has included also reward, addiction and ingestive behaviour. In mammals the endogenous opioid peptides are derived from the proteins pro-opiomelanocortin (POMC), proenkephalin, prodynorphin and pronociceptin/orphanin FQ. These precursors produce the opioid peptides \( \beta \)-endorphins, enkephalins, dynorphins and nociceptin. \( \beta \)-Endorphin binds with equal affinity to \( \mu \)- and \( \delta \)-receptors, whereas dynorphins bind to the \( \kappa \)-receptor. The opiate receptors are found in various neuronal networks in the brain, for instance in hypothalamic regions involved in the control of food intake and in the nucleus accumbens (reward centre). One important property of opiates is to reinforce the behaviour best described as “coming back for more” (Van Ree et al. 2000). Systemic injection of morphine causes rats to overeat, an effect that can be prevented by various opiate antagonists. When analyzing the type of food chosen under the influence of opiates, it was found that morphine stimulates the ingestion of food rich in sugar and fat (Yeomans et al. 1997). That it is the palatability of the food rather than its energy content that activates the opioid system is clear from experiments comparing diets rich in sugar with diets rich in artificial sweeteners. Such studies show that the sweet taste is important for opioid activation and not the energy content (Apfelbaum & Mandenoff 1981). It has also been shown that the involvement of the opioid system during intake of sweets is manifested as analgesia (Le Magnen et al. 1980). Palatable food activates the opioid reward system in the nucleus accumbens (Zhang et al. 2003). The nucleus accumbens receives input from the medial prefrontal cortex, hippocampus and amygdala as well as from the brain stem, while output signals that promote eating target the hypothalamus (Helm et al. 2003). In the rat microinjection of various \( \mu \)-opiate agonists including morphine, enhanced sucrose intake as well as intake of artificial sweeteners, while dynorphin and U 50 488, two \( \kappa \)-agonists, did not (Zhang & Kelley 1997 & 2002). Water intake was not affected, indicating that opioids are not involved in the control of water intake. In man, the opiate receptor antagonist naloxone was found to reduce the preference for palatable food, without affecting subjective ratings of hunger and satiety (Drewnowski et al. 1992). It is to be noted that opiate antagonists decrease the attractiveness of food without affecting its taste, i.e. the subjects are still able to sense the sweet taste, but it does not elicit the expected reward (Yeomans & Gray 1996; Kelley et al. 2002). Opioids stimulate food intake because the sensation of hunger is more intense. This conclusion was drawn from experiments in which rats had to press a bar to receive food (Glass et al. 1999). Upon intravenous infusion of opioid agonists the number of bar presses (i.e. the urgency) increased before the rats gave up (Glass et al. 1999). In contrast naloxone reduced the urgency of the food-seeking behaviour. Together these observations suggest that endogenous opioids are important to induce food-seeking behaviour.

Upon ingestion of palatable food the hypothalamic expression of opioid peptides and opioid receptors is increased, supporting the involvement of the opioid system in palatable food consumption. High-fat and sucrose diets were shown to increase the expression of prodynorphin/dynorphin in the arcuate nucleus and paraventricular nucleus (Kim et al. 1996; Welch et al. 1996). At the same time intracerebroventricular injection of opioids stimulated the intake of sucrose or sweeteners (Zhang & Kelley 2002) and fat (Ookuma et al. 1997). While opioids induce an increased appetite for palatable food, the intake of palatable food is decreased by opiate receptor antagonists. Enterostatin is a peptide produced by proteolytic cleavage of pancreatic procolipase in the gut and has been found to inhibit fat intake in an experimental rat model, provided the animals have been adapted to fat feeding during 14 days (Erlanson-Albertsson & York 1997). The mechanism of action for enterostatin occurs through an inhibition of the \( \kappa \) and \( \mu \) opioid systems to reduce fat intake. The target protein for enterostatin was however found to be the F1-ATPase \( \beta \)-subunit, enterostatin acting to inhibit ATP-production (Berger et al. 2002 & 2004; Park et al. 2004). This suggests that an ATP-dependent intracellular mechanism is important for regulation of fat intake, opening new fields of investigation concerning reward mechanisms.

Dopamine. Another neurotransmitter that seems to be involved in the reward response to food is dopamine. Several different dopaminergic pathways are thought to modulate eating behaviour (Wang et al. 2001; Del Parigi et al. 2003). Five subtypes of dopamine receptors mediate the effects of dopamine, subtype 2 being associated with food intake and reward (Blum et al. 2000). The dopaminergic circuitry is a target for several appetite-regulating peptides, like galanin (Rada et al. 1998), leptin (Szczypka et al. 2000) and cholecystokinin (Vaccarino 1994). Thus, microinjection of galanin into the nucleus accumbens stimulates dopamine and suppresses acetylcholine release, i.e. signals for initiation of
feeding (Rada et al. 1998). Leptin was found to lower dopa- 
mine release in the nucleus accumbens during feeding, sug-
gest ing that leptin suppresses the feeding-induced reward 
(Krugel et al. 2003). Dopamine is also involved in other 
aspects of eating behaviour, such as arousal and food seek-
ing (Grigson 2002).

Serotonin. A third neurotransmitter that may contribute to eating regulation is serotonin. Several observations sug-
gest that serotonin may be involved in the control of food in-
take as a satiety signal (Lawton et al. 1995). Brain serotonin 
levels are affected by many factors, including circulating 
levels of tryptophan and certain macronutrients (Halford & 
Blundell 2000). In the hypothalamus, serotonin inhibits 
neuropeptide Y expression, thus depressing hunger (Half-
ord & Blundell 2000). Whether serotonin specifically regu-
lates carbohydrate intake (Wurtman & Wurtman 1995) and/
or fat intake (Blundell & Lawton 1995) is debated. Dietary 
carbohydrates have been shown to raise brain serotonin turn-
over as observed in depressed patients overeating carbo-
hydrates to increase well-being (Wurtman & Wurtman 1995). 
On the other hand treatment with the anorexic agent fenflu-
ramine (Bray 2001), which is claimed to act by releasing sero-
tonin as well as inhibiting serotonin reuptake, has been 
shown to specifically reduce fat intake (Lawton et al. 1995). 
Opioid antagonism and serotonergic stimulation, using 
naloxone and fluoxetine (a selective serotonin reuptake inhibi-
tor), has been shown to reduce intake of fat and sucrose in 
animals (Hagan et al. 1997). That serotonin is important to 
relieve stress was demonstrated in experiments where diets 
rich in fat and carbohydrates were given to animals subjected 
to stress (Buwalda et al. 2001). A high-fat diet was found to 
reduce some of the behavioural responses to stressors more 
effectively than a carbohydrate-based diet. It was also found 
that desensitization of central nervous 5-HT1A receptors oc-
curred in animals receiving a carbohydrate-based diet but 
was absent in fat-fed animals (Buwalda et al. 2001). This ex-
periment supports a role for serotonin in relieving stress, but 
also explains the urge for eating fat to relieve stress.

Resistance mechanisms in appetite regulation 
with palatable food

In addition to activation of the reward system another ex-
planation for compulsive consumption of palatable food is a 
blunted response to satiety signals. This may occur in dif-
f erent ways: 1) an increased expression of hunger signals or 
their receptors 2) a reduced expression of satiety signals and 
their receptors and 3) a default receptor targeting and/or 
post-receptor signalling in response to palatable food, in 
either case leading to overeating.

An altered expression upon long-term exposure to palat-
able food has been described for several of the appetite regu-
lating peptides listed in table 1. Some of the hunger peptides 
like neuropeptide Y (Huang et al. 2004), the orexins (Wortley 
et al. 2003) and agouti-related peptide (Huang et al. 2003) are 
upregulated following a period of fat feeding, in line with an 
increased hunger for fat food. At the same time some satiety 
signals are down-regulated (Huang et al. 2003), thus lowering 
the satiety response to a fat meal. Such changes in peptide ex-
pression might explain over-eating.

Other hunger signals like ghrelin are down-regulated in 
response to intake of fat (Moesgaard et al. 2004). A high-
fat diet, on the other hand, upregulates several satiety sig-
als like leptin (Moraes et al. 2003), insulin, glucagon-like 
peptide 1 (van Citters et al. 2002) and enterostatin (Erlan-
son-Albertsson & York 1997). Since a palatable food regime 
leads to over-eating in spite of the change in appetite signals 
to restrict food intake, there must be either a blunted re-
sponse to satiety signals or food intake is stimulated by 
other factors acting within the reward system. High serum 
concentrations of leptin were noted in obese individuals 
(Maffei et al. 1995). There was also an inability of leptin to 
inhibit food intake in such individuals, a phenomenon 
called “leptin resistance” (Frederich et al. 1995; Leibl 
2002). It was found that a high-fat diet caused a sustained 
increase in circulating leptin in mice, and that the leptin 
levels reflected the amount of fat in the body (Frederich 
et al. 1995). However, despite increased leptin levels, animals 
on a high-fat diet became obese, suggesting that the high-
fat diet changed the ‘set point’ for body weight/body fat, at 
least in part by restraining the action of leptin (Frederich 
et al. 1995). Another explanation for the development of 
leptin resistance is an impaired ability of leptin to pass the 
blood-brain barrier (Banks et al. 1999; Banks & Farrell 
2003). The depressed passage of leptin in obese individuals 
 is supposed to be a consequence of a high-fat diet. A third 
possible explanation for leptin resistance is inhibition of 
post-receptor signalling. Such an inhibitor of leptin signal-
ling has been identified, the SOCS-3, (suppressor-of-cyto-
kine-signalling) (Bjorbaek et al. 1998), being upregulated by 
high-fat diet and proposed to be a leptin resistance signal 
(Steinberg et al. 2004).

The passage of insulin into the brain seems to be a key 
event in insulin-induced satiety. There are specific regions in 
the brain, e.g. the hypothalamus and the hindbrain, where 
insulin penetration occurs (Banks & Kastin 1998). That palat-
able diet may reduce insulin penetration through the 
blood brain barrier was demonstrated in animals fed a 
high-fat diet for several weeks (Burguera et al. 2000). This 
could contribute to the development of obesity in individ-
uals on a high-fat diet (Banks 2003). One might speculate 
that a high-fat diet causes a peripheral insulin resistance, 
which shuffles glucose to the brain. Gradually the blood-
brain barrier becomes resistant to the penetration of insulin 
and the satiating effect of insulin is lost as a result.

A blunted satiety response to cholecystokinin seems to 
develop in response to intake of food rich in fat (Covasa 
et al. 2000) and sucrose (Lam et al. 1998). The mechanism 
behind the blunted response is not known.

Does palatable food cause addiction?

Palatable food mobilizes opioids and dopamine in the re-
ward system. Opiates and dopamine, when injected into the
nucleus accumbens, will stimulate food intake, in particular sucrose and fat, thus creating a vicious circle. Such a reinforcement mechanism is in line with the view that palatable food may cause dependence (Gosnell & Krahn 1992; Nestler & Aghajanian 1997). The development of dependence is facilitated by factors that enhance the attractiveness of palatable food. The attractiveness of food depends not only on its taste and content of carbohydrate and fat, but also on the nutritional state of the individual, i.e. whether fasted or well fed (Cabanac & Lafrance 1990; Berridge 1991). Long-term food restriction has been shown to augment the rewarding effect not only of food but also of various drugs of abuse (Cabeza de Vaca & Carr 1998; Carr 2002) and intermittent feeding has been shown to increase the rewarding effect of food (Colantuoni et al. 2002). Not surprisingly therefore, binge eating can be provoked by food restriction (Hagan et al. 2003). A similar sensitizing effect on the reward system by intake restriction is observed for alcohol (Soderpalm & Hansen 1999). Thus food restriction sensitizes the reward system, which triggers the craving not only for food (palatable food in particular), but also for addictive drugs, including alcohol.

With an intermittent feeding protocol, using concentrated sugar solutions, sugar dependence has actually been shown to develop in rodents (Colantuoni et al. 2002). Classically, dependence occurs in two steps. In the first step the consumption of the specific item is increased; in the second step withdrawal symptoms become manifest in the absence of the consumed item. The withdrawal symptoms include anxiety, autonomic nervous system abnormalities, and changes in body temperature, tremor and shakes. In an experiment to study the addictive potential of sugar, rats were offered a 25% glucose solution together with food pellets 12 hr each day (Colantuoni et al. 2002). After one week the sugar intake had increased three times. Withdrawal of sugar precipitated symptoms such as teeth chatter, forepaw tremor and head shakes. Indirect evidence that the opioid system had been activated during the escalated sugar intake was provided by the precipitation of withdrawal symptoms...
in response to naloxone (Colantuoni et al. 2002). Anxiety, measured as avoidance behaviour, increased greatly in these rats upon withdrawal of sugar. During the development of sugar dependence there was an increased release of dopamine and a decreased release of acetylcholine in the nucleus accumbens; withdrawal of sugar reversed the effects (Colantuoni et al. 2002). Whether man develops dependence to palatable food and whether withdrawal symptoms develop is not known. Further studies are needed to explore the consequences of indulgence in palatable food and to understand how palatable food affects appetite-regulating systems and energy homeostasis.

Conclusions

In conclusion, appetite regulation involves hunger and satiety signals, released from various peripheral organs to signal to the brain. During energy deficiency the expression of hunger signals are raised, ghrelin in the stomach and neuropeptide Y and the orexins in the hypothalamus. In response to food intake, various satiety signals, e.g. cholecystokinin, glucagon-like peptide 1 and peptide YY (fig. 1a) are released from the intestine to reach the circulation, signaling to neurons in the brain through vagal afferents. Insulin and leptin are mobilized to induce satiety, adipose tissue releasing leptin in proportion to the weight of the fat mass (fig. 1a). After some time on a diet consisting of palatable food, the hypothalamic expression of hunger peptides such as neuropeptide Y and the orexins is increased. The expression of several satiety signals is also increased, but the signaling of insulin, leptin and cholecystokinin is blunted or inhibited, promoting over-eating. The continued eating is driven by reward rather than by energy deficit (fig. 1b), resulting in obesity.

In the brain energy deficit is registered in the hypothalamus through various nuclei including arcuate nucleus leading to release of hunger signals and activation of their receptors. Consumption of standard food generates information on its energy content and taste in the brain stem. This information is transmitted to the hypothalamus to release and/or up-regulate various satiety peptides, leading to termination of food intake (fig. 2). With palatable food, taste sensing is more intense than with standard food; information is transmitted to the reward centre in the nucleus accumbens, leading to release and/or up-regulation of reward mediators like dopamine, serotonin and opiates. The reward centre has connections with appetite-controlling neurons in the hypothalamus. With a diet consisting of palatable food, the time of food intake will be prolonged because of suppressed satiety signaling (fig. 2). This may lead to overeating and adiposity. In the future we will need to find ways to restrain compulsive intake of palatable food. The use of opiate antagonists as anti-obesity drugs might be considered.

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References


Moran, T. H., A. R. Baldessarini, C. F. Salorio, T. Lowery & G. J. Schwartz: Vagal afferent and effarent contributions to the inhi-


Vaccarino, F. J.: Nucleus accumbens dopamine-CCK interactions in...


