MiniReview

How Palatable Food Disrupts Appetite Regulation

Charlotte Erlanson-Albertsson

Section of Endocrinology and Metabolism, Department of Experimental Medicine, University of Lund, Lund, Sweden

(Received September 15, 2004; Accepted March 7, 2005)

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 (Froguel *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.

Author for correspondence: Charlotte Erlanson-Albertsson, Division of Diabetes, Metabolism and Endocrinology, Department of Experimental Medicine, University of Lund, Biomedical Center (BMC), F13, SE-221 84 Lund, Sweden (fax +46 46 2224022, e-mail Charlotte.Erlanson-Albertsson@med.lu.se).

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 (Klebig *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 (Dhillo 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 septal 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 hypothalamus 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 up-regulated 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 (Gavrila 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 (Gutzwiller 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 neurotransmittor 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 (OLETFA) 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 dilatation 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 postprandial 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, hyperinsulinaemia 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 (Flatt *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-opiomelanocortitropin 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-opiomelanocortitropin neurones (α-melanocyte-stimulating hormone) to inhibit food intake. Patients with a defect of the pro-opiomelanocortitropin 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-opiomelanocortitropin and defects in the action of pro-opiomelanocortitropin-derived peptides could help to explain obesity (Coll *et al.* 2004).

With a high-fat diet pro-opiomelanocortitropin-derived peptides appear to be important to enable the individual to resist overeating. This conclusion is based on studies of pro-opiomelanocortitropin-deficient mice, which respond to a high-fat diet with hyperphagia and obesity (Challis *et al.* 2004). The importance of pro-opiomelanocortitropin-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-opiomelanocortitropin mRNA expression in the arcuate nucleus (Huang *et al.* 2004). Pro-opiomelanocortitropin 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-opiomelanocortitropin molecule, endorphins are also produced, which stimulate rather than inhibit appetite. Mice lacking β-endorphin but not the other pro-opiomelanocortitropin-derived peptides were orexigenic, suggesting that endorphins are important in normal appetite regulation and that the different pro-opiomelanocortitropin-derived peptides interact in a complex manner in the regulation of energy homeostasis (Appleyard *et al.* 2003).

Table 1.

Peptides involved in appetite control.

Hunger peptides
Hypothalamus: NPY, AgRP, orexins, MCH
Stomach: Ghrelin
Satiety peptides
Hypothalamus: α-MSH
Gut: CCK, enterostatin, GLP-1, PYY
Pancreas: Insulin
Adipose tissue: Leptin

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.

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 favour 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 over-eating 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 signalling cascade that leads to satiety.

Table 2.

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

Peptides	Fat	Sucrose
Hunger peptides		
Hypothalamus:		
NPY	↓↑*	↑
Orexins	↑	–
AgRP	↑	–
Galanin	↑	–
MCH	–	–
Stomach:		
Ghrelin	↓	–
Satiety peptides		
Hypothalamus:		
α-MSH	↓	↑
Gut:		
CCK	–	–
GLP-1	↑	–
PYY	–	–
Enterostatin	↑	–
Insulin	–	–
Adipose tissue:		
Leptin	↑	–

↑ 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 *β-endorphins, enkephalins, dynorphins and nociceptin.* β-Endorphin binds with equal affinity to μ- and δ-receptors, whereas dynorphins bind to the κ-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 μ-opiate agonists including morphine, enhanced sucrose intake as well as intake of artificial sweeteners, while dynorphin and U 50 488, two κ-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 κ and μ opioid systems to reduce fat intake. The target protein for enterostatin was however found to be the F1-ATPase β-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 neurotransmittor 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 dopamine release in the nucleus accumbens during feeding, suggesting 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 seeking (Grigson 2002).

Serotonin. A third neurotransmittor that may contribute to appetite regulation is *serotonin.* Several observations suggest that serotonin may be involved in the control of food intake 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 (Halford & Blundell 2000). Whether serotonin specifically regulates carbohydrate intake (Wurtman & Wurtman 1995) and/or fat intake (Blundell & Lawton 1995) is debated. Dietary carbohydrates have been shown to raise brain serotonin turnover as observed in depressed patients overeating carbohydrates to increase well-being (Wurtman & Wurtman 1995). On the other hand treatment with the anorexic agent fenfluramine (Bray 2001), which is claimed to act by releasing serotonin 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 fluoxetin (a selective serotonin reuptake inhibitor), 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-HT$_{1a}$ receptors occurred in animals receiving a carbohydrate-based diet but was absent in fat-fed animals (Buwalda *et al.* 2001). This experiment 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 explanation for compulsive consumption of palatable food is a blunted response to satiety signals. This may occur in different 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 palatable food has been described for several of the appetite regulating 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 expression 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 signals like leptin (Moraes *et al.* 2003), insulin, glucagon-like peptide 1 (van Citters *et al.* 2002) and enterostatin (Erlanson-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 response 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; Leibel 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 signalling has been identified, the SOCS-3, (suppressor-of-cytokine-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 palatable 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 individuals 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 reward system. Opiates and dopamine, when injected into the
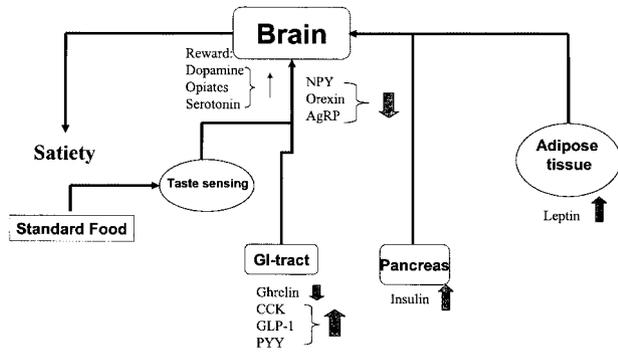
Fig. 1a. Hunger and satiety signalling during intake of a standard meal. Hunger signals, such as ghrelin in the stomach and NPY, orexin, AgRP in the hypothalamus, are depressed after intake of standard food, while satiety signals like CCK, GLP-1, PYY, insulin and leptin are raised. Food intake is terminated as a result. For abbreviations, see table 1.
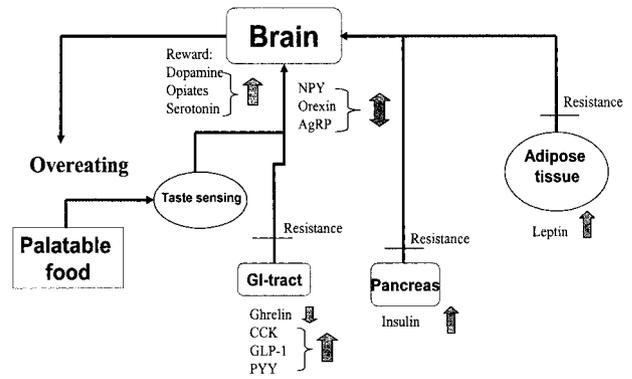
Fig. 1b. Hunger and satiety signalling after a period on a diet of palatable food. Hunger signals are either depressed, like ghrelin in the stomach and NPY in the hypothalamus, in response to a meal consisting of palatable food or raised, as for orexin and AgRP in the hypothalamus. Satiety signals like insulin and leptin are increased. Palatable food induces resistance to several satiety signals, documented for CCK, insulin and leptin, resulting in overeating. Food intake is driven by an increased activity in the reward system (dopamine, serotonin and opiates), triggered by the attractiveness of the taste. For abbreviations, see table 1.

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 depend-
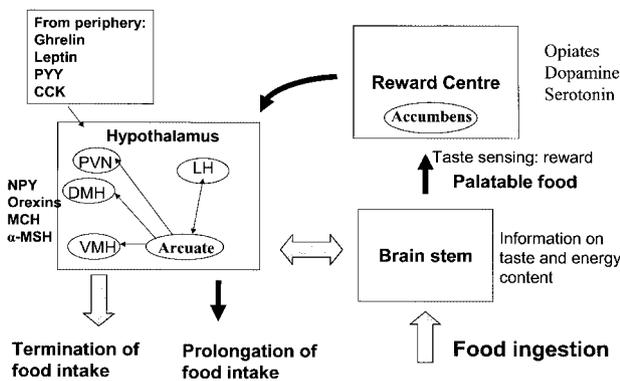

Fig. 2. Schematic picture of the pathways for appetite signalling in the brain during intake of standard food and palatable food, respectively. With standard food, signals are transmitted from the gastrointestinal tract to the brain stem, where the energy content and taste of the food is registered. In the absence of strongly attractive taste, hypothalamus performs the integrated energy sensing through the interaction of various appetite signals and their receptors in the hypothalamic nuclei, the arcuate nucleus being one important site for regulation of energy balance. Termination of food intake occurs. With palatable food the attractive taste of the food is registered, leading to an activation of the reward centre, releasing various reward signals, the nucleus accumbens being one important site. The reward centre has close connections to the hypothalamus, thereby influencing the hypothalamic energy homeostasis mechanisms. The end result is prolongation of food intake (LH; lateral hypothalamus, PVN; paraventricular nucleus, DMH; dorsomedial hypothalamus, VMH; ventromedial hypothalamus). For further abbreviations, see table 1.

ence 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 neurones 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 neurones 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.

References

Air, E. L., M. Z. Strowski, S. C. Benoit, S. L. Conarello, G. M. Salituro, X. M. Guan, K. Liu, S. C. Woods & B. B. Zhang: Small molecule insulin mimetics reduce food intake and body weight and prevent development of obesity. *Nature Med.* 2002, **8**, 179–183.

Allen, Y. S., T. E. Adrian, J. M. Allen, K. Tatemoto, T. J. Crow, S. R. Bloom & J. M. Polak: Neuropeptide Y distribution in the rat brain. *Science* 1983, **221**, 877–879.

Apfelbaum, M. & A. Mandenoff: Naltrexone suppresses hyperphagia induced in the rat by a highly palatable diet. *Pharmacol. Biochem. Behav.* 1981, **15**, 89–91.

Appleyard, S. M., M. Hayward, J. I. Young, A. A. Butler, R. D. Cone, M. Rubinstein & M. J. Low: A role for the endogenous opioid beta-endorphin in energy homeostasis. *Endocrinology* 2003, **144**, 1753–1760.

Banks, W. A.: Is obesity a disease of the blood-brain barrier? Physiological, pathological, and evolutionary considerations. *Curr. Pharm. Des.* 2003, **9**, 801–809.

Banks, W. A., C. R. DiPalma & C. L. Farrell: Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides* 1999, **20**, 1341–1345.

Banks, W. A. & C. L. Farrell: Impaired transport of leptin across the blood-brain barrier in obesity is acquired and reversible. *Amer. J. Physiol. Endocrinol. Metab.* 2003, **285**, E10–E15.

Banks, W. A. & A. J. Kastin: Differential permeability of the blood-brain barrier to two pancreatic peptides: insulin and amylin. *Peptides* 1998, **19**, 883–889.

Bannon, A. W., J. Seda, M. Carmouche, J. M. Francis, M. H. Norman, B. Karbon & M. L. McCaleb: Behavioral characterization of neuropeptide Y knockout mice. *Brain Res.* 2000, **868**, 79–87.

Baskin, D. G., D. Figlewicz Lattemann, R. J. Seeley, S. C. Woods, D. Porte, Jr. & M. W. Schwartz: Insulin and leptin: dual adiposity signals to the brain for the regulation of food intake and body weight. *Brain Res.* 1999, **848**, 114–123.

Batterham, R. L., M. A. Cohen, S. M. Ellis, C. W. Le Roux, D. J. Withers, G. S. Frost, M. A. Ghatei & S. R. Bloom: Inhibition of food intake in obese subjects by peptide YY3–36. *N. Engl. J. Med.* 2003, **349**, 941–948.

Batterham, R. L., M. A. Cowley, C. J. Small, H. Herzog, M. A. Cohen, C. L. Dakin, A. M. Wren, A. E. Brynes, M. J. Low, M. A. Ghatei, R. D. Cone & S. R. Bloom: Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature* 2002, **418**, 650–654.

Berger, K., U. Sivars, M. S. Winzell, P. Johansson, U. Hellman, C. Rippe & C. Erlanson-Albertsson: Mitochondrial ATP synthase–a possible target protein in the regulation of energy metabolism in vitro and in vivo. *Nutr. Neurosci.* 2002, **5**, 201–210.

Berger, K., M. S. Winzell, J. Mei & C. Erlanson-Albertsson: Enterostatin and its target mechanisms during regulation of fat intake. *Physiol. Behav.* 2004, **83**, 623–630.

Berridge, K. C.: Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat. *Appetite* 1991, **16**, 103–120.

Berridge, K. C.: Food reward: brain substrates of wanting and liking. *Neurosci. Biobehav. Rev.* 1996, **20**, 1–25.

Bi, S., E. E. Ladenheim, G. J. Schwartz & T. H. Moran: A role for NPY overexpression in the dorsomedial hypothalamus in hyperphagia and obesity of OLETF rats. *Amer. J. Physiol. Regul. Integr. Comp. Physiol.* 2001, **281**, R254–R260.

Billington, C. J., J. E. Briggs, S. Harker, M. Grace & A. S. Levine: Neuropeptide Y in hypothalamic paraventricular nucleus: a center coordinating energy metabolism. *Amer. J. Physiol.* 1994, **266**, R1765–R1770.

Bittencourt, J. C., F. Presse, C. Arias, C. Peto, J. Vaughan, J. L. Nahon, W. Vale & P. E. Sawchenko: The melanin-concentrating hormone system of the rat brain: an immuno- and hybridization histochemical characterization. *J. Comp. Neurol.* 1992, **319**, 218–245.

Bjorbaek, C., J. K. Elmquist, J. D. Frantz, S. E. Shoelson & J. S. Flier: Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol. Cell* 1998, **1**, 619–625.

Blum, K., E. R. Braverman, J. M. Holder, J. F. Lubar, V. J. Monastra, D. Miller, J. O. Lubar, T. J. Chen & D. E. Comings: Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. *J. Psychoactive Drugs* 2000, **32 Suppl**, i–iv, 1–112.

Blundell, J. E. & A. Gillett: Control of food intake in the obese. *Obes. Res.* 2001, **9, Suppl 4**, 263S–270S.

Blundell, J. E. & C. L. Lawton: Serotonin and dietary fat intake: effects of dexfenfluramine. *Metabolism* 1995, **44**, 33–37.

Bray, G. A.: Drug treatment of obesity. *Rev. Endocr. Metab. Disord.* 2001, **2**, 403–418.

Burguera, B., M. E. Couce, G. L. Curran, M. D. Jensen, R. V. Lloyd, M. P. Cleary & J. F. Poduslo: Obesity is associated with a decreased leptin transport across the blood-brain barrier in rats. *Diabetes* 2000, **49**, 1219–1223.

Buwalda, B., W. A. Blom, J. M. Koolhaas & G. van Dijk: Behavioral and physiological responses to stress are affected by high-fat feeding in male rats. *Physiol. Behav.* 2001, **73**, 371–377.

Cabanac, M. & L. Lafrance: Postingestive alliesthesia: the rat tells the same story. *Physiol. Behav.* 1990, **47**, 539–543.

Cabeza de Vaca, S. & K. D. Carr: Food restriction enhances the central rewarding effect of abused drugs. *J. Neurosci.* 1998, **18**, 7502–7510.

Callahan, H. S., D. E. Cummings, M. S. Pepe, P. A. Breen, C. C. Matthys & D. S. Weigle: Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. *J. Clin. Endocrinol. Metab.* 2004, **89**, 1319–1324.

Campfield, L. A., F. J. Smith, Y. Guisez, R. Devos & P. Burn: Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science* 1995, **269**, 546–549.

Carr, K. D.: Augmentation of drug reward by chronic food restriction: behavioral evidence and underlying mechanisms. *Physiol. Behav.* 2002, **76**, 353–364.

Challis, B. G., A. P. Coll, G. S. Yeo, S. B. Pinnock, S. L. Dickson, R. R. Thresher, J. Dixon, D. Zahn, J. J. Rochford, A. White, R. L. Oliver, G. Millington, S. A. Aparicio, W. H. Colledge, A. P. Russ, M. B. Carlton & S. O'Rahilly: Mice lacking pro-opiomelanocortin are sensitive to high-fat feeding but respond normally to the acute anorectic effects of peptide-YY (3–36). *Proc. Natl. Acad. Sci. USA* 2004, **101**, 4695–4700.

Cheung, C. C., D. K. Clifton & R. A. Steiner: Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. *Endocrinology* 1997, **138**, 4489–4492.

Clement, K., C. Vaisse, N. Lahlou, S. Cabrol, V. Pelloux, D. Cassuto, M. Gourmelen, C. Dina, J. Chambaz, J. M. Lacorte, A. Basdevant, P. Bougneres, Y. Lebouc, P. Froguel & B. Guy-Grand: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998, **392**, 398–401.

Colantuoni, C., P. Rada, J. McCarthy, C. Patten, N. M. Avena, A. Chadeayne & B. G. Hoebel: Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. *Obes. Res.* 2002, **10**, 478–488.

Coll, A. P., I. S. Farooqi, B. G. Challis, G. S. Yeo & S. O'Rahilly: Proopiomelanocortin and energy balance: insights from human and murine genetics. *J. Clin. Endocrinol. Metab.* 2004, **89**, 2557–2562.

Corp, E. S., M. Curcio, J. Gibbs & G. P. Smith: The effect of centrally administered CCK-receptor antagonists on food intake in rats. *Physiol. Behav.* 1997, **61**, 823–827.

Covasa, M., J. Grahn & R. C. Ritter: High fat maintenance diet attenuates hindbrain neuronal response to CCK. *Regul. Pept.* 2000, **86**, 83–88.

Cummings, D. E. & M. W. Schwartz: Genetics and pathophysiology of human obesity. *Annu. Rev. Med.* 2003, **54**, 453–471.

Davidoff, A. J., M. M. Mason, M. B. Davidson, M. W. Carmody, K. K. Hintz, L. E. Wold, D. A. Podolin & J. Ren: Sucrose-induced cardiomyocyte dysfunction is both preventable and reversible with clinically relevant treatments. *Amer. J. Physiol Endocrinol. Metab.* 2004, **286**, E718–E724.

Del Parigi, A., K. Chen, A. D. Salbe, E. M. Reiman & P. A. Tataranni: Are we addicted to food? *Obes. Res.* 2003, **11**, 493–495.

Dhillo, W. S., C. J. Small, S. A. Stanley, P. H. Jethwa, L. J. Seal, K. G. Murphy, M. A. Ghatei & S. R. Bloom: Hypothalamic interactions between neuropeptide Y, agouti-related protein, cocaine- and amphetamine-regulated transcript and alpha-melanocyte-stimulating hormone in vitro in male rats. *J. Neuroendocrinol.* 2002, **14**, 725–730.

Diano, S., B. Horvath, H. F. Urbanski, P. Sotonyi & T. L. Horvath: Fasting activates the nonhuman primate hypocretin (orexin) system and its postsynaptic targets. *Endocrinology* 2003, **144**, 3774–3778.

Dornonville de la Cour, C., M. Bjorkqvist, A. K. Sandvik, I. Bakke, C. M. Zhao, D. Chen & R. Hakanson: A-like cells in the rat stomach contain ghrelin and do not operate under gastrin control. *Regul. Pept.* 2001, **99**, 141–150.

Drewnowski, A., D. D. Krahn, M. A. Demitrack, K. Nairn & B. A. Gosnell: Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement. *Physiol. Behav.* 1992, **51**, 371–379.

Erickson, J. C., G. Hollopeter & R. D. Palmiter: Attenuation of the obesity syndrome of ob/ob mice by the loss of neuropeptide Y [see comments]. *Science* 1996, **274**, 1704–1707.

Erlanson-Albertsson, C. & D. York: Enterostatin – a peptide regulating fat intake. *Obes. Res.* 1997, **5**, 360–372.

Farooqi, I. S., J. M. Keogh, G. S. Yeo, E. J. Lank, T. Cheetham & S. O'Rahilly: Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *New Engl. J. Med.* 2003, **348**, 1085–1095.

Farooqi, I. S. & S. O'Rahilly: Monogenic human obesity syndromes. *Recent Prog. Horm. Res.* 2004, **59**, 409–424.

Flatt, P. R., C. J. Bailey, P. Kwasowski & S. K. Swanston-Flatt: Effects of diets rich in sucrose, coconut fat and safflowerseed oil on the development of the obese hyperglycaemic (ob/ob) syndrome in mice. *Diabetes Res.* 1990, **13**, 23–28.

Frederich, R. C., A. Hamann, S. Anderson, B. Lollmann, B. B. Lowell & J. S. Flier: Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat. Med.* 1995, **1**, 1311–1314.

Friedman, J. M. & J. L. Halaas: Leptin and the regulation of body weight in mammals. *Nature* 1998, **395**, 763–770.

Froguel, P., B. Guy-Grand & K. Clement: Genetics of obesity: towards the understanding of a complex syndrome. *Presse Med.* 2000, **29**, 564–571.

Gale, S. M., V. D. Castracane & C. S. Mantzoros: Energy homeostasis, obesity and eating disorders: recent advances in endocrinology. *J. Nutr.* 2004, **134**, 295–298.

Gallwitz, B. & W. E. Schmidt: [GLP-1 receptor gen "knock out" causes glucose intolerance, but no alterations of eating behavior]. *Z. Gastroenterol.* 1997, **35**, 655–658.

Gao, J., L. Ghibaudi, M. van Heek & J. J. Hwa: Characterization of diet-induced obese rats that develop persistent obesity after 6 months of high-fat followed by 1 month of low-fat diet. *Brain Res.* 2002, **936**, 87–90.

Gavrila, A., J. L. Chan, L. C. Miller, K. Heist, N. Yiannakouris & C. S. Mantzoros: Circulating melanin-concentrating hormone (MCH), agouti-related protein (AGRP), and alpha melanocyte-stimulating hormone ({alpha}-MSH) levels in relation to body composition; alterations in response to food deprivation and recombinant human leptin administration. *J. Clin. Endocrinol. Metab.* 2005, **90**, 1047–1054.

Gerozissis, K., M. Orosco, C. Rouch & S. Nicolaidis: Insulin responses to a fat meal in hypothalamic microdialysates and plasma. *Physiol. Behav.* 1997, **62**, 767–772.

Giraudo, S. Q., C. M. Kotz, M. K. Grace, A. S. Levine & C. J. Billington: Rat hypothalamic NPY mRNA and brown fat uncoupling protein mRNA after high-carbohydrate or high-fat diets. *Amer. J. Physiol.* 1994, **266**, R1578–R1583.

Glass, M. J., E. O'Hare, J. P. Cleary, C. J. Billington & A. S. Levine: The effect of naloxone on food-motivated behavior in the obese Zucker rat. *Psychopharmacology (Berl)* 1999, **141**, 378–384.

Gosnell, B. A.: Sucrose intake predicts rate of acquisition of cocaine self-administration. *Psychopharmacology (Berl)* 2000, **149**, 286–292.

Gosnell, B. A. & D. D. Krahn: The relationship between saccharin and alcohol intake in rats. *Alcohol.* 1992, **9**, 203–206.

Grigson, P. S.: Like drugs for chocolate: separate rewards modulated by common mechanisms? *Physiol. Behav.* 2002, **76**, 389–395.

Gutzwiller, J. P., J. Drewe, S. Ketterer, P. Hildebrand, A. Krautheim & C. Beglinger: Interaction between CCK and a preload on reduction of food intake is mediated by CCK-A receptors in humans. *Amer. J. Physiol. Regul. Integr. Comp. Physiol.* 2000, **279**, R189–R195.

Hagan, M. M., P. C. Chandler, P. K. Wauford, R. J. Rybak & K. D. Oswald: The role of palatable food and hunger as trigger factors in an animal model of stress induced binge eating. *Int. J. Eat. Disord.* 2003, **34**, 183–197.

Hagan, M. M., F. D. Holguin, C. E. Cabello, D. R. Hanscom & D. E. Moss: Combined naloxone and fluoxetine on deprivation-induced binge eating of palatable foods in rats. *Pharmacol. Biochem. Behav.* 1997, **58**, 1103–1107.

Halford, J. C. & J. E. Blundell: Separate systems for serotonin and leptin in appetite control. *Ann. Med.* 2000, **32**, 222–232.

Helm, K. A., P. Rada & B. G. Hoebel: Cholecystokinin combined with serotonin in the hypothalamus limits accumbens dopamine release while increasing acetylcholine: a possible satiation mechanism. *Brain Res.* 2003, **963**, 290–297.

Herve, C. & D. Fellmann: Changes in rat melanin-concentrating hormone and dynorphin messenger ribonucleic acids induced by food deprivation. *Neuropeptides* 1997, **31**, 237–242.

Huang, X. F., M. Han, T. South & L. Storlien: Altered levels of POMC, AgRP and MC4-R mRNA expression in the hypothalamus and other parts of the limbic system of mice prone or resistant to chronic high-energy diet-induced obesity. *Brain Res.* 2003, **992**, 9–19.

Huang, X. F., X. Xin, P. McLennan & L. Storlien: Role of fat amount and type in ameliorating diet-induced obesity: insights at the level of hypothalamic arcuate nucleus leptin receptor, neuropeptide Y and pro-opiomelanocortin mRNA expression. *Diabetes Obes. Metab.* 2004, **6**, 35–44.

Ito, M., A. Gomori, A. Ishihara, Z. Oda, S. Mashiko, H. Matsushita, M. Yumoto, H. Sano, S. Tokita, M. Moriya, H. Iwaasa & A. Kanatani: Characterization of MCH-mediated obesity in mice. *Amer. J. Physiol. Endocrinol. Metab.* 2003, **284**, E940–E945.

Kaga, T., A. Inui, M. Okita, A. Asakawa, N. Ueno, M. Kasuga, M. Fujimiya, N. Nishimura, R. Dobashi, Y. Morimoto, I. M. Liu & J. T. Cheng: Modest overexpression of neuropeptide Y in the brain leads to obesity after high-sucrose feeding. *Diabetes* 2001, **50**, 1206–1210.

Kawai, K., K. Sugimoto, K. Nakashima, H. Miura & Y. Ninomiya: Leptin as a modulator of sweet taste sensitivities in mice. *Proc. Natl. Acad. Sci. USA* 2000, **97**, 11044–11049.

Kelley, A. E.: Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. *Neurosci. Biobehav. Rev.* 2004, **27**, 765–776.

Kelley, A. E., V. P. Bakshi, S. N. Haber, T. L. Steininger, M. J. Will & M. Zhang: Opioid modulation of taste hedonics within the ventral striatum. *Physiol. Behav.* 2002, **76**, 365–377.

Kim, E. M., C. C. Welch, M. K. Grace, C. J. Billington & A. S. Levine: Chronic food restriction and acute food deprivation decrease mRNA levels of opioid peptides in arcuate nucleus. *Amer. J. Physiol.* 1996, **270**, R1019–R1024.

Kim, J. K., R. E. Gimeno, T. Higashimori, H. J. Kim, H. Choi, S. Punreddy, R. L. Mozell, G. Tan, A. Stricker-Krongrad, D. J. Hirsch, J. J. Fillmore, Z. X. Liu, J. Dong, G. Cline, A. Stahl, H. F. Lodish & G. I. Shulman: Inactivation of fatty acid transport protein 1 prevents fat-induced insulin resistance in skeletal muscle. *J. Clin. Invest.* 2004, **113**, 756–763.

Kim, M. S., C. Y. Yoon, K. H. Park, C. S. Shin, K. S. Park, S. Y. Kim, B. Y. Cho & H. K. Lee: Changes in ghrelin and ghrelin receptor expression according to feeding status. *Neuroreport* 2003, **14**, 1317–1320.

Klebig, M. L., J. E. Wilkinson, J. G. Geisler & R. P. Woychik: Ectopic expression of the agouti gene in transgenic mice causes obesity, features of type II diabetes, and yellow fur. *Proc. Natl. Acad. Sci. USA* 1995, **92**, 4728–4732.

Koob, G. F. & M. Le Moal: Drug abuse: hedonic homeostatic dysregulation. *Science* 1997, **278**, 52–58.

Korner, J., E. Savontaus, S. C. Chua, Jr., R. L. Leibel & S. L. Wardlaw: Leptin regulation of Agrp and Npy mRNA in the rat hypothalamus. *J. Neuroendocrinol.* 2001, **13**, 959–966.

Krude, H., H. Biebermann & A. Gruters: Mutations in the human proopiomelanocortin gene. *Ann. New Y. Acad. Sci.* 2003, **994**, 233–239.

Krugel, U., T. Schraft, H. Kittner, W. Kiess & P. Illes: Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur. J. Pharmacol.* 2003, **482**, 185–187.

Lam, W. F., H. A. Gielkens, S. Y. de Boer, C. B. Lamers & A. A. Masclee: Influence of hyperglycemia on the satiating effect of CCK in humans. *Physiol. Behav.* 1998, **65**, 505–511.

Lawton, C. L., J. K. Wales, A. J. Hill & J. E. Blundell: Serotoninergic manipulation, meal-induced satiety and eating pattern: effect of fluoxetine in obese female subjects. *Obes. Res.* 1995, **3**, 345–356.

Le Magnen, J., P. Marfaing-Jallat, D. Miceli & M. Devos: Pain modulating and reward systems: a single brain mechanism? *Pharmacol. Biochem. Behav.* 1980, **12**, 729–733.

Leibel, R. L.: The role of leptin in the control of body weight. *Nutr. Rev.* 2002, **60**, S15–S19; discussion S68–84, 85–87.

Levine, A. S., C. M. Kotz & B. A. Gosnell: Sugars and fats: the neurobiology of preference. *J. Nutr.* 2003, **133**, 831S–834S.

Lin, S., L. H. Storlien & X. F. Huang: Leptin receptor, NPY, POMC mRNA expression in the diet-induced obese mouse brain. *Brain Res.* 2000, **875**, 89–95.

Loos, R. J. & C. Bouchard: Obesity–is it a genetic disorder? *J. Intern. Med.* 2003, **254**, 401–425.

Lord, J. A., A. A. Waterfield, J. Hughes & H. W. Kosterlitz: Endogenous opioid peptides: multiple agonists and receptors. *Nature* 1977, **267**, 495–499.

Maffei, M., J. Halaas, E. Ravussin, R. E. Pratley, G. H. Lee, Y. Zhang, H. Fei, S. Kim, R. Lallone, S. Ranganathan, *et al.*: Leptin levels in human and rodent: measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. *Nature Med.* 1995, **1**, 1155–1161.

Moesgaard, S. G., B. Ahren, R. D. Carr, D. X. Gram, C. L. Brand & F. Sundler: Effects of high-fat feeding and fasting on ghrelin expression in the mouse stomach. *Regul. Pept.* 2004, **120**, 261–267.

Montague, C. T., I. S. Farooqi, J. P. Whitehead, M. A. Soos, H. Rau, N. J. Wareham, C. P. Sewter, J. E. Digby, S. N. Mohammed, J. A. Hurst, C. H. Cheetham, A. R. Earley, A. H. Barnett, J. B. Prins & S. O'Rahilly: Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 1997, **387**, 903–908.

Moraes, R. C., A. Blondet, K. Birkenkamp-Demtroeder, J. Tirard, T. F. Orntoft, A. Gertler, P. Durand, D. Naville & M. Begeot: Study of the alteration of gene expression in adipose tissue of diet-induced obese mice by microarray and reverse transcription-polymerase chain reaction analyses. *Endocrinology* 2003, **144**, 4773–4782.

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

bition of food intake by cholecystokinin. *Amer. J. Physiol.* 1997, **272**, R1245–R1251.

Naslund, E., B. Barkeling, N. King, M. Gutniak, J. E. Blundell, J. J. Holst, S. Rossner & P. M. Hellstrom: Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. *Int. J. Obes. Relat. Metab. Disord.* 1999, **23**, 304–311.

Nesse, R. M. & K. C. Berridge: Psychoactive drug use in evolutionary perspective. *Science* 1997, **278**, 63–66.

Nestler, E. J. & G. K. Aghajanian: Molecular and cellular basis of addiction. *Science* 1997, **278**, 58–63.

Niimi, M., M. Sato & T. Taminato: Neuropeptide Y in central control of feeding and interactions with orexin and leptin. *Endocrine* 2001, **14**, 269–273.

Ookuma, K., C. Barton, D. A. York & G. A. Bray: Effect of enterostatin and kappa-opioids on macronutrient selection and consumption. *Peptides* 1997, **18**, 785–791.

Owji, A. A., Z. Khoshdel, F. Sanea, M. R. Panjehshahin, M. Shojaee Fard, D. M. Smith, H. A. Coppock, M. A. Ghatei & S. R. Bloom: Effects of intracerebroventricular injection of glucagon like peptide-1 and its related peptides on serotonin metabolism and on levels of amino acids in the rat hypothalamus. *Brain Ress* 2002, **929**, 70–75.

Park, M., L. Lin, S. Thomas, H. D. Braymer, P. M. Smith, D. H. Harrison & D. A. York: The F1-ATPase beta-subunit is the putative enterostatin receptor. *Peptides* 2004, **25**, 2127–2133.

Pelchat, M.: Of human bondage: Food craving, obsession, compulsion and addiction. *Physiol. & Behav.* 2002, **76**, 347–352.

Pert, C. B. & S. H. Snyder: Opiate receptor: demonstration in nervous tissue. *Science* 1973, **179**, 1011–1014.

Polson, D. A. & M. P. Thompson: Adiponutrin mRNA expression in white adipose tissue is rapidly induced by meal-feeding a high-sucrose diet. *Biochem. Biophys. Res. Commun.* 2003, **301**, 261–266.

Qu, D., D. S. Ludwig, S. Gammeltoft, M. Piper, M. A. Pelleymounter, M. J. Cullen, W. F. Mathes, R. Przypek, R. Kanarek & E. Maratos-Flier: A role for melanin-concentrating hormone in the central regulation of feeding behaviour. *Nature* 1996, **380**, 243–247.

Rada, P., G. P. Mark & B. G. Hoebel: Galanin in the hypothalamus raises dopamine and lowers acetylcholine release in the nucleus accumbens: a possible mechanism for hypothalamic initiation of feeding behavior. *Brain Res.* 1998, **798**, 1–6.

Raposinho, P. D., D. D. Pierroz, P. Broqua, R. B. White, T. Pedrazzini & M. L. Aubert: Chronic administration of neuropeptide Y into the lateral ventricle of C57BL/6J male mice produces an obesity syndrome including hyperphagia, hyperleptinemia, insulin resistance, and hypogonadism. *Mol. Cell Endocrinol.* 2001, **185**, 195–204.

Rossi, M., S. J. Choi, D. O'Shea, T. Miyoshi, M. A. Ghatei & S. R. Bloom: Melanin-concentrating hormone acutely stimulates feeding, but chronic administration has no effect on body weight. *Endocrinology* 1997, **138**, 351–355.

Sakurai, T., A. Amemiya, M. Ishii, I. Matsuzaki, R. M. Chemelli, H. Tanaka, S. C. Williams, J. A. Richarson, G. P. Kozlowski, S. Wilson, J. R. Arch, R. E. Buckingham, A. C. Haynes, S. A. Carr, R. S. Annan, D. E. McNulty, W. S. Liu, J. A. Terrett, N. A. Elshourbagy, D. J. Bergsma & M. Yanagisawa: Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* 1998, **92**, 573–585.

Saper, C. B., T. C. Chou & J. K. Elmquist: The need to feed: homeostatic and hedonic control of eating. *Neuron.* 2002, **36**, 199–211.

Schwartz, M. W., J. L. Marks, A. J. Sipols, D. G. Baskin, S. C. Woods, S. E. Kahn & D. Porte, Jr.: Central insulin administration reduces neuropeptide Y mRNA expression in the arcuate nucleus of food-deprived lean (Fa/Fa) but not obese (fa/fa) Zucker rats. *Endocrinology* 1991, **128**, 2645–2647.

Schwartz, M. W., S. C. Woods, D. Porte, Jr., R. J. Seeley & D. G.

Baskin: Central nervous system control of food intake. *Nature* 2000, **404**, 661–671.

Segal-Lieberman, G., R. L. Bradley, E. Kokkotou, M. Carlson, D. J. Trombly, X. Wang, S. Bates, M. G. Myers, Jr., J. S. Flier & E. Maratos-Flier: Melanin-concentrating hormone is a critical mediator of the leptin-deficient phenotype. *Proc. Natl. Acad. Sci. USA* 2003, **100**, 10085–10090.

Shearman, L. P., R. E. Camacho, D. Sloan Stribling, D. Zhou, M. A. Bednarek, D. L. Hreniuk, S. D. Feighner, C. P. Tan, A. D. Howard, L. H. Van der Ploeg, D. E. MacIntyre, G. J. Hickey & A. M. Strack: Chronic MCH-1 receptor modulation alters appetite, body weight and adiposity in rats. *Eur. J. Pharmacol.* 2003, **475**, 37–47.

Shi, Y.: Beyond skin color: emerging roles of melanin-concentrating hormone in energy homeostasis and other physiological functions. *Peptides* 2004, **25**, 1605–1611.

Shigemura, N., R. Ohta, Y. Kusakabe, H. Miura, A. Hino, K. Koyano, K. Nakashima & Y. Ninomiya: Leptin modulates behavioral responses to sweet substances by influencing peripheral taste structures. *Endocrinology* 2004, **145**, 839–847.

Sipols, A. J., J. Bayer, R. Bennett & D. P. Figlewicz: Intraventricular insulin decreases kappa opioid-mediated sucrose intake in rats. *Peptides* 2002, **23**, 2181–2187.

Smith, G. P. & J. Gibbs: Cholecystokinin: a putative satiety signal. *Pharmacol. Biochem. Behav.* 1975, **3**, 135–138.

Söderpalm, A. H. & S. Hansen: Alcohol alliesthesia: food restriction increases the palatability of alcohol through a corticosterone-dependent mechanism. *Physiol. Behav.* 1999, **67**, 409–415.

Stanley, B. G. & S. F. Leibowitz: Neuropeptide Y injected in the paraventricular hypothalamus: a powerful stimulant of feeding behavior. *Proc. Natl. Acad. Sci. USA* 1985, **82**, 3940–3943.

Steinberg, G. R., A. C. Smith, S. Wormald, P. Malenfant, C. Collier & D. J. Dyck: Endurance training partially reverses dietary-induced leptin resistance in rodent skeletal muscle. *Amer. J. Physiol. Endocrinol. Metab.* 2004, **286**, E57–E63.

Strubbe, J. H., D. Porte, Jr. & S. C. Woods: Insulin responses and glucose levels in plasma and cerebrospinal fluid during fasting and refeeding in the rat. *Physiol. Behav.* 1988, **44**, 205–208.

Sun, G., Z. Tian, T. Murata, K. Narita, K. Honda & T. Higuchi: Central and peripheral immunoreactivity of melanin-concentrating hormone in hypothalamic obese and lactating rats. *J. Neuroendocrinol.* 2004, **16**, 79–83.

Szczypka, M. S., M. A. Rainey & R. D. Palmiter: Dopamine is required for hyperphagia in Lep(ob/ob) mice. *Nat. Genet.* 2000, **25**, 102–104.

Tartaglia, L. A., M. Dembski, X. Weng, N. Deng, J. Culpepper, R. Devos, G. J. Richards, L. A. Campfield, F. T. Clark, J. Deeds & *et al.*: Identification and expression cloning of a leptin receptor, OB-R. *Cell* 1995, **83**, 1263–1271.

Taubes, G.: As obesity rates rise, experts struggle to explain why. *Science* 1998, **280**, 1367–1368.

Tritos, N. A. & E. Maratos-Flier: Two important systems Clark, J. Deeds, *et al.*: Identification and expression cloning trating hormone. *Neuropeptides* 1999, **33**, 339–349.

Tschop, M., D. B. Flora, J. P. Mayer & M. L. Heiman: Hypophysectomy prevents ghrelin-induced adiposity and increases gastric ghrelin secretion in rats. *Obes. Res.* 2002, **10**, 991–999.

Tschop, M., D. L. Smiley & M. L. Heiman: Ghrelin induces adiposity in rodents. *Nature* 2000, **407**, 908–913.

Tschop, M., C. Weyer, P. A. Tataranni, V. Devanarayan, E. Ravussin & M. L. Heiman: Circulating ghrelin levels are decreased in human obesity. *Diabetes* 2001, **50**, 707–709.

Turton, M. D., D. O'Shea, I. Gunn, S. A. Beak, C. M. Edwards, K. Meeran, S. J. Choi, G. M. Taylor, M. M. Heath, P. D. Lambert, J. P. Wilding, D. M. Smith, M. A. Ghatei, J. Herbert & S. R. Bloom: A role for glucagon-like peptide-1 in the central regulation of feeding. *Nature* 1996, **379**, 69–72.

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

psychostimulant reward and related behaviors. *Neurosci. Biobehav. Rev.* 1994, **18**, 207–214.

van Citters, G. W., M. Kabir, S. P. Kim, S. D. Mittelman, M. K. Dea, P. L. Brubaker & R. N. Bergman: Elevated glucagon-like peptide-1-(7–36)-amide, but not glucose, associated with hyperinsulinemic compensation for fat feeding. *J. Clin. Endocrinol. Metab.* 2002, **87**, 5191–5198.

Van Ree, J. M., R. J. Niesink, L. Van Wolfswinkel, N. F. Ramsey, M. M. Kornet, W. R. Van Furth, L. J. Vanderschuren, M. A. Gerrits & C. L. Van den Berg: Endogenous opioids and reward. *Eur. J. Pharmacol.* 2000, **405**, 89–101.

Wang, G. J., N. D. Volkow, J. Logan, N. R. Pappas, C. T. Wong, W. Zhu, N. Netusil & J. S. Fowler: Brain dopamine and obesity. *Lancet* 2001, **357**, 354–357.

Welch, C. C., E. M. Kim, M. K. Grace, C. J. Billington & A. S. Levine: Palatability-induced hyperphagia increases hypothalamic Dynorphin peptide and mRNA levels. *Brain Res.* 1996, **721**, 126–131.

Williams, L. M., C. L. Adam, J. G. Mercer, K. M. Moar, D. Slater, L. Hunter, P. A. Findlay & N. Hoggard: Leptin receptor and neuropeptide Y gene expression in the sheep brain. *J. Neuroendocrinol.* 1999, **11**, 165–169.

Woods, S. C., M. W. Schwartz, D. G. Baskin & R. J. Seeley: Food intake and the regulation of body weight. *Annu. Rev. Psychol.* 2000, **51**, 255–277.

Woods, S. C., R. J. Seeley, D. G. Baskin & M. W. Schwartz: Insulin and the blood-brain barrier. *Curr. Pharm. Des.* 2003, **9**, 795–800.

Wortley, K. E., G. Q. Chang, Z. Davydova & S. F. Leibowitz: Peptides that regulate food intake: orexin gene expression is increased during states of hypertriglyceridemia. *Amer. J. Physiol. Regul. Integr. Comp. Physiol.* 2003, **284**, R1454–R1465.

Wren, A. M., L. J. Seal, M. A. Cohen, A. E. Brynes, G. S. Frost, K. G. Murphy, W. S. Dhillo, M. A. Ghatei & S. R. Bloom: Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.* 2001, **86**, 5992.

Wren, A. M., C. J. Small, C. V. Fribbens, N. M. Neary, H. L. Ward, L. J. Seal, M. A. Ghatei & S. R. Bloom: The hypothalamic mechanisms of the hypophysiotropic action of ghrelin. *Neuroendocrinology* 2002, **76**, 316–324.

Wurtman, R. J. & J. J. Wurtman: Brain serotonin, carbohydrate-craving, obesity and depression. *Obes. Res.* 1995, **3**, **Suppl 4**, 477S–480S.

Yeo, G. S., I. S. Farooqi, S. Aminian, D. J. Halsall, R. G. Stanhope & S. O'Rahilly: A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat. Genet.* 1998, **20**, 111–112.

Yeo, G. S., E. J. Lank, I. S. Farooqi, J. Keogh, B. G. Challis & S. O'Rahilly: Mutations in the human melanocortin-4 receptor gene associated with severe familial obesity disrupts receptor function through multiple molecular mechanisms. *Hum. Mol. Genet.* 2003, **12**, 561–574.

Yeomans, M. R. & R. W. Gray: Selective effects of naltrexone on food pleasantness and intake. *Physiol. Behav.* 1996, **60**, 439–446.

Yeomans, M. R., R. W. Gray, C. J. Mitchell & S. True: Independent effects of palatability and within-meal pauses on intake and appetite ratings in human volunteers. *Appetite* 1997, **29**, 61–76.

Zamir, N., G. Skofitsch & D. M. Jacobowitz: Distribution of immunoreactive melanin-concentrating hormone in the central nervous system of the rat. *Brain Res.* 1986, **373**, 240–245.

Zhang, M., C. Balmadrid & A. E. Kelley: Nucleus accumbens opioid, GABAergic, and dopaminergic modulation of palatable food motivation: contrasting effects revealed by a progressive ratio study in the rat. *Behav. Neurosci.* 2003, **117**, 202–211.

Zhang, M. & A. E. Kelley: Opiate agonists microinjected into the nucleus accumbens enhance sucrose drinking in rats. *Psychopharmacology (Berl.)* 1997, **132**, 350–360.

Zhang, M. & A. E. Kelley: Intake of saccharin, salt, and ethanol solutions is increased by infusion of a mu opioid agonist into the nucleus accumbens. *Psychopharmacology (Berl.)* 2002, **159**, 415–423.

Zigman, J. M. & J. K. Elmquist: Minireview: From anorexia to obesity – the yin and yang of body weight control. *Endocrinology* 2003, **144**, 3749–3756.