OBESITEXT Chapter 3.1:– The regulation of energy intake

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Take-Home Points

- **Regulation of food intake occurs homeostatically via activation of peripheral signals in the GI tract and adipose tissue, which directly monitor incoming nutrient and nutrient stores, and central systems (e.g., the hypothalamus), which receive these signals and alter behavioral and metabolic output to balance energy intake with need**
- **These signals engage in significant interaction with one another, often by making other signals more or less effective (e.g., increased levels of the adipose hormone leptin due to greater fat stores makes the satiety signal CCK more effective decreasing meal size).**
- **In addition to the hypothalamus, the hippocampus is involved in regulating food intake by cognitive mechanisms including explicit recall of prior meals and associative learning about the relationship of feelings of hunger/satiety to the consequences of eating.**
- **These signals act via numerous behavioral mechanisms, including altering meal initiation, termination and size, increasing or decreasing the motivation to seek and consume food, causing subjective feelings of hunger or satiety, or changing the perceived reward value of food.**
- **Obesity, or chronic consumption of a high-fat, energy-dense diet, can lead to changes in the sensitivity to these signals resulting in decreased ability to regulate and may contribute to the persistence of obesity. Cognitive function and sensitivity to the rewarding aspects of food are also affected by chronic obesity.**

Introduction

Energy balance requires that an organism match caloric intake relatively precisely with caloric expenditure. In humans, an error of only +11 kcal/day results in a one pound weight gain over the course of a year. Over the past 40 years, the average body weight of American adults has increased at rate of less than that one pound per year, but the steady increase has yielded an increase of an average of 3 BMI points, bringing the average adult from a healthy weight into the overweight category (1). This increase brings with it a significantly increased risk of a number of health problems, including type 2 diabetes, high blood pressure, and cardiovascular disease and has a total financial cost estimated at $139 billion per year (2). In attempting to identify potential biological causes and treatments for this widely-occurring disorder, it is critical to understand the mechanisms which regulate energy homeostasis. In this chapter, we will review both peripheral and central signaling mechanisms relating to the food intake side of the equation, including how these signals function with respect to specific aspects of food intake-related behavior, and a brief overview of how this system may become dysregulated during states of chronic overconsumption and obesity.

Environmental Signals

There are a variety of external factors that play a significant role in food intake, including social situations, time cues, food-related stimuli (e.g., sight, smell) and other learned information. While it is evident that these types of signals can have a definite impact on when to consume a meal, what foods to choose and how much to eat, the focus of this chapter will be on the molecular mechanisms involved in controlling these ingestive behaviors.

Peripheral Signals

Gastric Mechanoreceptors

After food is ingested, it moves into the gastrointestinal tract where the volume and the nutritive content of the meal is detected via mechanical and chemosensory mechanisms. The results of sham feeding experiments indicate clearly that detection of food in the gastrointestinal (GI) tract plays a large role in determining the amount consumed. In these studies, animals with open gastric fistulas which allow food to drain out of the stomach consume much larger volumes than animals consuming food normally, an effect which can be overcome by concurrently infusing nutritive solutions directly into the duodenum (3, 4). Gastric mechanoreceptors are located on vagal afferent and splanchnic nerve fibers and detect food volume by responding to stretch or pressure in the walls of the stomach (5, 6). Experiments in rats using pyloric occlusion to prevent contents from emptying into the intestines have demonstrated that satiety, as indicated by reduction in subsequent food intake, can occur based on gastric signals, that this is due predominantly to food volume, rather than caloric content, and that this effect is dependent on an intact vagus (7-9). However, it appears that the volumes required to reduce food intake are substantially greater than the volumes generally consumed in a single meal. Further, under the majority of self-controlled feeding conditions in rodents, intake was not significantly altered by pyloric occlusion (10, 11), indicating that, while gastric distension can act as a satiety signal, it may not be an important regulator during normal feeding situations. Although the idea that gastric distension may contribute to meal termination is consistent with data supporting a volumetric control of food intake, the data on gastric mechanoreceptors and satiety suggest that other mechanisms are likely at work in this phenomenon.

Gastrointestinal Satiety Signals

Although the stomach is thought to be primarily responsive to food volume, nutrient entry into the stomach also induces the release of gastrin releasing peptide (GRP), a member of the bombesin-like peptide family. GRPs (including GRP-10, -27 and -29) in humans and animals act as satiety signals by reducing meal size, prolonging time to begin the next meal and enhancing the satiating effects of a meal (12,13).

The intestinal tract is highly sensitive to the caloric content of ingested foods. Beginning in the duodenum, the detection of nutrients activates the release of a number of peptides, often termed “satiety signals”, which act primarily to terminate consumption of a meal. The most well known of these is cholescystokinin (CCK), an octapeptide that is released from the duodenum and, to a lesser extent, the ileum in response to nutrients (14). CCK activates receptors on the vagus nerve which terminates in the hindbrain at the nucleus of the solitary tract (NTS). As nutrients enter into and move through the GI tract, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are secreted from the ileum and colon, while apolipoprotein A-IV (Apo A-IV) is synthesized in response to intestinal fat absorption (15-17). CCK and other GI peptides are differentially responsive to the macronutrient composition of a meal. CCK and gastrin are released more readily by protein ingestion, which is confirmed by the finding that protein hydrolysates directly stimulate CCK receptors in enteroendocrine cells (18,19). Consumption of carbohydrates and fats yields greater GLP-1 release, whereas Apo A-IV synthesis is induced exclusively by fat absorption and PYY is most responsive to protein and fats (20-22). In obese individuals, PYY is more responsive to fats than carbohydrates (23) and, in humans, exogenous administration of PYY_{3-36} increases both ratings of satiety and plasma free fatty acids (24). Since most meals consist of multiple nutrient components, this allows for the integration of nutrient and caloric information by GI signals, and these varying profiles of satiety signal activation may contribute to differences in the relative satiety value of the macronutrients (25,26), as well as possibly affecting macronutrient selection and intake at later meals.

All of these GI “satiety signals” reduce food intake when administered to animals either systemically or centrally, and when administered peripherally in humans (24,27-34), although it should be noted that there is some controversy surrounding the efficacy of the active form of PYY_{3-36} to reduce food intake

and body weight in humans and non-human animal models (35,36). These peptides effect reductions in food intake primarily by acting to terminate the current meal, although longer-term effects have been suggested for GLP-1 and PYY (37). The observation that antagonists of CCK and GLP-1 receptors results in increased food intake (38-40) more strongly indicates that these hormones function endogenously to control feelings of satiety and meal termination. The idea that these hormones are the natural mechanism for ending a meal is also supported by the observation that meal ingestion, infusion of calories into the GI tract and exogenous administration of several of these peptides, including CCK and bombesin/GRP, all result in animals displaying a similar set of behaviors, termed the “behavioral satiety sequence” (41-43). However, genetic deletion of these peptides or their receptors yields mixed results. For example, PYY knockout mice and OLETF rats, which lack the CCK-1 receptor (CCK-1R) due to a spontaneous mutation, display marked hyperphagia and obesity (44,45). However, rats genetically manipulated to possess the specific CCK-1R-null gene that characterizes the spontaneous OLETF phenotype do not display the same hyperphagia and obesity, suggesting that the genetic mutation affecting CCK-1R is not the sole contributor to these characteristics in OLETF rats (46). Additionally, GLP-1R-null mice display normal feeding behaviors and body weight (47). Of course, the majority of these genetic studies employ techniques that typically result in absence of the peptide or receptor throughout development allowing the function to be taken over by other systems. Overall, we can conclude that GI peptides play an important role in meal size and meal termination, with the endogenous function of some of these peptides being critical regulation of energy intake under normal ingestive conditions, while the role of others may be redundant with or compensated for by other systems.

Pancreatic Satiety Hormones

Outside of the GI tract, the pancreas also secretes peripheral meal-related hormones that act to reduce food intake. Insulin and amylin are co-secreted from pancreatic ß-cells in proportion to the amount of food consumed (48,49). While the function of insulin seems to relate more to the long-term regulation of body adiposity (see below), amylin serves as a short-term signal that acts to reduce food intake by decreasing meal size (50). Exogenous, peripherally administered amylin reduces food intake, while systemic antagonists have the opposite effect, again indicating an endogenous role for this hormone in satiety (51-53). Glucagon is secreted from pancreatic A-cells very rapidly following meal onset, particularly meals high in protein, and acts via the liver to limit meal size in rodents and humans, an effect which can be reversed by administration of a glucagon-specific antibody (54-59).

Ghrelin

To date there is only one identified orexigenic, or appetite stimulating, gut peptide. Ghrelin is an endogenous ligand for the growth hormone secretogogue receptor (GHSR) that is synthesized in and secreted from gastric epithelium (60). Ghrelin produced by neurons in the hypothalamus also exerts orexigenic effects on appetite (61). Administration of exogenous ghrelin increases food intake in both humans and non-human animals (62-65), while GHSR antagonism *increases* food intake and body weight in rodents (66). Further supporting the notion that this hormone plays an endogenous role in food intake, peripheral ghrelin levels rise when fasting and prior to either scheduled or spontaneous meal ingestion and are reduced following nutrient consumption (62,67-74), with a greater suppression in response to carbohydrate or protein ingestion compared to fat (75-79). Genetic ghrelin deletion initially suggested that this peptide may have more critical effects on metabolic functions than on food intake and body adiposity, as the latter measures are normal in ghrelin knockout mice (80,81). However, mice lacking the GHSR display resistance to high-fat diet-induced obesity via mechanisms that include reduced food intake and reduced body adiposity, in addition to metabolic changes (82).

In 2005, another peptide was identified from the gene encoding ghrelin, dubbed obestatin or ghrelin-associated peptide (83). While ghrelin stimulates food intake and gastroduodenal motility, obestatin reduces food intake and inhibits gastrointestinal motility in fed, but not fasted, animals (83,84). Subsequent research on obestatin produced conflicting results of its effect on hypophagia, interaction

with ghrelin, gastrointestinal motility and its ability to activate GPR39, the putative obestatin receptor (85-89). Though there is some potential with respect to the role of obestatin (or obestatin/ghrelin balance) in pathological eating (e.g., anorexia nervosa), based on the current, conflicting state of the findings on this peptide, categorizing obestatin as an important peripheral signal for food intake and body weight regulation seems unjustified.

Adiposity Signals

Signals from the GI tract are acutely sensitive to nutrients entering the system and function primarily to regulate short-term intake on a meal-to-meal basis. However, the body also stores fuel for times of food shortage, mainly in the form of fat. One early hypothesis for the long-term regulation of body weight was that food intake and metabolic rate was adjusted based on the detection and regulation of the amount of adipose tissue present in the body (i.e., the “lipostatic hypothesis”; 90,91). To date, two major hormones have been identified and found to meet the criteria qualifying them as adiposity signals: insulin, which is produced in pancreatic ß-cells, and leptin, which is secreted directly from adipocytes. These two peptides are secreted in proportion to the amount of body fat and have access to the brain where they act via central effector systems in the hypothalamus, as well as the hindbrain, to reduce food intake (92,93). Receptors for both insulin and leptin are found in the arcuate nucleus of the hypothalamus, a critical region for the control of energy homeostasis and central administration of both hormones potently reduces food intake (94-102). Hypothalamic administration of insulin antibodies has the opposite effect, increasing food intake and body weight (102,103) and rodents which are genetically incapable of leptin production (ob/ob mice) or have a dysfunctional leptin receptor (Zucker fatty or *fa/fa* rats and *db/db* mice) display an obese, hyperphagic phenotype (104-106), as do mice with a brain-specific deletion of the insulin receptor or disruption of pancreatic beta-cell and hypothalamic insulin receptor substrate 2 (107,108). Similarly, congenitally leptin-deficient humans are morbidly obese and markedly hyperphagic, as are those with leptin receptor mutations, although the symptoms are less severe (109,110).

In the hypothalamus, leptin receptors are located on both orexigenic neurons (i.e., neuropeptide Y (NPY)/agouti-related peptide (AgRP); 97) and some anorexigenic neurons (i.e., proopiomelanocortin (POMC)/cocaine- and amphetamine-related transcript (CART); 111). Insulin receptor expression is high in the arcuate nucleus with insulin receptor substrate-2, a key element mediating insulin effects on food intake, co-localizing there with NPY and α-melanocyte stimulating hormone (α-MSH) (112,113), as well as POMC, though insulin activates a different population of these cells than leptin, allowing for “cross-talk” between these signals (114). Broadly speaking, increases in the amount of stored fat increase circulating levels of insulin and leptin which, in turn, act via central regulatory mechanisms to reduce orexigenic signaling and increase anorexigenic signaling, allowing these peripheral adiposity signals to influence food intake.

Central Regulation

Hypothalamus

The primary forebrain regulation of food intake behavior is thought to occur in the hypothalamus. Early evidence indicated that lesions in this area had profound effects on ingestive behavior. Lesions of the ventromedial hypothalamus (VMH) result in drastically increased food intake and obesity, while lateral hypothalamic area (LHA) lesions yield hypophagia and reduced growth. These findings led to the hypothesis that these two areas controlled food intake by acting as the “satiety” and “feeding” centers, respectively, in the brain (115). Although this is now acknowledged to be a vast oversimplification of the regulation of food intake and body weight, the hypothalamus is still considered the key region for central control of energy homeostasis. A good deal more is now known regarding the molecular mechanisms at work in this area that act to control energy intake. The arcuate nucleus contains two populations of neurons that seem to be the first-order relay neurons in responding to adiposity signals from the periphery. The first arcuate neuronal population co-expresses the peptides NPY and the melanocortin

receptor antagonist AgRP, while the second population of neurons contains POMC, the pre-cursor to the melanocortin receptor agonist α-MSH, and CART. Central infusion of NPY or AgRP potently stimulates food intake (116-118), while icv administration of α-MSH or CART inhibits food intake (119,120), suggesting that these two neuronal populations represent a primary orexigenic and its opposing anorexigenic pathway, respectively, in the central regulation of energy homeostasis.

In support of the endogenous function of these peptides, food deprivation increases expression of AgRP and NPY mRNA, while decreasing POMC and CART gene expression (121-124). Overexpression of agouti or AgRP yields hyperphagia and obesity, as does disruption of the genes encoding the melanocortin-4 receptor, POMC or CART (125-129). Recently developed optogenetic techniques demonstrated that specific stimulation of AGRP neurons invoked cell number-dependent, light-frequency and duration dependent feeding response in well-fed mice, indicating that independent activation of AGRP cells could cause short-term feeding (130). Finally, while there is compensation for developmental deletion of the NPY or AgRP genes or neonatal destruction of NPY/AgRP neurons, ablation of these neurons in adult mice yields dramatic reductions in food intake and bodyweight, while the reverse occurs with ablation of POMC neurons (131-135). In humans, through relatively rare, genetic POMC deficiency also leads to an obese phenotype, as do a number of mutations of the MC-4 receptor. In addition, it has been suggested that variations in the POMC gene may be a contributing factor in obesity in the larger population (135).

As discussed above, leptin and insulin receptors are located on both orexgenic and anorexigenic cell types, suggesting that these neurons are responsive to circulating levels of adiposity signals and act as effectors for altering food intake in response to shifts in energy balance (at least those reflected in body adiposity). Leptin and insulin both cross the blood-brain barrier via independent, saturable transport mechanisms (136,137), indicating that peripheral production of these hormones can have central action. Indeed, as predicted, central insulin and leptin increase hypothalamic POMC expression, leptin increases activity in POMC neurons and melanocortin antagonists can block leptin-induced anorexia (138-141). These melanocortinergic neurons project from the arcuate to other areas of the hypothalamus, such as the paraventricular nucleus (PVN) and the LHA where several additional peptides that influence food intake and body weight are synthesized. The second-order neurons acting to regulate energy homeostasis in the PVN synthesize and release anorexigenic compounds, such as corticotrophin-releasing hormone (CRH), TRH, and oxytocin (142-147), while those in the LHA and adjacent perifornical area (PFA) are orexigenic, such as melanin-concentrating hormone (MCH) and orexin A and B (aka hypocretin 1 and 2) (148-151).

While leptin and insulin appear to control energy balance over a longer time scale, short-term peripheral signals, such as ghrelin and nesfatin also appear to act via the hypothalamic system to regulate intake. Receptors for ghrelin are also located on arcuate AgRP/NPY neurons, which are activated by central ghrelin administration to increase food intake (152-154). Administration of peripheral ghrelin activates neurons in the ARC as well, and AgRP and NPY have been demonstrated to be requisite mediators of the hyperphagia induced by systemic ghrelin (155,156). On the opposite side of the intake equation, nesfatin-1 appears to be a central satiety signal that acts in the hypothalamus independent of leptin function (likely via melanocortin pathways). Central injection of this peptide reduced food intake and body weight, while infusion of targeted antisense oligonucleotides produce the opposite effect, and fasting decreased nesfatin expression in the PVN (157). Following the identification of nesfatin-1 in the brain, it was found that this peptide is also secreted peripherally from endocrine cells in the stomach, where it is co-localized with ghrelin, and has been shown to cross the blood-brain barrier where it acts on neurons located in the PVN and arcuate nucleus of the hypothalamus (158-161). Similar to central administration, peripherally delivered nesfatin-1 reduces food intake and this anorexigenic effect was abolished in mice pre-treated with capsaicin suggesting a vagally-mediated pathway between peripheral nesfatin-1 and central sites of action (162). Not surprisingly, like other vagally mediated GI satiety signals (e.g., CCK), nesfatin-1 influences food intake by reducing the size of individual meals and increasing the length of inter-meal intervals (163).

Hindbrain

In contrast to ghrelin and nesfatin-1, which are secreted from the stomach, most short-term signals arising from lower in the GI tract tend to be received and integrated in the hindbrain. Receptors for mechanical and chemical signals in the gut are found on afferent terminals of the vagus nerve, which tranduces these sensory signals and relays information to the nucleus of the solitary tract (NTS) (164). Studies using a chronic decerebrate rat model have demonstrated that these signals from the periphery (e.g., gastric preloads, CCK) can act to reduce meal size in the absence of hypothalamic input (165,166), however, there are a number of reciprocal connections between hypothalamic and hindbrain nuclei which suggest an integration of information from both sites acts to control food intake and energy balance (167-169). In addition, there are neurons expressing receptors for leptin, melanocortins and NPY, as well as POMC/α-MSH found in brainstem nuclei (170-175). Administration of synthetic MC receptor agonists and antagonists, AgRP, or NPY or its receptor agonists to the fourth ventricle all yield similar effects on food intake as when they are delivered to hypothalamic sites via the third ventricle (176-179). Leptin appears to exert a modulatory influence on brainstem controls of feeding, as well, as its administration alters the responsiveness of NTS neurons to gastric distension and CCK, as well as mediating the effects of these and other peripheral factors on food intake (180-184). Selective leptin-R ablation in GLP-1 expressing neurons in the hindbrain produced an obese phenotype characterized by hyperphagia and increased metabolic rate in mice (185). Although the evidence clearly demonstrates a role for both hypothalamic and hindbrain sites in the regulation of food intake, it is still unclear which aspects are controlled by each of these areas and how these regions interact to ultimately regulate energy balance.

"Gut" Peptides in the CNS

In addition to acting through the vagus, a number the peptides identified primarily as peripheral signals also function directly at CNS sites to affect energy homeostasis. Receptors for these peptides are often found in hindbrain areas, such as the NTS and DMH as well as in the circumventricular organs, allowing for central monitoring of the status of these circulating hormones (186). Whereas CCK-A receptors predominate in the GI tract, CCK-B receptors found largely in the CNS. It appears that CCK-A receptors are the primary mediators of food intake and satiety both peripherally and centrally, however under some conditions, central CCK-B receptors may be involved (187,188). Central CCK receptors, however, do not appear to be necessary for the intake suppressive effects of peripheral CCK and observed "central" feeding effects may be due to stimulation of peripheral receptors (189-191), indicating an independent role for centrally-produced CCK in food intake. CCK is produced and released in a number of brain regions, including the hypothalamus, but also the caudate nucleus, hippocampus, striatum, and cortical areas, and in addition to ingestive behavior, central CCK is implicated in anxiety, pain, and cognition, functions which seem predominantly related to CCK-B receptor activity (192-197).

Beyond CCK, peripheral PYY 3-36 may cross the blood-brain barrier to act at Y_2 receptors in the ARC, inhibiting NPY activity and stimulating POMC neurons (29,198). Direct central administration of PYY, however, produces a strong hyperphagic effect, likely acting via Y-family receptors, which also mediate NPY actions, in other brain regions, such as the PVN and hindbrain (178,199,200). GLP-1 and its receptors are also located in the hypothalamus as well as the brainstem, and icv infusion of GLP-1 reduces food intake in fasted rats, likely acting in the PVN, while the receptor antagonist $exendin_{9-39}$ increased feeding behavior (201,202).

Hippocampus

Just as conventional thinking about the localization of brain function firmly seats control of ingestive behavior in the hypothalamus, the hippocampus is typically considered the region responsible for memory. This dates back to the observation that Patient HM was unable to create new long-term memories after surgery that lesioned the hippocampus and associated structures (203). In addition to broad-scope anterograde amnesia, HM repeatedly reported the same level of hunger/fullness when asked by researchers, and would continue to eat as long as food was placed in front of him (204).

Studies of hippocampal lesions in animal models have yielded somewhat contradictory outcomes in terms of food intake and body weight, with the most common result being a pattern of increased number of meals/food contacts without an increase in either food intake or body weight (205,206), though other studies found increases in food intake that did not result in body weight changes and increases in both food intake and body weight relative to controls (207-209). The most recent study, employing a more specific lesioning technique and controlling for the effects of surgical recovery, found that hippocampal lesioned rats showed increased body weight, which could be attributed both to increases in food intake and to alterations in metabolic function (210).

Furthermore, like HM, rats with selective hippocampal lesions appear unable to detect or interpret signals of hunger and satiety, as they are unable to learn a discrimination based on this internal state or to perform this discrimination when it is learned prior to the lesion, indicating it is an impairment in using hunger states, rather than a learning defiicit (206,211). In humans, activity in the hippocampus during periods of food restriction and negative energy balance is supportive of this region playing a role in response to these states (212).

With respect to physiology, the hippocampus has bidirectional connections with traditional “feeding centers” including the hypothalamus and the brainstem, which may serve to communicate signals of energy balance to this region (213,214). Administration of either leptin or ghrelin alters food intake when injected directly into the ventral hippocampus, with leptin reducing and ghrelin increasing consummatory and appetitive behaviors (215,216) and inactivation of the dorsal hippocampal after a meal inhibits the onset of the next meal, suggesting a role for this region in meal initiation (217).

Estrogens

There are a number of other peptides that affect food intake outside of those listed above. Estrogen has inhibitory effects on food intake that are observed both as cyclic changes in caloric consumption with hormonal fluctuations in females and as a dramatic increase in food intake following ovariectomy (218). Further, mice lacking lacking estrogen receptor alpha (ERα) have increased body adiposity (219). Recent experiments show that centrally administered estradiol acts in the medial preoptic area, arcuate nucleus and dorsal raphe to decrease food intake (220). Experiments utilizing peripherally administered estrogens suggest a modulatory effect on the function of a number of other food intake-related peptides, including leptin, insulin, ghrelin, CCK, and the melanocortins (218,221). Sensitivity to central leptin and insulin differ between female and male rats, with females being more sensitive than males to leptin, while the reverse is true for insulin, and estrogen is responsible for this sensitivity (222,223). ERβ is found on subcutaneous adipose tissue and likely plays a role in the observation that subcutaneous fat deposition is increased by the administration of estradiol (223,224).

Other Neurotransmitter Systems

Serotonin

Monoamine systems, including dopamine (DA) and serotonin (5-HT) have also been shown to be involved in food intake. Activation of serotonin receptors using subtype-specific agonists or reuptake inhibitors (SSRIs) has been clearly demonstrated to reduce food intake and has been strongly targeted as an effective weight-loss treatment (225). It is likely that serotonin has it’s effects on body weight regulation through interaction with both hypothalamic and extra-hypothalamic systems, as receptors for this transmitter are widespread and co-localized with a number of key feeding peptides (e.g., melanocortins, orexins, ghrelin and leptin) (226). Dexfenfluramine, a broad serotonergic agonist, was one component of the weight loss treatment Fen-Phen, which was highly effective at producing weight loss in animal subjects and overweight/obese human patients (227,228). However, this treatment was removed from the market due to dangerous cardiovascular side effects (229). The weight loss success of these drugs, however, led to the search for more targeted serotonergic compounds for this purpose. The

selective 5-HT2C receptor agonist lorcaserin has been shown to produce effective weight loss in short- and long-term clinical trials and in 2012 was approved by the FDA to treat obesity (230,231), in spite of a still very general understanding of the mechanism by which serotonin influences food intake and body weight.

Dopamine

Animals treated with DA receptor agonists also exhibit reductions in food intake with activation of D1, D2 and D3 receptor subtypes seeming to alter different aspects of appetitive and consummatory behaviors with DA1 and DA3 receptors appearing to play the most specific roles in ingestion (232-234). The mesolimbic DA system in particular is posited to be robustly involved in food anticipation and learned appetitive behaviors, particularly those related to highly palatable foods, as indicated by increases in dopamine release in these regions in response to food and food stimuli (235-237). Reductions in short-term tests of sucrose licking and sham feeding in rats treated with dopamine antagonists supports the notion that the effects of dopamine are primarily on taste hedonics, rather than post-ingestive effects (238,239). In particular, the mesolimbic DA system is posited to be robustly involved in food anticipation and learned appetitive behaviors, particularly those related to highly palatable foods, as indicated by increases in dopamine activity in these regions in response to food and food stimuli in both humans and non-human animals (235,236).

Acetylcholine

Although not given as much attention as other neurotransmitter systems, recent studies also indicate a role for cholinergic systems in food intake, as well, particularly within the nucleus accumbens-ventral tegmental pathway. Specifically, injections of muscarinic acetylcholine (mACh) receptor antagonists into the accumbens reduces consummatory, but not appetitive behaviors, in rats, and this effect appears to interact with the opioid, but not dopaminergic systems (240-242). Antagonism of nACh receptors in the VTA reduces ghrelin-induced food intake, likely through a reduction in the reward value of the food, as indicated by impaired development of a food-conditioned place preference (243). Outside of mesolimbic regions, nicotine, an nACh receptor agonist, has been shown to have a suppressive effect on food intake via binding to acetylcholine receptors on POMC neurons, activating anorexigenic MC4 pathways (244).

Opioids

The opioid system also has a potent effect on food intake, although, like dopaminergic effects, this system seems to reflect the hedonic impact of food with greater responsiveness to the palatability of the food than the energy status of the organism (245,246). Opioid agonists typically stimulate intake of preferred foods, while antagonists have the opposite effect (246). More recent evidence finds that opioid effects on feeding are particularly potent when acting in conjuction with endocannabinoids (247,248).

Endocannabinoids

Activation of cannabinoid (specifically, CB1) receptors by either exogenous or endogenous ligands (e.g., Δ9-THC, anandamide) stimulates food intake, while pharmacological CB1 antagonists (e.g., rimonabant) reduce food intake generally in fasted animals. Endocannabinoid levels are elevated in the hypothalamus during food deprivation and are reduced by food consumption and by leptin, indicating they are likely also involved in homeostatic control of food intake (249,250). Rimonabant has also been demonstrated to be effective at producing weight loss in humans (251). The presence of endocannabinoids in limbic regions and their interaction with opioids to modulate food intake suggests that this system also functions to affect intake of palatable foods (252).

Behavioral Effects of Molecular Genetics

There are a number of ways by which the numerous peptides and neural systems described here may act to alter food intake. They may alter meal initiation (i.e., the likelihood of beginning an eating bout), which is generally observed as a change in meal frequency, or they may alter meal termination (i.e., how much is consumed prior to ending a meal), which is generally observed as a change in meal size. They may also affect the subjective feelings that an individual interprets as “hunger” or “fullness” and uses to determine when to begin or end a meal or the subjective palatability or reward value associated with eating particular foods.

Meal Initiation, Meal Termination and Food Selection

Meal pattern analysis indicates that size of individual meals is the mechanism by which total food intake is generally altered. Increased meal size is the primary response to fasting and is almost exclusively responsible for the elevated caloric intake in rats bred for their susceptibility to diet-induced obesity (253-255). Furthermore, although some reports show overweight and obese humans consume both larger and more frequent meals, there is evidence that it is meal size that differs most significantly between those gaining weight and those maintaining their current weights (256,257). When analyzing the component of food intake that is influenced by peptides found either peripherally or centrally, it is meal size that is most often found to be affected, leading some to suggest that meal termination is more strongly controlled by biological processes, while there a vast number of environmental influences that are more likely to be involved in meal initiation (i.e., availability of food, time of day, cognitive factors, learned associations/signals) (258). The majority of the peripheral satiety hormones, including CCK, gastrin releasing peptide/bombesin, GLP-1 agonist exendin-4, amylin and leptin, appear to act by reducing meal size with little or no effect on meal frequency (27,28,50,259-263). However, one study found that an obesogenic phenotype characterized by high meal frequency was significantly correlated with polymorphism and haplotype variants in leptin and leptin-R genes (264). Not surprisingly, as central leptin effectors, melanocortin agonists have been shown to reduce meal size, while MC antagonists have the opposite effect (265,266). Similarly, icv administration of CART decreased and NPY increased meal size (267,268). In contrast to these signaling molecules, ghrelin acts to increase intake by playing a role in meal initiation and food anticipation (67,71,269,270), which is consistent with its role as a “hunger” signal (see below). Recent data indicates that there may be a meal anticipatory effect for GLP-1, as well (271).

In addition to influencing total energy intake via changes in these basic meal parameters when a constant test diet is used, some systems also differentially affect food selection or intake based on the macronutrient compositions of the diet. While NPY and AgRP both increase total caloric intake, NPY appears to induce greater appetitive and consummatory behaviors for foods high in carbohydrates, while the melanocortin system selectively affects fat intake and responding for fat-associated stimuli (199,272-275). Not surprisingly, leptin, acting to inhibit both NPY and AgRP, reduces intake of both carbohydrates and fats (276).

Interoceptive States: “Hunger” and “Satiety”

A number of these peripheral signals seem to be responsible for the subjective feelings of “hunger” or “satiety”. These states can be assessed in a rodent model using a experimental design known as the “deprivation intensity discrimination paradigm”, in which rats are trained to discriminate between internal cues associated with 24 hours or 1 hour of food deprivation by receiving a reinforcer in a specific environment under only one of these conditions (277,278). The generalization between these deprivation states and those of a variety of potential hunger- or satiety-inducing peptides is tested by administering an exogenous dose of the peptide of interest and measuring the animal’s behavior in the training environment. These types of experiments have suggested that ghrelin produces interoceptive cues similar to that of 24-hr food deprivation (i.e., “hunger”), while CCK and leptin produce cues similar to 1-hr food deprivation (i.e., “fullness”) (279-281). Other peptides that influence food intake, such as NPY,

bombesin, and MC-R agonists and antagonists do not appear to produce cues that generalize to either deprivation state, suggesting that their mechanism of action is independent of inducing a subjective feeling of “hunger” or “satiety” (280, 282-284). In humans, rating scales are often used to measure the subjective sensations perceived by subjects following administration of pharmacological agents associated with food intake regulation. These ratings are frequently, but not always, correlated with or predictive of consummatory behaviors, suggesting that, as in animals, these reported sensory stimuli may represent only one mechanism of altering food intake (285,286). Mechanical distention of the stomach and systemic infusion of CCK seem to produce consistent increases in self-reported ratings of “fullness” and decreases in ratings of “hunger”, while the effects of infusions of GLP-1 and PYY on these sensations are not as clear (33,287-291). Conversely, increased “hunger” ratings have been observed following treatment with peripheral ghrelin and CCK-A receptor antagonists (63,292). Ghrelin levels are also correlated with reported hunger levels and meal initiation in humans in the absence of external cues associated with meals, including time and food-related stimuli (71).

Reward Value, “Hedonic” Eating and Food Motivation

While the peripheral and hypothalamic systems have largely been viewed as involved in the homeostatic aspects of food intake based on energy balance, other systems, primarily the dopaminergic, opioidergic and, more recently, cannabinoid systems, seem to influence intake based on palatability, or subjective “reward value” of the food being consumed (245,246,252,293). Extensive work has characterized the roles of dopamine and opioids in reward-related eating as associated with “wanting” and “liking” palatable foods, respectively (245,294,295). However, the involvement of cannabinoids in metabolic processes, the interconnection of hypothalamic circuits with those in mesolimbic and striatal regions involved in reward, the effect of “feeding peptides” (such as leptin, ghrelin, and GLP-1) in the nucleus accumbens to alter appetitive and consummatory behaviors, and evidence of interaction between these systems is further blurring the lines (249,296-301,212).

Food motivation is often measured by the use of operant conditioning procedures – most commonly, a progressive ratio (PR) test in which the number of responses required increases for each reinforcer earned. The maximum number of responses that an animal is willing to engage in to earn a reinforcer is termed the “break point” and considered a measure of motivation. A number of studies have tested the administration of feeding peptides and hormones in this paradigm. As would be predicted, increases in PR break point have been observed in response to ghrelin, orexin-A, NPY, a CB1 receptor agonist and deletion of melanocortin-4 receptors, while decreases were observed after administration of leptin, insulin, a CB1 receptor antagonist, a GLP-1 agonist or deletion of CB1 receptors (272,302-306). While reductions in appetitively motivated behavior may stem from a number of underlying, modulatory mechanisms (e.g., shifts in hunger state, recall of the food value, etc.), this measure is a reliable indicator of the effort that will be expended to obtain food, which is both necessary for consumption and appears to be correlated with future weight gain in humans (307).

Cognitive Function

Learning and memory processes are critical to the regulation of food intake behaviors. Flavor-flavor and flavor-nutrient learning contribute significantly to learned food preferences and engaging explicit memories of eating episodes or manipulating attention to food during an eating episode can alter food intake (308,309). The hippocampus appears to be critically involved in the ability to use hunger and satiety as discriminative cues to control behavior, as described above (206,211) – and the ability to use those cues to determine eating, or not, in the presence of food cues has been posited as a model that describes the way in which we regulate energy balance (310). Several of the molecules discussed here as “feeding” peptides have been shown to play roles in various cognitive functions, both food-related and non-food-related (311,312). In particular, there is substantial evidence for ghrelin and leptin acting in the hippocampus to alter physiological function associated with memory, such as altering long-term potentiation and other measures of synaptic plasticity (313,314), as well as to influence a number of

food-motivated and food-seeking behaviors (215,216), which are necessary precursors to intake in animals and humans in environments with readily available food..

Regulatory Disturbances Associated with Obesity

Prolonged high-fat diet consumption, leading to obesity, in both humans and non-human animal models alters the endogenous profiles and the efficacy of a number of these energy balance-related signaling molecules. As would be expected, leptin and insulin levels are elevated in overweight subjects, as these adiposity signals circulate in levels proportional to the amount of body fat (315-317). Obese humans and rodents consuming diets high in fat also display peripheral reductions in circulating ghrelin and fasting PYY levels (318-321), although diet-induced obesity in rodents does not alter the effectiveness of PYY (322). Rodents who have been maintained on a diet high in saturated fat exhibit reduced expression of NPY and AgRP mRNA in the hypothalamus (323,324), although levels of these peptides measured in the cerebrospinal fluid of humans did not differ significantly between lean and obese subjects (325). These increases in the anorexigenic signals leptin and insulin and decreases in orexigens, such as ghrelin, AgRP and NPY would be predicted based on the state of positive energy balance in obese individuals and would be expected to reduce food intake and body weight. However, these individuals tend to remain at elevated weights and, frequently continue to gain weight, suggesting that these systems become dysfunctional in obesity. In fact, there is a large body of evidence supporting just that notion. Studies have clearly demonstrated that diet-induced obese humans and animals become resistant to the anorectic effects of both peripheral and central leptin, as well as central insulin (316,326-331). A number of experiments have demonstrated that obesity and consumption of high-fat diet impair the transport of leptin across the blood-brain barrier, reduce the sensitivity of intracellular signaling pathways activated by insulin and leptin, reduce the capacity of these hormones to act through central effector systems such as NPY and melanocortin pathways and decrease hypothalamic NPY and CCK levels (332-339). Diet-induced obese rodents also appear to be less sensitive to the food intake-reducing effects of centrally administered melanocortin agonists (316).

Although peripheral satiety signals tend to maintain normal basal levels in obese subjects, several of these peptides, including CCK, PYY and Apo A-IV are less responsive to nutrient influx into the gut, with decreased release following meals and reduced satiety effects. Postprandial ghrelin levels tend to remain high, which may contributing further to reduced feelings of satiety (340-343). However, there appears to be reduced responsiveness (i.e., “resistance”) to administration of both ghrelin and GLP-1 in obese animals (319,344,345). Chronic high-fat diet consumption in rats leads to reduced operant responding for sucrose, as well as impaired conditioned place preference and altered mesolimbic dopamine function (346). Correspondingly, neuroimaging assays have indicated a reduction in central dopamine D2 receptors in obese humans, as well as increases in neural activity in reward areas during food anticipation, but decreased activity during consumption, leading to speculation that this may indicate decreased reward sensitivity and result in compensatory overeating (347-349).

In addition to changes in sensitivity in regulatory and reward systems, changes in memory structures, primarily the hippocampal formation, have also been observed following diet-induced obesity. These changes include reductions in BDNF levels, reductions in the capacity for LTP, decreases in neurogenesis, and loss of blood-brain barrier integrity (350-353), along with behavioral deficits that mimic the impairments observed following hippocampal damage, such as poor performance in spatial memory tasks and inhibitory learning (350,353). It has been proposed that these impairments are part of a “vicious cycle” that contributes to the maintenance of obesity by further impairing the ability to use hunger/satiety signals to regulate eating based on prior associative learning (310).

However, a major difficulty with these types of studies, in which comparisons are made between obese and lean populations, is the inability to dissociate whether these alterations cause obesity or are a consequence of chronic overeating and increased body adiposity (e.g., 356). Prospective studies in humans have been minimal and interpretation complex, with attempts to predict weight gain or future BMI based on neural activity in reward regions in response to palatable food cues yielding inconsistent

results (357,358). A particularly useful tool in addressing this issue has been the development of selectively bred rats either prone or resistant to obesity induced by the consumption of high-fat, calorically dense diets (359). Studies of these animals on standard low-energy-density diets prior to divergence in weight gain and body adiposity have demonstrated that animals prone to diet-induced obesity also have a pre-disposition to insulin and leptin resistance, reduced central leptin signaling, reduced central insulin and leptin receptor binding, and increased expression of hypothalamic NPY, indicating that these factors may play a role in the development of obesity (328,331,360-369). On the other hand, no differences were observed in melanocortin binding and ghrelin and GHSR expression were reduced in obesity-prone relative to obesity-resistant rats, suggesting that these systems are not implicated in the onset of hyperphagia and weight gain (360,362).

Conclusion

The control of food intake involves the detection and integration of many different stimuli beginning with gastrointestinal detection of food volume and nutrient content acting to limit consumption within meals and peripheral adiposity signals acting via central sites and interacting with other peptides and hormones to balance short-term intake with long-term energy stores. In addition, there are a number of systems which act to select particular foods based on their nutrient content or, outside of homeostatic regulation, based on their palatability or reward value. These signals can alter a range of behaviors, including appetitive behavior, consumption, food selection, the interoceptive states labeled “hunger” and “satiety”, and even memory and other cognitive functions, to ultimately control energy intake. In spite of this complex regulatory system, a large proportion of the population of the United States is currently overweight or obese, suggesting a dysfunction. In fact, obesity and the consumption of high-fat diets appear to induce resistance to a number of the signals designed to limit intake in the face of positive energy balance, complicating the search for effective treatments. However, furthering a careful understanding of ingestive behaviors and the biological mechanisms that underlie them is the best hope for identifying a way to reverse the current obesity epidemic.

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