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REGULATION OF ENERGY INTAKE

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INTRODUCTION

Body weight in adults is remarkably stable over the course of months to years. This stability in body weight occurs despite large fluctuations in caloric intake, thus demonstrating that energy intake and energy expenditure are precisely matched. Indeed it has been shown under defined experimental conditions that changes in body weight result in compensatory alterations in energy expenditure which attempt to return body weight to the baseline value (1,2). This tight matching of energy intake and energy expenditure occurs in the central nervous system, primarily in the hypothalamus. In order for the central nervous system to regulate energy intake and energy expenditure it must continuously and accurately monitor the body's energy balance (intake, expenditure, and storage). The hypothalamus receives information relevant to energy balance through metabolic, neural and hormonal signals. Some signals regulate energy intake over short time periods, for example acting to terminate a feeding episode, while others are active in the long-term regulation of energy intake insuring the maintenance of adequate energy stores. In this chapter the signals that regulate energy intake will be reviewed. The central regulation of energy expenditure is discussed in the following chapter.

ENVIRONMENTAL CUES REGULATING FOOD INTAKE

The central nervous system receives multiple neural signals prior to the ingestion of food. These early neural signals arise from visual, auditory, and olfactory cues, and are processed before food is actually ingested. The insular cortex, orbitofrontal cortex and the piriform cortex integrate signals related to sight, taste and olfaction in humans and primates (3) with other cortical modalities such as memory of past experiences (place, safe vs toxic food, etc) to influence food intake. Many of these external sensory cues contribute to the cephalic phase response to food, which consists of increased salivation and gastrointestinal hormone secretion, among other responses. The cephalic phase response is believed to prime the body to better absorb and use nutrients. Differences between lean and obese subjects in cephalic phase responses have been observed but the effect of these differences on food intake are not well understood. For example, viewing pictures of food resulted in greater regional cerebral blood flow (a measure of neural activation) in the right parietal cortex and was associated with greater feelings of hunger in obese compared to lean women (4). Greater insulin secretion during the

cephalic phase in obese compared to lean subjects has been observed, but this may reflect higher basal hormone levels or dietary restraint status (5).

SATIETY SIGNALS FROM THE GASTROINTESTINAL TRACT

Gastrointestinal Mechanoreceptors and Chemoreceptors

During the ingestion and digestion of food the brain receives information from mechano- and chemosensitive receptors that line the alimentary canal (6). These neural signals provide information involved in the "short-term" regulation of feeding (Figure 1). Short-term signals primarily regulate satiety, or the size of individual meals. These feeding-induced signals are transmitted via vagal afferent fibers to the nucleus of the solitary tract (NTS) in the hindbrain. Major outputs from the NTS project to medullary motor nuclei and to forebrain areas including the hypothalamic nuclei (arcuate, dorsomedial and paraventricular), the lateral hypothalamus and to the insular cortex. Short and long term signals (information encoding the size of energy stores) of energy intake are integrated in the hypothalamic nuclei.

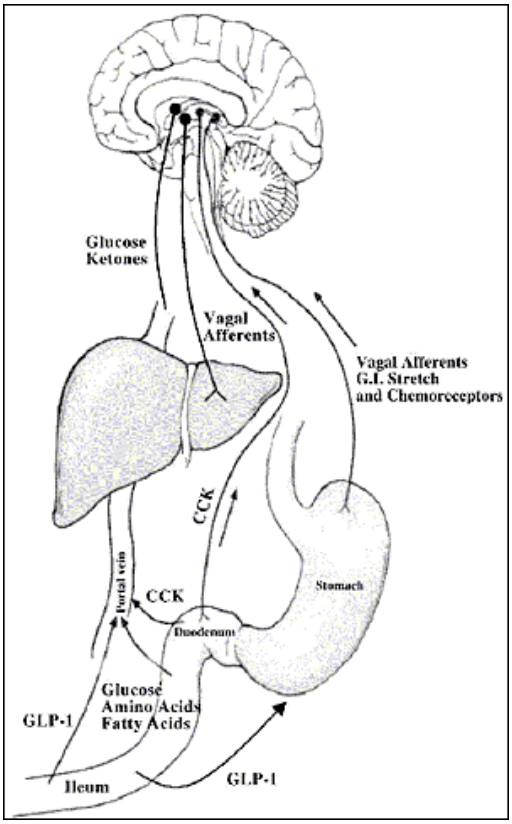

Figure 1.Gastrointestinal signals regulate food intake. The majority of signals from the GI tract regulate the size of individual meals. Mechanoreceptors quantitating stretch of the stomach, and chemoreceptors activated by nutrients in the GI tract, transmit information via vagal and sympathetic afferents to the hindbrain nuclei. This information is then transmitted to the hypothalamus and other forebrain structures for integration with additional signals regulating food intake. Vagal afferents from the liver signal the presence of specific nutrients. Glucose and ketones act as signals to the CNS directly on

responsive neurons in the hypothalamus. Gastrointestinal hormones such as CCK bind receptors in the liver to activate vagal afferents, or access the CNS via the circulation. Other hormones such as GLP-1 inhibit feeding by slowing gastric emptying. Figure reproduced with permission from reference 7.

Mechanoreceptors located in the esophagus and stomach signal stretch and luminal touch to the brain. These receptors thus signal the amount of food consumed during the meal. Rolls et al (8) have demonstrated that an increase in the volume of food consumed at a meal reduces caloric intake at the following meal. The caloric content of the meal was not as strong a determinant of intake at the following meal as was volume. These observations thus suggest that meal volume is an important determinant of food intake. As discussed by Blundell and Stubbs, weight and volume are learned cues with high functional validity, ie. the regulatory system is operating according to previous experience. In light of this, it has been shown that the response of human subjects to food volume or weight can be altered with diet manipulation (9).

The capacity of the stomach of obese humans has been estimated to be approximately 75% larger than that of lean individuals (10), although more recent studies using non-invasive measurements do not fully support this observation (11). Despite this discrepancy, it is reasonable that a larger volume of food would be needed to fully activate stretch or touch receptors in a larger volume stomach. Following gastric bypass surgery to reduce stomach size, patients report greater feelings of fullness and less hunger after a meal, implicating stomach mechanoreceptors in the regulation of food intake (12). Gastric distension activates multiple cortical and subcortical regions in the human brain (13).

In addition to stomach size, the amount of time that food is present in the stomach could also influence mechano- and chemosensitive satiety signals and it is a reasonable hypothesis that an enhanced rate of gastric emptying could predispose to overeating. However, this has been a controversial area of research with studies demonstrating enhanced gastric emptying rate in obese humans but others finding no difference or even a slower emptying rate. More recently, it has been reported that there is no difference in the 3 h gastric emptying rate in lean and obese men in a tightly controlled study (14). However, the percentage of gastric emptying in the first 30 min of the study was greater in the obese subjects and this was normalized to that in lean subjects after major weight loss. Further work will be needed to fully understand the role of gastric emptying in the regulation of food intake, as several of the gastrointestinal hormones to be discussed below are hypothesized to regulate this process.

Gastrointestinal Hormones

The entry of nutrients into the stomach and intestine elicits the release of several gastrointestinal hormones, the majority of which act to inhibit food intake (Table 1). These hormones are synthesized in the gut and signal the central nervous system through vagal or sympathetic afferents, and through the circulation (Figure 1). Circulating hormones gain acess to the central nervous system through the circumventricular organs, which are specific areas of the brain where the blood brain barrier is porous. The median eminence and arcuate nucleus of the hypothalamus contain receptors for many circulating hormones and factors, which regulate food intake. In addition, many of the gastrointestinal peptides and their receptors are also synthesized in the brain and act there as neurotransmitters regulating food intake.

TABLE 1. GASTROINTESTINAL PEPTIDES REGULATING FOOD INTAKE

Peptide	Stimulus	Site of Production	Site of Action	Effect on food intake
CCK	protein and fat	small intestinebrain	vagal afferents	decrease

GLP-1	nutrientsgut hormones gut neural signals	ileum/colon	gastric emptyingbrain	decrease
Ghrelin	fasting	stomach	brain	increase
Apo A-IV	fat absorption	intestine/liver	brain	decrease
Enterostatin	fat	stomach/intestine	vagal afferents	decrease
GRP/ Bombesin	gastric mucosa	food ingestion	vagal afferentsbrain	decrease

Cholecystokinin (CCK)

The role of CCK in the regulation of food intake has been extensively studied (15). CCK is widely distributed in the gastrointestinal tract, concentrated in the duodenum and jejunum, and produced by the intestinal mucosa in two forms CCK-33 and CCK-8. Two receptors for CCK have been characterized. The CCKA receptor is located primarily in the gastrointestinal tract and the CCKB receptor is found in the brain. Release of CCK in the gut is stimulated by protein and fat. CCK slows gastic emptying and reduces food intake in both animals and humans by terminating the feeding episode. Vagotomy blocks the effect of CCK on food intake, indicating that gastrointestinal CCK regulates food intake primarily through vagal afferent signals to the brain rather than through endocrine mechanisms. Long-term administration of CCK does not result in weight loss by virtue of the fact that the reduction in food intake at each meal is offset by the consumption of more meals. This emphasizes the fact that CCK is a short-term inhibitor of food intake, and that signals of long-term energy balance such as leptin (discussed below) can override the CCK signal. Interestingly, CCK may interact with some of the long-term signals of energy balance such as estrogen, leptin and insulin. Intracerebroventricular administration of leptin at low doses, which do not affect food intake, potentiate the CCK-induced reduction in food intake.

CCK-8 and the CCKB receptor are found in the brain. CCK-8 fulfills the criteria for a neurotransmitter and is usually colocalized in nerve endings with other neurotransmitters such as dopamine and GABA (16). It is hypothesized that CCK may potentiate the effects of dopamine to reinforce eating behavior (17). CCK injected into the central nervous system will decrease food intake in rodents and this appears to involve the CCKA receptor. The exact mechanisms through which centrally released CCK regulates food intake will require further investigation.

Glucagon-like Peptide 1 (GLP-1)

GLP-1 is produced by post-translational processing of proglucagon in the L-cells of the intestinal mucosa (18). The majority of these L-cells are located in the distal ileum and colon and GLP-1 secretion is regulated by both nutritional signals and neural/hormonal signals originating from more proximal areas of the gut. GLP-1 is present in the circulation as two equally potent molecular forms, GLP-17-37 and GLP-17-36amide, but is rapidly degraded by exopeptidase dipeptidyl peptidase IV to the inactive molecules GLP-19-36amide and GLP-19-37. There is one 59-kDa GLP-1 receptor, which is present in the gut and other tissues including the CNS and endocrine pancreas. GLP-1 inhibits gastric emptying in humans at concentrations within the physiologic range that might be achieved after meal ingestion. GLP-1 also suppresses appetite and food consumption with peripheral administration in normal and diabetic humans.

Exendin-4 is a novel 39-amino acid peptide isolated from the venom of the Gila monster Heloderma suspectum. It shares 53% sequence homology with GLP-17-36amide and interacts with the same membrane receptor. Exendin-4 has a significantly greater half-life in human serum (~33 min) compared

to GLP-1 (~3 min). Exendin-4 has recently been shown to significantly lower fasting plasma glucose, delay gastic emptying, and reduce food intake in healthy human volunteers (19). Exendin-4 may potentially be useful in the future in the treatment diabetes and obesity.

Ghrelin

Ghrelin is a 28 amino acid peptide that was originally identified as an endogenous ligand for the growth hormone secretagogue receptor (20). Ghrelin is acylated on serine-3, a modification observed for the first time in mammalian physiology, and this acylation appears to be necessary for its biological activity. Ghrelin is produced predominately by the stomach, but also in lesser amounts by the GI tract, kidney and in the hypothalamus. Recently, adminstration of ghrelin to rodents was shown to induce obesity by increasing food intake and reducing fat utilization. In human studies of ghrelin effects on GH release, feelings of hunger were noted as a side effect in a majority of the test subjects. Serum ghrelin is reduced in obese humans and following acute overfeeding. Circulating ghrelin is increased with fasting in humans. Ghrelin regulates food intake by binding specific receptors in the hypothalamus and activating well-characterized arcuate nucleus neurons, which produce neuropeptide Y (NPY) and agouti related peptide (AGRP) to stimulate feeding. Ghrelin has also been reported to act on other signalling pathways in the hypothalamus and much work is underway to fully understand the signalling pathways and role of ghrelin in the regulation of food intake.

Apolipoprotein A-IV (Apo A-IV)

This protein is produced by the liver and intestine and incorporated into chylomicrons and lipoproteins (21). The synthesis of apo A-IV is stimulated by fat absorption. Apo A-IV inhibits food intake by acting in the central nervous system and its rapid synthesis following lipid absorption suggests a major role in the short-term regulation of food intake. Apo A-IV message and protein have recently been found in the rat hypothalamus (22). Fasting reduces hypothalamic Apo A-IV and refeeding with lipid increased its levels. These data provide strong support for Apo A-IV in the regulation of food intake.

Enterostatin

Enterostatin is a pentapeptide derived by tryptic digestion of pancreatic procolipase in the intestinal lumen (23). Procolipase synthesis and release is stimulated by a high fat diet. Procolipase is found in stomach, small intestine and pancreatic secretions. Enterostatin inhibits food intake and in particular, fat intake when given to rodents as an intraperitoneal injection, or directly into the central nervous system. The inhibition of fat intake with peripheral enterostatin administration is dependent on intact vagal afferents but enterostatin has also been detected in the circulation. Enterostatin given intravenously in humans did not reduce food intake (24).

Gastrin-Releasing Peptide (GRP)

GRP is one member of a family of peptides which include neuromedin B, neuromedin C and bombesin. Bombesin was originally isolated from frog skin and is functionally related to GRP and the neuromedins (25). These peptides are produced by the gastric mucosa and bind to three distinct receptors, the GRP, the neuromedin B, and the bombesin-3 receptor. GRP and bombesin given peripherally will stimulate release of gastrin, CCK, insulin and other gut peptides (17). Bombesin and GRP inhibit food intake in both rodents and humans through both vagal afferents and direct centrally mediated effects (26).

REGULATION OF ENERGY INTAKE BY PANCREATIC HORMONES

The primary function of the pancreatic hormones insulin and glucagon is the regulation of glucose homeostasis. However, the fact that the pancreas secretes these hormones in response to feeding also places them in a position to signal energy intake to the central nervous system (Table 2). Further, basal insulin levels are proportional to adiposity, implicating circulating insulin as a signal of energy stores in the body. Amylin, co-secreted by the b -cell with insulin, has more recently been implicated in the regulation of energy intake.

TABLE 2. PANCREATIC HORMONES REGULATING FOOD INTAKE

Peptide	Stimulus	Site of Production	Site of Action	Effect on food intake
Insulin	carbohydrate	b -cell	brain	decrease
Amylin	carbohydrate	b -cell	brain	decrease
Glucagon	cephalic response	a -cell	liver/vagalafferents	decrease

Insulin

Secretion of insulin is stimulated by glucose and amino acids but not dietary fat. Insulin receptors are found in many brain areas and are localized in hypothalamic nuclei regulating feeding behavior. Insulin is transported into the CNS across the blood brain barrier by an active, saturable process, and also gains access through the circumventricular organs. Administration of insulin directly into the brain of rodents decreases food intake. In contrast, increases in peripheral insulin levels in the absence of feeding result in hypoglycemia, which is a stimulus for food intake (27).

Circulating insulin levels are proportional to the amount of body fat; therefore, insulin not only signals nutrient intake but also acts as a measure of energy stores in the body (Figure 2). Insulin release, both basal and in response to food intake, increases as body fat increases to maintain glucose homeostasis in the presence of insulin resistance. It has been hypothesized that this increase in insulin secretion thus results in greater insulin delivery to the brain, where it acts to limit further weight gain. Administration of insulin directly into the brain at a dose that has no effect on food intake has been demonstrated to enhance the response to subthreshold doses of CCK. These observations show that insulin acts in concert with short-term signals to limit food intake (28).

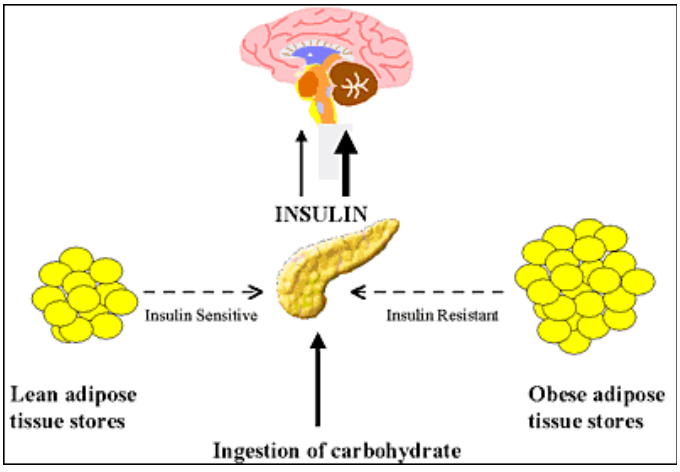

Figure 2.Insulin signals the intake of nutrients and acts as measure of energy stores in the adipose

tissue. Both basal and nutrient-induced insulin release increase as body fat increases to maintain normal glucose homeostasis in the presence of insulin resistance, which develops in concert with the greater fat depots in the obese subject. It has been hypothesized that this increase in insulin secretion thus results in greater insulin delivery to the brain, where it attempts to limit further weight gain.

Glucagon

Although counterintuitive with respect to glucose homeostasis, most meals with the exception of pure carbohydrate, elicit a transient increase in glucagon release. This increase in glucagon secretion is part of the cephalic phase response to food intake. The increase in glucagon is not dependent on nutrients in the gut as it has been demonstrated to occur during the first few minutes of sham-feeding when food is prevented from reaching the GI tract (29). Glucagon decreases meal size when given peripherally or directly into the CNS in animals. The peripheral effects of glucagon involve the liver and are mediated by vagal afferents, although the mechanism is not well understood. Glucagon has been shown to decrease food intake in humans when given alone, but not in combination with CCK (26).

Amylin (islet amyloid polypeptide or IAPP)

Amylin is a 37 amino acid peptide that is similar in sequence to calcitonin gene-related peptide (CGRP), a neuropeptide synthesized in the brain and gut. In addition to synthesis in the b -cell, amylin is found in endocrine cells in the gut, visceral sensory neurons and the hypothalamus (30). Amylin is a potent inhibitor of gastric emptying. Peripheral or central administration of amylin inhibits food intake in rodents and amylin-deficient knock-out mice weigh more than wild-type controls (27). The amylin analog pramlintide is currently being evaluated for effects on food intake in humans.

ENERGY STORES REGULATE ENERGY INTAKE

In order to efficiently match energy intake to energy expenditure and maintain energy stores, the hypothalamic centers regulating energy balance need to monitor the amount of energy stored in the adipose tissue. Leptin is a hormone secreted by the adipose tissue that provides this information to the central nervous system.

Leptin is the 146 amino acid peptide product of the LEP gene (originally termed ob gene), which is most highly expressed in adipose tissue (31), but is also detectable in other tissues including muscle (32), and placenta (33). Serum leptin increases with increasing adipose tissue mass in humans and is therefore a signal of energy stores (34). Leptin is significantly greater in women than in men with an equivalent amount of fat. Reproductive hormones, as well as body fat distribution, appear to contribute to the difference in leptin between men and women (35). Leptin is also a signal of energy stores in children and newborns in whom serum concentrations are highly correlated with adiposity (36).

A reduction in adipose tissue mass with weight loss results in a decrease in serum leptin. In contrast, an increase in the adipose tissue mass significantly increases circulating leptin. These observations demonstrate that serum leptin is a dynamic signal to the CNS of the amount of energy stored in the adipose tissue (36).

In addition to acting as a signal of current energy stores, serum leptin also provides information about extremes in caloric intake (Figure 3). Serum leptin falls dramatically during fasts of 24 h or longer and

will increase again within 4-5 hr of refeeding despite the fact that adipose tissue mass does not change over this time period (37). Insulin and glucose, through hexosamine biosynthesis, appear to regulate changes in leptin release that occur in the absence of changes in fat mass (32,38). The fall in serum leptin with fasting provides a signal to the CNS that food intake has not recently occurred and in part, initiates the complex response of the body to defend energy stores (39). The reduction in leptin with caloric restriction may have important implications with respect to success in dieting. The decrease in leptin that occurs with hypocaloric diets, independent of any reduction in adipose tissue, signals to the hypothalamus to increase food intake and decrease energy expenditure in an attempt to maintain energy stores constant. This normal physiologic response to caloric restriction is therefore counterproductive to the goal of a weight loss program and may contribute to difficulties in compliance.

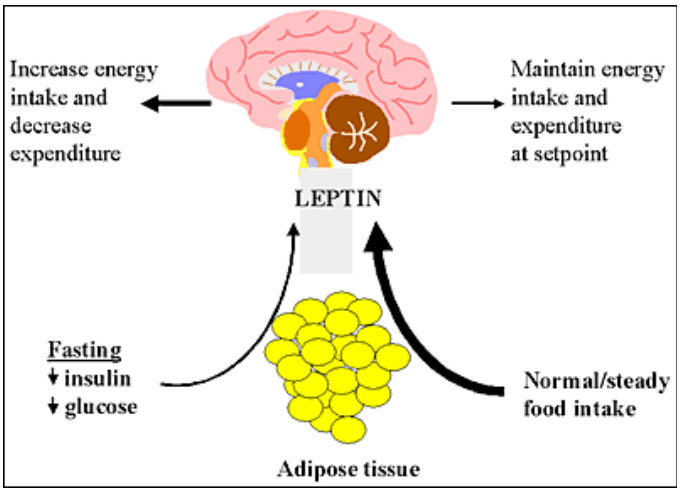

Figure 3.Leptin is present in the circulation in proportion to the amount of adipose and thus acts as a measure of energy stores. A fall in leptin in the absence of changes in the amount of adipose tissue also signals to the central nervous system that the body has entered a fasting state. The reduction in insulin and glucose with fasting has been implicated in the fall in leptin.

The leptin receptor is detectable in several areas of the CNS but is highly expressed in the hypothalamus. As is insulin, leptin is actively transported across the blood brain barrier by a saturable transport system and also has access to the arcuate nucleus of the hypothalamus through the median eminence (one of the circumventricular organs that lacks a blood-brain barrier). The leptin receptor is a cytokine receptor, which regulates the transcription of specific genes through the JAK/STAT second messenger pathway (40). Leptin binding to its receptor in the arcuate nucleus reduces the expression of neuropeptides that stimulate food intake and increases expression of neuropeptides that reduce feeding (see chapter 5 for details).

Leptin has been tested as a potential weight loss therapy in three separate trials in humans. In the first case, a 9 year old girl with absolute leptin deficiency due to a defect in the LEP gene was treated with exogenous leptin at a dose calculated to achieve a peak serum leptin concentration equivalent to 10 percent of the child's predicted normal serum leptin concentration (70 ng/ml), calculated on the basis of age, sex and body composition. Recombinant leptin treatment of this nine-year-old patient led to a sustained reduction in weight, predominantly as a result of a loss of fat. The chief effect of leptin was its suppressive effect on food intake. Therapy had no effect on energy expenditure (41).

A second study tested the efficacy of leptin in obese subjects with normal leptin production; therefore, leptin levels were elevated in the test group (42). In this study leptin produced a small dose-dependent weight loss after 24 weeks of treatment by subcutaneous injection. The most common adverse event was injection site reactions. None of the subjects receiving recombinant leptin experienced clinically

significant adverse effects on major organ systems. There was no effect of recombinant leptin on glycemic control or insulin action, in contrast to observations in animal studies.

In the third trial pegylated leptin (PEG-OB) was tested for its ability to induce weight loss (43 Pegylation has been used to increase serum half-life and reduce immunogenicity of injected proteins, and did so for leptin as well. PEG-OB treatment produced significant suppression of appetite, as measured by eating/hunger questionnaires, but no significant changes in body weight. Circulating leptin levels in the actively treated group were not significantly elevated, with the exception of only two time points over the 12-week study period, therefore it is likely that the dose of leptin used was not sufficient to induce weight loss. Additional studies will be needed to determine if leptin will be an effective as a therapy for weight loss.

ADDITIONAL REGULATORS OF FOOD INTAKE

A number of hormones influence food intake, although in many cases this effect is not usually considered their primary physiologic role. Glucocorticoids function in the central nervous system to stimulate carbohydrate and fat intake by increasing neuropeptide Y and inhibiting CRH. (44). Although glucocorticoids are not elevated in obese humans, it has recently been appreciated that 11 b -hydroxysteroid dehydrogenase type 1, which reactivates cortisol from cortisone, is very active in several brain areas including the hypothalamus (45). The contribution of this amplifer of glucocorticoid action to the regulation of food intake is currently under investigation. Thyroid hormones influence food intake indirectly through effects on energy expenditure. Increased energy expenditure in hyperthyroidism stimulates food intake to maintain energy balance. In contrast, energy intake is decreased in hypothyroidism in which energy expenditure is reduced and weight gain develops. Somatostatin, released by delta cells of the pancreas, inhibits gastrointestinal motility, endocrine and exocrine secretion, and decreases food intake in both rodents and humans (26). Growth hormone and growth hormone releasing hormone (GHRH) increase food intake (7). Estradiol is associated with a reduction in food intake in humans and ovariectomy in animals increases food intake in an estrogen reversible manner. Progesterone in combination with estrogen increases food intake (17). Prolactin increases food intake in animals but its relevance to human obesity is not established (26). Cytokines inhibit feeding when administered to animals or humans and during pathological conditions such as infection, inflammation or malignancy (46). Cytokines may indirectly regulate food intake through effects on leptin release (47) and insulin sensitivity (48).

REGULATION OF FOOD INTAKE BY NUTRIENTS

Glucose

The glucostatic hypothesis proposes that glucose utilization rate or changes in plasma glucose concentration may be signals to start or stop eating (49). It has been demonstrated that a small transient fall in glucose precedes feeding in both rodents and humans (50,51). Further, hypoglycemia or inhibition of glucose metabolism also increase food intake (26). Glucose-sensitive neurons present in the hypothalamus and other brain areas are involved in the regulation of food intake by glucose (Figure

1 (52)). Of interest with respect to the development of obesity is the recent suggestion that carbohydrate ingested in the form of liquids (soda, fruit juice, power drinks) has weak satiety properties compared to carbohydrate in solid foods (53,54). There is evidence for an increase in caloric intake with beverage consumption in the US, and this poorly compensated for increase in energy intake could contribute to the development of obesity.

Fat

Infusion of lipid into the small intestine slows gastric emptying and reduces food intake at a test meal (9). Intravenous infusion of lipid emulsion inhibits food intake in baboons, and ketones and certain fatty acids in the circulation also inhibit food intake (7). In contrast inhibition of fatty acid oxidation increases food intake (26). The satiety producing properties of fat have been proposed to be weak and easily overcome by other factors such as the positive or pleasant feel of fat in the mouth, and the greater energy density of high fat foods, which can lead to overconsumption and the development of obesity (9). Rolls and colleagues have shown that manipulation of the fat content of the diet, while maintaining palatability, had little effect on energy intake, further suggesting that fat is poorly signalled to the CNS. In contrast these investigators have shown that people tend to consume a constant weight of food (55). These observations suggest that the greater energy density of high fat foods is not adequately accounted for by the central nervous system and that these foods can contribute to overeating and obesity.

Protein

Protein suppresses energy intake in humans to a greater extent than any of the other macronutrients when examined in either free-living conditions or in the laboratory. The inhibition of food intake by protein appears to involve oral somatosensory input (smell and taste to identify protein in the diet) and learning processes. The amino acid composition of the dietary protein may also play an important role in regulating food intake. The effects of protein on food intake are likely mediated by direct effects of circulating amino acids on the brain, as well as effects in peripheral tissues. The exact mechanism(s) through which protein regulates food intake are still poorly understood (9).

CONCLUSIONS

The regulation of food intake is a complex process, which involves signals from many sources including the gastrointestinal tract, adipose tissue stores and pancreas. Many of the signals discussed in this chapter have been pharmacologically manipulated in rodents and humans in an attempt to reduce food intake and body weight. These experiments have been met with varying degrees of success. Additional work will be necessary to refine our understanding of the processes regulating food intake and to identify successful therapeutic interventions with which to combat the epidemic of obesity. Future successful therapy is likely to rely on a combination of interventions targeted at several of the processes that regulate food intake.

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