Overview of the Physiological Control of Eating

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Introduction

Aim

In this chapter we discuss the physiology of eating, with a particular focus on its relevance to the present obesity epidemic. The physiology of eating comprises the functional organization of eating behavior, the types of exteroceptive and interoceptive information that affect eating, the neural and endocrine sensory mechanisms relaying this information to the central nervous system (CNS), and the CNS neural networks that process and integrate this and other information to control eating (fig. 1). We emphasize the role of eating in the regulation of body weight. These topics have taken on new importance with the obesity epidemic. It is well recognized that overeating together with reduced exercise are the proximal causes of obesity. Therefore, better understanding of the physiology of eating and its role in body weight regulation, or dysregulation, should lead to new and hopefully more effective approaches for the therapeutic control of eating in obese persons or persons at special risk for obesity and obesity-related diseases.

The Functional Organization of Eating

Eating in humans and other mammals is functionally organized into discrete meals. Meals are produced by four separable functional processes with at least partially independent underlying neural mechanisms. Although each process includes both behavioral and subjective phenomena, for simplicity we use single names for both aspects. The four processes are: (1) processes related to the initiation of meals (hunger
processes); (2) processes related to the evaluation of the food that stimulate or inhibit eating during the meal; this is one aspect of food reward; (3) processes related to inhibitory feedbacks from postigestive food stimuli that act to terminate eating at the end of the meal (satiation), and (4) processes inhibiting eating during the intermeal interval (postprandial satiation). As will become clear, each of these processes is affected both by phasic inputs, for example, inputs related to the secretion of hormones from the gut before, during and after meals, and by tonic inputs, for example, inputs related to the mass of the adipose tissue and, therefore, body weight.

An important implication of the fact that at least partially separate mechanisms control different meal processes is that summary measures of food intake, e.g. g/day, may conflate independent underlying processes. For example, in some situations, meal size and meal frequency change in opposite ways, so that the patterns of spontaneous eating can be different even though total amount eaten is not. A related point is that parts of the overall eating-control neural network with functionally antagonistic effects may operate simultaneously. Thus, eating-inhibitory controls might arise in one part of the network (e.g. homeostatic signals related to metabolic fuel utilization)
at the same time as eating-stimulatory controls are activated in other parts of the network (e.g. signals related to orosensory food reward). The existence of such partially autonomous controls may be part of the reason why existing treatments based on pharmacological manipulation of single signaling molecules have not been effective in normalizing disordered eating.

Regarding the subjective phenomena associated with eating, our view, following William James [1], is that the most parsimonious explanation for the richness of eating-related emotional and cognitive experiences is that they evolved as causal agents contributing to the overall control of eating and its orchestration with other biological functions. How conscious processes actually affect neuronal function and behavior is, of course, beyond the scope of available methodologies, although imaging methods now produce at least hints that eating behavior and some of the subjective phenomena associated with eating arise in the same neural networks and are modulated by the state of energy balance. The chapters by Neary and Batterham [2], Kringelbach and Stein [3] and Stice and Dagher [4] touch upon this fascinating topic.

There are levels of organization of eating behavior both above and below the levels of meals. Subordinate to the level of meals is the microstructure of eating, including, for example, analyses of licking, biting, chewing or swallowing food during meals. This level of analysis seems to hold great potential for tracking eating behaviors via the lower motor neurons and central pattern generators that produce the movements of eating back into the higher, more integrative levels of the neural networks for eating. Superordinate levels include the control exerted by biological rhythms, such as circadian and reproductive rhythms, both of which potently affect human eating. The most important superordinate level, however, is the level mediating the regulation of body weight. That is, when adiposity or body weight is perturbed, the organism tends to eat in a way that corrects the error. The physiology of such weight-regulatory influences is a major theme of this book and is introduced in more detail in the next section.

Eating and Homeostasis

Because eating is our only source of metabolic fuel and of a number of essential nutrients, it is an integral part of homeostatic regulation. Myriad studies have demonstrated that both the regulation of metabolic energy supply and the regulation of micronutrient balance powerfully influence how much is eaten and what is eaten. As a consequence, homeostasis is a major conceptual scheme used to understand eating.

Body weight, at least in adulthood, is a relatively accurate surrogate for the state of energy balance over longer periods (i.e. periods during which changes in gut contents, hydration, etc., can be ignored). Over such periods, changes in body weight in adults usually reflect changes in adiposity, i.e. mainly the amount of energy substrate stored as triacylglycerols in the adipose tissue (there is also ectopic storage of
triacylglycerols in liver, muscle and other tissues). Thus, longer-term state of energy balance is described by the energy balance equation:

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\text{Energy stored} = \text{Energy ingested} - \text{energy expended}.
\]

The relative stability of body weight over longer periods appears possible only if an active regulatory system senses energy stored and, depending on its level, appropriately adjusts energy ingested or energy expended. Figure 2 depicts how this system is believed to function. The brain registers and integrates (\(\Sigma\)) feedback signals which reflect deviations from the desired state (1), and adjusts eating and energy expenditure (the controlled variables) (2), so that the regulated variable, energy stored, is maintained in a relatively narrow envelope (3). The regulation of energy homeostasis and body weight is discussed further in this chapter as well as in the chapter by Hillebrand and Geary [5].

As also shown in figure 2, the feedback signals that are not related to energy homeostasis also affect the controlled variables. These include signals related to the sensory

**Fig. 2.** Schematic of the components of homeostatic regulatory systems involved in the control of eating. Regulated parameters (lower left box) are held relatively constant, in part by changes in controlled or variable parameters (lower right box). The negative feedback control system thought to regulate body adiposity is shown in bold font; other regulated variables controlling eating are shown in normal font. In adiposity regulation: (1) Feedback signals reflecting deviations from the desired value (set point) in the regulated parameter, adiposity, are detected by the brain, (2) causing compensatory changes in eating or energy expenditure, which (3) affect adiposity. In addition, (4) eating produces other feedback signals to the brain that affect the control of meal onset, rate of eating, and meal termination. Finally, (5) other exogenous and endogenous signals outside these feedback loops also affect eating. Modified with permission from Langhans et al. [281].
properties (especially, food palatability), volume and composition of the food (4). In addition, signals that are not related to the regulated or the controlled variables can also influence the system (5). Under certain circumstances, these latter two categories of signals can substantially disrupt regulation. There is little doubt that a main cause of the obesity epidemic in developed countries is the easy availability of increasingly palatable and energy-dense foods together with the decreased need (or opportunity) to exercise – for weight regulation, an ‘obesifying’ or ‘toxic’ environment.

Finally, several types of systems can produce regulation, and not all of them include the same components shown here. Whether energy homeostasis or other regulations affecting eating include reference values, or set points, as shown in figure 2, or whether constancy results from equilibria among feedback mechanisms without reference values, remains a matter of active debate.

**Oro sensory Signals in the Control of Eating**

Flavor is a complex perception that arises from olfactory, gustatory, tactile and thermal food stimuli affecting receptors in the oro-nasopharynx. This sensory information can control eating independent of other pre- or postabsorptive consequences of eating, although association with such consequences normally determines much of the functional meaning of flavor stimuli.

The first type of process through which flavor affects eating is discrimination. This refers to flavor’s informational content, i.e. identification of the type (e.g. ‘it’s sweet’) and intensity (‘it’s as sweet as candy’) of food stimuli, independent of the stimulus’ rewarding qualities described below. Discriminative processes enable flavor stimuli to contribute to eating-related associative learning, which is important for both physiology (e.g. cephalic phase gastric and endocrine reflexes) and behavior (flavor-cued food selection, conditioned hunger and satiation).

The second type of process to which flavor stimuli contribute is reward. ‘Food reward’ is used to describe three potentially distinct ways in which flavor stimuli can influence eating: (1) Positive and negative flavor feedbacks that stimulate or inhibit ongoing eating. These can be either unconditioned or conditioned, are relatively automatic or reflexive, and are potent controllers of meal size. (2) Flavor hedonics, i.e. the pleasant or unpleasant subjective experiences of food stimuli (‘I like sweet’), which are also thought to be sufficient to affect eating. (3) The reinforcing properties of flavor stimuli, meaning the sufficiency of flavor alone to produce long-term learned changes in behavior [3, 6].

The neural processes producing flavor hedonics are mainly cortical, based in part in specialized cortical regions which receive inputs from gustatory, olfactory and other senses (fig. 3). This makes food reward especially amenable to functional imaging techniques, as exemplified in three chapters [2–4]. Although we experience the effects of positive and negative feedbacks on eating and food palatability simultaneously, neural analyses indicate that these are often independent, separable processes.
The direct effect of flavor on ingestion can be demonstrated in rats that sham feed with open gastric cannulas, which prevents significant accumulation of food in the stomach or entry of food into the duodenum (fig. 4) [7]. Similar tests can be done in humans by instructing subjects to take food into the mouth, to chew, etc., normally, but to spit it out rather than swallowing it [8]. In sham-feeding rats, the rate of ingestion varies directly with the concentration of preferred flavors, such as sugar or oil, and inversely with the concentration of nonpreferred flavors, such as bitter or salt.

Other terms and concepts are also used in the analysis of flavor’s effects on eating. The terms ‘palatability’ and ‘preference and aversion’ are very common, and palatability has recently been further divided into ‘wanting’ and ‘liking’ processes [9]. ‘Incentive reward’ and ‘craving’ are also often discussed. All of these terms have been applied to both human and animal research. The extent to which they reflect different functional categories with different underlying physiological mechanisms remains an experimental question.

Although some preferences (sweet) and aversions (bitter, sour) for basic gustatory stimuli appear to be innate, preferences and aversions for the vast majority of flavors are learned. Gastrointestinal and postabsorptive consequences of the food can reinforce such learning [10]. This occurs in conditioned satiations, conditioned aversions (including the marked aversions for flavors associated with acute upper
gastrointestinal illness), and ‘specific hungers’ (preferences for flavors associated with foods containing vitamins or minerals that can be learned during states of nutritional deficiency; this occurs for most micronutrients) [11]. In these situations, it is the discriminative, i.e. non-hedonic, aspects of the flavors that are important for learning, and increases or decreases in flavor hedonics are part of what is learned. The majority of human flavor preferences, however, are based not on physiological consequences of eating but on emotional, cognitive, and cultural associations attached to various foods, independent of their nutritional or physiological properties [10, 12, 13]. Indeed, mere exposure, i.e. familiarity, is sufficient to condition flavor preferences. This phenomenon likely explains much of the marked cultural variety in which foods are preferred, the social contexts or times of day when they are eaten, etc. [14] (and perhaps the preference for variety considered below). Because they dramatically affect patients’ success in adhering to therapeutic dietary regimens, the origins and plasticity of human food preferences are important areas for behavioral and physiological research.

The increased availability of highly palatable foods in our society is considered a main cause of the increased prevalence of obesity. Consistent with this, differences in the palatability of both sweet and fat flavors have been shown between thinner and heavier humans [15–17]. Genetic variation in human flavor processing may also
contribute to obesity. Obese individuals seem to be both less sensitive to the sensory intensity of sweet flavors and to enjoy both sweet and fat flavors whose sensory intensity is matched more than nonobese individuals do [15]. Furthermore, otitis media, a common childhood ear infection, can produce lifelong changes in flavor perception if the infection involves the trigeminal and glossopharyngeal nerves, which lie near the middle ear. Both children and adults with histories of severe otitis media have been reported to prefer sweets more than the general population and are at higher risk for overweight or obesity [15].

Variety is an important contributor to palatability. In both rats and humans, offering a variety of nutritionally identical foods with different, preferred flavors leads to larger meals than does offering only one of the alternatives, even the single most preferred one. The decrease in meal size when only one flavor is offered is referred to as sensory-specific satiety [18]. Flavor variety has also been shown to increase intake in the longer term in rats, leading to increased body weight [19].

**Gastrointestinal and Pancreatic Signals in the Control of Eating**

**Introduction**

The gastrointestinal (GI) system, pancreas and liver cooperate in the digestion and absorption of ingested food. A wide variety of physiological signals controlling eating also arise in these organs. In this section we describe what are classically considered **preabsorptive** GI signals. The next section, on metabolic controls, focuses on **postabsorptive** signals, which arise in the liver and outside the gut. This division, however, is only heuristic and organizational. For example, as described below, some pancreatic hormones are also released in the first minutes of eating via neuroendocrine reflexes and contribute to satiation, and we discuss these here as well. In addition, as considered in the next section, recent data suggest that metabolic controls of eating may also arise within the GI system, in the intestinal epithelia.

The GI system and the brain communicate via chemical and neural signals (fig. 5). The chemical signals include GI and pancreatic peptides whose release is affected by eating. Secretion of all but one of these, ghrelin, increases during and after meals. Ghrelin secretion, in contrast, increases during intermeal intervals. Neural signals include vagal and spinal visceral afferents originating in the gut.

Because of the important role of chemical messengers in the control of eating, it is useful to review some of the basic aspects of this sort of chemical signaling. Many GI chemical signals involved in the control of eating have a classical endocrine mode of action, i.e. specialized cells synthesize the signal molecule and in response to particular stimuli secrete it into the extracellular space, from which it diffuses into local capillaries, travels in the blood to a distant site, and binds to specific receptors that initiate its biological action. Some GI chemical signals, however, have a paracrine mode of
action, which differs in that the signal molecule acts locally, reaching the target cells before entering the blood. Some signal molecules seem to have both modes of action. In addition, circulating levels of GI chemical signals are often many times higher in the hepatic portal vein than in the general circulation, which may be an important consideration when assessing the physiological actions of GI signals that act locally or in the liver. Another complexity arises in the case of endocrine signals that act in the brain to affect eating. Because of the selective barrier and active transport features of the blood-brain barrier (BBB), brain levels of hormones and metabolites are not simple mirrors of plasma levels. This issue is taken up in the chapter by Banks [20]. Finally, in the case of most gut hormones (ghrelin, cholecystokinin = CCK, glucagon-like peptide-1 = GLP-1, etc.) the same molecule is also synthesized by CNS neurons and acts as a neurotransmitter, often with a role in eating. This greatly complicates the interpretation of the phenotypes of mice with global null mutations (knockouts) of the molecule or its receptors.

Endocrine signals, because they appear in the systemic circulation, have been especially intensively investigated. This work has often utilized sets of explicit empirical criteria, modeled on classic endocrinological concepts, for the determination of which endogenous endocrine signals are normally involved in the control of eating.

Fig. 5. Schematic of some important GI controls of eating. These act on the brain through neural (right) and endocrine (left) routes, as described in the text. Neural receptors: C = chemoreceptors; M, mechanoreceptors; Hormones: CCK = cholecystokinin; GLP-1 = glucagon-like peptide-1; PYY = peptide YY. Modified with permission from Langhans et al. [280].
i.e. play *physiological* and not just *pharmacological* roles [21–23]. Evaluation of pharmacological signals is of course also important, as therapeutics can be based on either physiological or pharmacological actions of particular signals. The two major endocrine criteria for physiological function are called the physiological dose criterion and the antagonist criterion. The former is that administration of the hormone in amounts that mimic the endogenous (physiological) changes that occur at its site of action related to eating should be sufficient to produce the hypothesized effect on eating. The latter is that acute antagonism of the endogenous hormone at the time of its action on eating should reverse the effect. It is important that the antagonism be acute because physiological systems react to chronic manipulations, so the result of chronic antagonists is often to reveal active compensatory responses rather than essentially normal function except for one missing signal. This is another reason that complicates the physiological interpretation of the phenotypes of transgenic animals with global null mutations of specific genes. The sections below introduce some of the GI signals that at present appear to be particularly important in the physiological control of eating (for more detailed reviews, see [21, 24–29]). The therapeutic potential of several gut hormones is discussed in this volume by Wölnerhanssen and Beglinger [30].

**Ghrelin**

Ghrelin (fig. 5), a hormone discovered in 1999 [31], is the endogenous ligand for the growth hormone secretagogue receptor (GHS-R). Ghrelin is synthesized and secreted mainly by gastric X cells, but also by neurons in the CNS and other tissues. Gastric ghrelin has attracted great interest because it is the only gut peptide whose secretion is stimulated during fasting and inhibited by eating, and because it is the only gut peptide whose administration stimulates eating, which has been shown in rats and humans [21, 31–33].

The physiological status of ghrelin is not fully established. For example, it is unknown whether mimicking physiological ghrelin levels, especially the physiological pre-prandial rise in circulating ghrelin, is sufficient to trigger eating. GHS-R antagonists have been reported to decrease eating, but their selectivity remains uncertain [34]. An interesting alternative approach is the use of specific ghrelin spiegelmers [35, 36], which have recently been shown to reduce weight gain in mice offered a high-fat diet [37]. Another promising therapeutic approach related to ghrelin is based on pharmacological antagonism [38–40] of the recently discovered enzyme ghrelin O-acyltransferase [41], which catalyzes production of the biologically active acylated form of ghrelin.

The site of ghrelin’s eating-stimulatory action is controversial. Some reports suggest that ghrelin acts peripherally to generate a vagal signal [42, 43]. More recent work, however, indicates that the eating-stimulatory effect of ghrelin does not require vagal afferent signaling [44]. Activation of GHS-R in the brain, especially those in the
hypothalamic arcuate nucleus (Arc) and the brainstem, are sufficient to stimulate eating and are a likely mechanism for the endogenous eating effects of ghrelin [44, 45]. Neurons in these areas also synthesize and release ghrelin, and the relative contributions of hormonal and neuronal ghrelin on eating have not yet been distinguished.

**Gastric Mechanoreception**

The stomach is richly innervated with mechanoreceptors (fig. 5) that respond during and after meals and that signal the brain via both vagal and splanchnic visceral afferents. The effects of gastric mechanoreceptor signaling on eating have been studied in relative isolation in rats equipped with gastric cannulas, from which fluids can be infused or drained from the stomach, and pyloric cuffs, which can be inflated to prevent food from entering the intestines [46–48]. These experiments indicate that: (1) when gastric cannulas are used to prevent ingested liquid food from accumulating in the stomach, meal size is dramatically increased; (2) when ingested food is prevented from entering the intestines by inflating pyloric cuffs, meal size is about normal; (3) when fluid loads are infused into the stomach of rats with closed pyloric cuffs, eating is inhibited in proportion to the volume infused, and (4) the effect of gastric fill on eating is identical whether nutrient or non-nutrient loads are used. This indicates that gastric volume is an adequate stimulus for mechanoreceptors that can contribute to the control of eating. These signals, however, do not appear sufficient for the normal control of meal size in rats because intragastric infusions inhibit eating in rats with closed pyloric cuffs only when the total gastric fill (ingesta plus infusion) is markedly larger than the control meal size.

The pyloric cuff model does not fully assess the contribution of gastric mechanoreception to the control of eating. In both rats and rhesus monkeys, the intrameal rate of gastric emptying of liquid diet is about five times the postmeal rate [47]. As described above, the prevention of normal intrameal gastric emptying in the cuff-closed condition produces abnormal increases in gastric volume at meal end. It also prevents any interaction between gastric and postgastric signals. Many data indicate that such interactions are normally important; some examples are described in the chapter by Schwartz [49]. Thus, although gastric signals may not be sufficient for the control of meal size, they may indeed contribute importantly.

The role of gastric signals has also been studied in humans. Inflation of a gastric balloon before meals increases feelings of fullness and reduces meal size in normal-weight and obese subjects [50, 51]. The crucial signal may be related to fill of the antrum rather than fill of the fundus because sonographically measured antral cross-sectional areas after meals, but not fundal areas, correlated with fullness at meal end [52] and with the size of the next meal [53]. When the antral area was increased with a balloon before, but not during, the test meal, however, similar volumes had no effect on eating [54]. This may reflect a crucial role for interactions between gastric volume and postgastric
food stimuli to elicit satiation, although Oesch et al. [54] were not able to detect such an interaction with satiating intraduodenal fat infusions (this method is described in the next section). Finally, a recent imaging study suggests that perceptions of fullness arising from increased gastric volume involve the amygdala and the insular cortex [55].

**Intestinal Cholecystokinin**

Cholecystokinin (CCK) (fig. 5) secreted mainly from duodenal I cells during and after meals has long been considered an essential physiological control of gastric emptying, gall bladder emptying, and exocrine pancreatic secretion. The classic report of Gibbs et al. [22] that intraperitoneal injections of CCK selectively inhibit eating established satiation as another potential physiological function of CCK, and CCK has remained the paradigmatic gut peptide eating-control signal. CCK was the first gut peptide whose satiating action fulfilled the criteria described above for a physiological control of eating in humans [21, 56–58]. There are two reports that increases in CCK mimicking prandial levels are sufficient to inhibit eating in humans [59, 60], supporting the physiological dose criterion described above. There are also, however, several reports that near physiological doses do not affect eating (moderate pharmacological doses, in contrast, decrease eating in humans without subjective or physical side effects). One explanation for the variable effects of lower doses is that CCK appears to interact synergistically with other eating-control signals, so that test conditions may be crucial. In addition, in both humans and rats, selective CCK-1 receptor antagonists have been shown to increase meal size (and the perception of hunger in humans) and to block the satiating effect of intraduodenal infusions of fat, in which CCK plays a significant role [56]. According to Geary’s [21] scheme, CCK exemplifies a fully coupled endocrine satiating signal, i.e. the adequate stimulus (food in the small intestine) almost immediately leads to hormone secretion, which in turn affects eating within minutes. This tight linkage would seem to be an advantage both for the analysis of physiological mechanisms and for the development of pharmacotherapy. Whether long-term treatment with CCK or CCK agonists can be used effectively to control body weight, however, remains unclear [61, 62].

The effects of spontaneous mutations in the CCK-1 receptor to induce overeating and obesity lend further support to CCK’s physiological role [21, 58]. The complication is that in rats and humans, CCK is also a CNS neurotransmitter, and CCK-1 receptors in the dorsomedial hypothalamus appear to mediate eating effects [63]. Thus, some of the phenotype of the knockout animals might be related to purely CNS CCK.

Intestinal CCK’s satiating action appears to arise locally, in the gut. For example, Cox et al. [64] found that doses of CCK or of CCK-1R antagonists that had no effect on eating in rats when infused systemically were sufficient to affect eating when infused into the superior pancreatico-duodenal artery, which perfuses the pyloric area, the proximal duodenum and the pancreas. This local action of CCK appears to elicit a vagal afferent
signal because subdiaphragmatic vagal deafferentiation (SDA) is sufficient to block the satiating effect of exogenous CCK. These and many studies of neural activation using c-Fos immunocytochemistry imply that the central neural processing of CCK satiation begins in the NTS. This is consistent with many subsequent findings, including some reviewed here (see chapters by Baskin and Blevins [65] and Schwartz [49]).

**Intestinal Glucagon-Like Peptide 1 (GLP-1)**

The active form of GLP-1 (fig. 5), GLP-1[7–36 amide], is synthesized by L-cells mainly in the jejunum and is released during and after meals, especially carbohydrate- or fat-containing meals. Evidence suggesting that GLP-1 elicits satiation and perhaps postprandial satiety has accumulated rapidly in recent years. Other data suggest a similar role for peptide YY (PYY), which is released from the same L-cells [66–69]. Remotely controlled intraperitoneal or hepatic-portal infusions of GLP-1 during spontaneous meals selectively reduced meal size in rats [70], but whether physiological doses of GLP-1 were sufficient for these effects was not established. The situation in tests of humans is similar [24]. So far, administration of a GLP-1 antagonist has been reported to increase eating in rats in only one study, and then under rather limited conditions [71]. The conclusion of Williams et al. [71] was that endogenous GLP-1 is sometimes involved in the control of eating, but that the circumstances under which this happens and why the phenomenon is not more general, requires further work.

The study of GLP-1’s physiological effects is complicated by the fact that it is rapidly broken down by the enzyme dipeptidyl-peptidase IV (DPP-IV), which is expressed in most capillaries, so that only a fraction of intestinal GLP-1 released during meals reaches the liver, and even less reaches the general circulation. For this reason, the GLP-1 analog exendin-4 (Ex-4), which is not rapidly cleaved by DPP-IV, is often used. Peripheral administration of Ex-4 produces a potent and lasting inhibition of eating [72, 73]. Administration of GLP-1 or of Ex-4 directly into the PVN or of Ex-4 into the dorsal hindbrain also inhibit eating [72, 74]. Ex-4, however, has biological potency orders of magnitude higher than that of GLP-1 [75], so studies using it require very cautious interpretation. In particular, it remains uncertain whether sufficient intestinal GLP-1 reaches the systemic circulation to affect posthepatic sites. An alternative hypothesis is that GLP-1 acts locally on vagal nerve endings in the lamina propria of the intestinal mucosa before entering the mesenteric capillaries [70].

We recently observed that the satiating action of intraperitoneal infusions of GLP-1 during spontaneous meals was substantially reduced in rats with SDA, whereas the satiating action of hepatic-portal infusions of GLP-1 was not [70]. These data suggest that exogenous GLP-1 can act in more than one site to inhibit eating, that one of the sites is preferentially accessed by intraperitoneal infusions, and that GLP-1 acting at this latter site inhibits eating via a vagal afferent signal. Whether the same is true for endogenous GLP-1 remains to be determined.
Amylin

Four hormones produced by the pancreatic islets, insulin, glucagon, somatostatin and amylin, or islet amyloid polypeptide, have been implicated in the control of eating [76]. Of these, amylin is most actively investigated these days, both as an acute satiation signal, as described here, and as an adiposity signal, as described in the chapter by Lutz [77]. Amylin is synthesized by pancreatic beta cells and co-secreted with insulin beginning in the first minutes of meals. Intraperitoneal injection of amylin just before meals or hepatic portal vein infusion of amylin during meals dose-dependently reduces meal size in rats [76, 78–80]. The smallest effective doses to inhibit eating were about double the endogenous levels [81], so whether amylin meets the physiological dose criterion is not certain. The failure of exogenous amylin to mimic the dynamics of endogenous secretion or, as discussed above, the lack of endogenous synergies may explain the apparent failure. More conclusively, the amylin receptor antagonist AC187 increased meal size in rats [82, 83]. Amylin’s satiating effect has not been investigated in detail in humans. Amylin acts on receptors in the area postrema (AP) to inhibit eating. Lesion of the AP eliminates its effect, direct administration of amylin into the AP inhibits eating, and AP administration of AC187 increases eating [82].

Metabolic Signals in the Control of Eating

Introduction

Eating is part of the homeostatic regulation of body weight and of the availability of metabolites and essential nutrients. Physiological principles therefore suggest that metabolism feeds back to control eating. Parenteral administration of metabolic fuels often reduced food intake, whereas pharmacologic inhibition of fuel utilization increased it, and metabolic inhibitors also attenuated the eating-inhibitory effects of intravenous nutrient infusions [84]. This suggests that fluctuations in the availability or utilization of energy-yielding substrates – mainly glucose and fatty acids – or a common denominator of their utilization, control eating. Sensing of fuel availability or utilization leading to altered eating occurs in both the periphery and the brain [85, 86] (fig. 6). Unresolved is whether the effects of metabolic inhibitors are physiologically relevant or only emergency responses. While the threshold decrease in glucose utilization or fatty acid oxidation for a stimulation of eating is probably greater than what occurs before spontaneous meals, the fact that a signal is rarely activated in affluent people who eat three or more scheduled, ample meals each day does not necessarily mean that it is un-physiological. Also, if an integrated metabolic signal contributes to meal initiation, a pharmacological change in the utilization of a single metabolite might well be required to trigger a meal.
A small but consistent decline in blood glucose levels prior to spontaneous meals has been described in rats [87] and man [88] and may act as a pattern whose recognition contributes to meal initiation [89]. It is unclear which mechanism causes blood glucose to decrease prior to meals and whether this is accompanied by a decrease in glucose utilization. Blood glucose concentration and glucose utilization increase substantially in response to carbohydrate ingestion, and intravenous glucose infusions have often been shown to inhibit eating [84]. In some studies the satiating potency of glucose was increased by insulin [90], suggesting that the involved glucose sensors are partly sensitive to insulin. Studies in transgenic mice lacking the glucose transporter-2 (GLUT-2) [91] provide evidence for a physiological role of glucose in the control of eating: GLUT2-KO mice that express a transgenic glucose transporter only
in their beta cells so as to rescue insulin secretion eat substantially more than corresponding wild-type (WT) mice and show increased hypothalamic orexigenic and decreased anorexigenic neuropeptide expression during the fasted-to-fed transition [91]. Thus, the absence of GLUT2 compromised the function of glucose sensors which are involved in the control of eating and influence hypothalamic neuropeptides.

Because of its unique location and function, the liver was considered likely to be involved in the control of food intake early on [92]. Infusion of physiologic amounts of glucose into the hepatic portal vein (HPV) reduces food intake more than equivalent infusions into the jugular vein [93–95], and intrameal HPV infusions of small amounts of glucose or glucose and insulin acutely and selectively reduced spontaneous meal size in the rat [96]. Thus, a meal-related increase in hepatic portal glucose concentration may contribute to satiation (fig. 6). The available electrophysiological and anatomical data indicate that vagal afferents terminating in the wall of the HPV function as hepatic glucose sensors, as originally suggested by Niijima [97].

In the brain, glucose-sensing neurons, i.e. neurons that regulate their membrane potential and firing rate in response to glucose, are present at different levels from the hindbrain to the hypothalamus (fig. 6) [98] and, together with peripheral glucose sensors, represent an anatomical and functional network that monitors glucose availability and is involved in glucose homeostasis and food intake control [99]. Glucose phosphorylation by glucokinase (GK) is the rate-limiting step in ATP production and is essential for effects of glucose on membrane potential and ion channel function of glucose-sensing neurons. GK, GLUT2, the sulfonylurea receptor-1 (SUR1), and the GLP-1 receptor are co-localized in several brain areas [100, 101] and have been proposed to be involved in central glucose sensing and control of food intake, but the exact role of GLUT2 in brain glucose-sensing is not fully understood [100, 102]. Glucose-sensing neurons also change their firing rate in response to other metabolites and hormones (e.g. insulin, leptin) [103], i.e. they appear to integrate different inputs, and their output controls neuroendocrine and autonomic responses as well as eating. Also, glucose availability influences the expression and turnover of several catabolic and anabolic neuropeptides [103] which presumably mediate the effects of glucose-sensing on eating. These hypothalamic circuits are discussed in detail in the chapter by Moran [86].

Signals Derived from Fatty Acids

Acute pharmacologic inhibition of fatty acid oxidation (FAO) is usually accompanied by a stimulation of eating in animals and man [104]. Some findings suggest that the current rate of FAO is crucial for this effect. In contrast, long-term inhibition of peripheral FAO by chronic administration of the carnitine palmitoyl-transferase (CPT-1) inhibitor etomoxir in rats increased muscle and liver fat content and induced insulin resistance, but did not induce hyperphagia [105]. Also, transgenic mice with reduced peripheral FAO and humans with genetic disturbances in fatty
acid metabolism are not hyperphagic or obese [106, 107]. Together, these findings suggest that chronic inhibition of peripheral FAO does not affect eating.

The prominent role of FAO as an energy source for the liver suggested the hypothesis that hepatic FAO sensors generate signals that affect eating [84, 108]. Several recent findings, however, question the hypothesis that hepatic fatty acid oxidation influences eating and suggest that there is an alternative, or at least an additional, site where fatty acid oxidation is sensed [109]. Nevertheless, it is clear that the eating-stimulatory effect of intraperitoneal administration of the fatty acid oxidation inhibitor mercaptoacetate originates in the abdomen because it was completely blocked by subdiaphragmatic vagal deafferentiation [110]. Together these findings therefore suggest that MA acts in the intestine to stimulate eating. This idea and the more general possibility that enterocytes may act as energy flow sensors in the control of eating are discussed in more detail in the chapter by Langhans [85]. Finally, fatty acids and/or fatty acid metabolism can also be sensed centrally, in the mediobasal hypothalamus, and this also affects eating (fig. 6) [86, 111]. As discussed in the chapter by Moran [86], the physiological relevance of this effect is still unclear.

**An Integrated Metabolic Signal**

The recent identification of the molecular switches and signaling pathways in cellular metabolism has spurred a revival of old hypotheses proposing that eating is controlled by an integrated ‘energostatic’ or ‘ischymetric’ signal rather than by the utilization of one particular metabolite (see [84], for review). Reduction of cellular energy availability due to a decrease in fatty acid oxidation or glucose utilization increases the AMP/ATP ratio and activates the ubiquitous cellular energy sensor AMP kinase (AMPK) which exists in the periphery and the brain. AMPK activation or deactivation in the hypothalamus increases or decreases food intake [112, 113], suggesting that changes in cellular energy status contribute to the control of eating. The mammalian target of rapamycin (mTOR) is another cellular sensor of fuel availability and energy [114], and increased mTOR signaling in the hypothalamus decreased food intake and body weight in the rat. mTOR appears to colocalize mainly with Arc NPY/AgRP neurons [114]. Interestingly, central administration of L-leucine also increased hypothalamic mTOR and decreased food intake and body weight. As mTOR stimulates protein synthesis, these findings suggest that mTOR is involved in the control of cell growth and proliferation by energy availability. AMPK and mTOR both also respond to hormones involved in the control of energy balance (AMPK to leptin and ghrelin, mTOR to leptin) and thus may represent cellular sensors that integrate fuel availability and endocrine signals. In contrast to mTOR, AMPK activity is increased by fuel deficiency and decreased by metabolites and leptin [113], and activation of AMPK inhibits mTOR activity [114], suggesting that these fuel-sensitive kinases have reciprocal functions. An emerging concept is that changes in AMPK- and mTOR-sensing in the brain in
response to fuel surplus inhibit eating, whereas similar changes in the periphery may limit nutrient uptake into tissues, i.e. cause insulin resistance.

**Adiposity Signals**

*Introduction*

As described above, there is evidence for an active physiological regulation of long-term energy balance and, therefore, body weight in adults. Perhaps the strongest evidence for such regulation are the many reports that, in both animals and humans, experimental manipulations of body weight in adults provoke compensatory changes in energy intake and expenditure that serve to return weight to the normal level (see [115, 116], for reviews).

Given the obvious epidemiological evidence that western populations are rapidly growing markedly fatter, however, it is equally clear that this regulatory system does not work perfectly in the environment in which most of us live. Nevertheless, the fact that even small constant errors in the balance between energy intake and expenditure would lead to much larger body weight gains than we are actually experiencing suggests that the regulatory system is actually quite powerful – for example, a constant positive imbalance of only 1% would lead to a gain of over 1 kg/year adipose tissue. Although most humans gain weight during the decades of middle age, very few gain the more than 30 kg that this calculation suggests.

The fact that body weight changes in adult individuals are mainly due to fluctuations in body adiposity suggests that the level or state of adiposity is the regulated variable. What aspect of adiposity does the brain sense? Over 50 years ago, Kennedy [117] hypothesized that circulating factors whose plasma levels reflect the size of the fat stores regulate adiposity by controlling food intake and energy expenditure. These signals were originally called lipostatic signals; these days the term adiposity signals is favored. The basal levels of leptin, insulin, amylin and other hormones may function as such signals (fig. 7). The following paragraphs review some of the principal evidence in favor of leptin and insulin, and several chapters take up current issues related to these candidate adiposity signals [5, 49, 65, 77].

**Leptin**

A series of elegant experiments demonstrated in the 1970s that the dramatic obesity and diabetes phenotypes of ob/ob and db/db mice were caused by single-gene mutations of an unknown hormone and its receptor, respectively [118, 119]. A significant new chapter in the physiology of eating opened in 1994 when Zhang et al. [120] used molecular genetic methods to identify the adipocyte hormone leptin
as the missing signal in ob/ob mice. This was quickly followed by identification of the leptin receptor and its db mutation [121, 122]. The human leptin gene is now known as LEP, its mouse homolog as lep, and these mutations as lepob and LRdb. Six variants of the leptin receptor, LR, have been discovered in mice; the long, signaling form is LRb.

Several lines of evidence beyond these gene mutation syndromes support the role of leptin as an adiposity signal (fig. 7). Cross-sectional studies have revealed high correlations between basal leptin levels and adiposity in humans and animals [5]. Leptin is actively transported into the Arc and binds to LRb, on two populations of Arc neurons that contribute to the control of eating (see below), and local injections of leptin into this area or the adjacent third cerebral ventricle reduce food intake, increase energy expenditure, and reduce body weight in rats and mice [123–125]. LRb are located in other brain areas as well, and local administration of leptin in these areas also reduces food intake [126–128]. Peripheral administration of leptin also reduces food intake, by selectively decreasing meal size [129, 130].

**Fig. 7.** Adiposity signals (leptin, insulin and amylin) affect eating by modulating the action of meal-related, mainly vagally mediated satiation signals, such as cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1). Leptin may act on receptor both in the caudal brainstem and hypothalamus; insulin acts in the hypothalamus; and amylin acts in the AP. The hypothalamic actions of leptin and (presumably) insulin activate descending pathways to the caudal hindbrain. See text for further details.
Perhaps the strongest physiological evidence that leptin is an adiposity signal is the report by Zhang et al. [131] in 2007 that continuous infusion of a leptin antagonist into the third cerebral ventricle over the course of several days led to increased eating and body weight. These data strongly implicate leptin in the physiological control of eating, although they do not directly link leptin to adiposity signaling. Tests in overweight human subjects who lost weight by dieting have produced evidence that leptin meets the physiological dose criterion for an adiposity signal, at least during underweight [132]. After the subjects lost weight, their basal energy expenditure decreased (eating was not measured). Then, leptin was infused in amounts that re-established pre-dieting leptin levels. This was sufficient to return basal energy expenditure to the pre-dieting level. This interesting result is one of several that supports the hypothesis that reduced plasma leptin levels affect eating and energy expenditure more potently than do increased plasma levels, suggesting that leptin may function physiologically as a starvation signal more than as an obesity signal [21, 131–134].

**Insulin**

Basal plasma and cerebrospinal levels of insulin are equally tightly linked to body adiposity, insulin receptors are present in the hypothalamus, and the actions of central insulin on food intake and energy expenditure are similar to those of leptin in many respects [5, 135, 136] (fig. 7). Moreover, male and female mice with genetic deletions of neuronal insulin receptors are obese and female mice are also hyperphagic [137], indicating that insulin receptor signaling in the brain is important for the control of body weight. Insulin crosses the BBB via a receptor-mediated process [138], and it acts through the same hypothalamic neuropeptide system as leptin [139].

**From Long-Term Energy Balance to Single Meals**

Any signal which controls body weight by changing food intake must modulate the frequency or the size of single meals and, therefore, must interact with the short-term, meal-control signals. As described above, exogenous leptin and insulin selectively reduce meal size [129, 130, 140, 141], so should interact with reward or satiation signals, which also affect meal size. In line with this, both leptin [142] and insulin [143] have been shown to enhance the satiating effect of CCK, although the insulin effect may not be a selective meal size effect. Finally, the compensatory hypophagia that follows experimentally induced increases in body weight is also mainly due to a reduction of nocturnal meal size, further supporting the hypothesis that adiposity signals influence eating mainly through changes in meal size [116]. In their chapters, Blevins and Baskin [65] and Schwartz [49] describe recent progress on the mechanisms underlying this interaction.
Central Nervous System Integration

Introduction

Eating is mediated by a very complex, anatomically diffuse neural network that is organized hierarchically, redundantly and recurrently. This section introduces some principal nodes in this network, their key signaling molecules, and their main functions in the control of eating and regulation of body weight, as presently understood. Both the discovery of new facts and the generation of new concepts are proceeding rapidly in this area, as reflected in the chapters by Blevins and Baskin [65], Bouret [144], Sullivan and Grove [145], and Schwartz [49]. To introduce these developments, we begin with a historical perspective, aimed at providing a sense of the evolution of how the CNS mechanisms controlling eating have been analyzed and interpreted. We then discuss some of the key anatomical nodes and neurochemical signaling molecules. For reasons that will become clear in the next section, we begin with the hypothalamus.

The experimental analysis of the integrative action of the CNS in the control of eating has progressed in overlapping waves, each initiated by methodological advances. The first wave began six decades ago with the development of stereotaxic surgery. This method led to the discoveries that circumscribed lesions of the ventromedial hypothalamic area (VMH) induce hyperphagia, reductions in energy expenditure, and weight gain and that similar lesions of the lateral hypothalamic area (LHA) induce opposite effects [146, 147]. This work led directly to the concept of hypothalamic ‘centers’ for eating and weight regulation (fig. 8) [148]. During the subsequent decades, lesion and neuropharmacological work elaborated and better differentiated the functions of these areas [149–151]. Also, the Arc, paraventricular (PVN) and dorsomedial (DMN) hypothalamic nuclei as well as several nonhypothalamic areas were implicated in the neural circuitry for eating and weight regulation [152–154].

A second wave began around 1970, with the advances in neuroanatomical methods, especially fluorescence, immunocytochemical and tract-tracing methods. These led to a new, chemical neuroanatomy [155–158]. Early landmarks in this era include the demonstrations that adrenergic receptors in part mediate the hypothalamic control of eating [159], that chemical lesions of ascending dopaminergic pathways traversing the LHA are sufficient to replicate the syndrome of aphagia and adipsia produced by electrolytic lesions of the LHA [160], and that descending oxytocin projections from the hypothalamus to the caudal brainstem contribute to hypothalamic lesion-induced obesity [161]. An especially important development was the increasing realization that eating and related neuroendocrine and autonomic responses are coordinately organized by a diffuse neural network extending from the cerebral cortex and basal telencephalic structures caudally through the hypothalamus and into the caudal brainstem [162, 163]. As a consequence, eating and weight-regulatory functions cannot be localized to particular discrete ‘centers’. Therefore, we do not use this terminology here.
A third wave of progress, based on the application of molecular genetic techniques, began, as described above, with the discovery of leptin [120] in 1994 and the leptin receptor [121] within 2 years. The first demonstrations that exogenous leptin acts in the brain to inhibit eating and to restrain adiposity came in 1995 [123–125]. The outlines of the CNS mechanisms for this effect emerged soon after. By 1996, it had been shown that leptin crosses the BBB via a saturable carrier system which is especially active in the Arc [164], that Arc neurons densely express LRb mRNA [165], that these same neurons also express mRNA for the neurotransmitter neuropeptide Y (NPY) [166], whose administration stimulates eating, and for pro-opiomelanocortin (POMC),

![Fig. 8. Schematic frontal section of the hypothalamus indicating the localization of cell bodies expressing orexigenic and anorexigenic neuropeptides, some of their intra-hypothalamic projections, their hormone and metabolite sensitivities and the putative functional roles of extrahypothalamic projections form the PVN and LHA (based on the effects of orexigenic and anorexigenic neuropeptide administration). Note the bilateral symmetry of the hypothalamus (labels and projections are shown only unilaterally). Hypothalamic areas: Arc = Arcuate nucleus; LHA = lateral hypothalamic area; PVN = paraventricular nucleus; VMH = ventromedial hypothalamic area. Neuropeptides: AgRP = agouti-related peptide; BDNF = brain-derived neurotropic factor; CART = cocaine- and amphetamine-related transcript; CRH = corticotropin-releasing hormone; GRP = gastrin-releasing peptide; MCH = melanin-concentrating hormone; NPY = neuropeptide Y; OT = oxytocin; POMC = pro-opiomelanocortin. Metabolites: LCFA = long-chain fatty acids. See text for further details. Modified with permission from Langhans et al. [280].]
from which the eating-inhibitory neurotransmitter α-melanocyte-stimulating hormone (α-MSH) is cleaved, and that antagonism of hypothalamic α-MSH signaling via melanocortin-4 receptors (MC4R) blocks the eating-inhibitory effect of exogenous leptin [167]. We now know that these same neurons also function as metabolic sensors and express receptors for insulin, ghrelin and serotonin, to name just a few of the substances emphasized here. These studies provided a novel window into the brain networks controlling eating, whose elaboration continues [114, 168–173].

A fourth wave has already begun, based on increasingly sophisticated functional imaging methods [6, 174–176]. Because many of these methods can be linked explicitly to molecular and genetic techniques, they hold unprecedented promise for translating basic animal research into human functional neuroscience and into therapeutics. The chapters by Neary and Batterham [2], Kringelbach and Stein [3], and Stice and Dagher [4] describe some of these developments.

**Hypothalamus**

**Arcuate nucleus (Arc).** Figure 9 shows a schematic of some critical aspects of the organization of the Arc [114, 168–173]. A key role in weight regulation is suggested by the fact that, as described above, receptors for the putative adiposity signals leptin, insulin, and ghrelin are expressed by Arc NPY and POMC (α-MSH) neurons. The former also expresses agouti-related peptide (AgRP), another eating-stimulatory peptide, and the latter, cocaine- and amphetamine-related transcript (CART), which inhibits eating. Several mechanisms contribute to the functional coordination of these two sets of neurons. For example, the activity of the POMC/CART neurons is inhibited by NPY acting at Y1 receptors on POMC cell bodies [177, 178] and by gamma-amino butyric acid (GABA)-mediated inhibitory synapses on projections from the NPY/AgRP neurons. Both populations of Arc neurons also receive serotoninergic (5HT) inputs, the POMC/CART neurons via 5HT-2CR and the NPY/AgRP neurons via 5HT-1BR, which modulate their activity in a similar fashion as leptin [172]. Finally, the principal projection targets of these Arc neurons are the PVN and LH. This basic circuit is thought to orchestrate the eating, neuroendocrine and autonomic responses contributing to energy homeostasis. In particular, increases in adiposity are thought to generate catabolic responses (i.e. the inhibition of eating and stimulation of energy expenditure) through this circuit, and decreases in adiposity to generate anabolic responses (stimulation of eating and inhibition of energy expenditure). Chronic pharmacological stimulation of the Arc-PVN NPY system stimulates eating, reduces energy expenditure, and results in obesity [179–181]. In contrast, chronic administration of NPY antisense mRNA into the Arc decreased food intake and reduced body weight [38]. Both intracerebroventricular insulin and intracerebroventricular leptin reduce Arc NPY mRNA. Furthermore, NPY neuronal activity is increased in animals in which body weight has been reduced by food restriction and is decreased in dietary-obese animals [182]. In
contrast to MC4R KO mice, however, NPY or NPY receptor KO mice eat normally, presumably due to redundancy and developmental compensation. This is an example of the caution required in drawing physiological conclusions from knockout phenotypes.

The synthesis presented above is based on a tremendous data base. Nevertheless, because available methodologies do not permit truly crucial physiological experiments, the extent to which it reflects normal physiological function is uncertain. Some outstanding issues that are currently under investigation include: (1) the extent to which adiposity signals act at sites outside the Arc, for example, the caudal brainstem (fig. 10) [162], (2) whether Arc signaling is more physiologically active during
underweight or during overweight, (3) what the physiologically relevant dynamic properties of the circuit are, for example, how do the state of adiposity and the current flux of energy substrate combine to affect its activity, (4) whether the effects on eating and energy expenditure are always coordinated, and what factors might dissociate them [183], and (5) how lasting changes in adiposity affect the operation of the system. The last question is especially interesting with regard to the well-recognized progressive resistance of obese subjects to repeated doses of leptin [165, 184] or insulin [76] (see chapters by Banks [20] and Münzberg [185]).

**Paraventricular Nucleus (PVN) and Lateral Hypothalamic Area (LHA).** Figure 8 depicts the main Arc projections controlling eating. In the PVN, α-MSH terminals synapse on MC3R and MC4R [186–188], and NPY terminals synapse on Y1, Y4 and Y5 NPY receptor subtypes [179, 189]. PVN neurons express several anorexigenic neuroactive substances, including corticotropin-releasing hormone (CRH), oxytocin (OT), gastric-releasing peptide (GRP), and thyrotropin-releasing hormone (TRH). For this reason, and because PVN lesions produce hyperphagia and obesity, the PVN
seems to be predominately a catabolic integratory site. In contrast, the LHA appears to be a mainly anabolic site. It receives many orexigenic projections from the Arc, expresses orexigenic peptides including melanin-concentrating hormone (MCH) and the orexins (ORX), and LHA lesions produce aphagia. Nevertheless, LHA neurons also express anorexigenic substances, such as CART and dynorphin. Interestingly, in contrast to the more unidirectional Arc-PVN connections, there are prominent reciprocal LHA-Arc projections, which may be related to the more heterogeneous expression profiles of its neurons.

Although the orexigenic effects of NPY appear to arise from a synergistic activation of Y1, Y2, Y4 and Y5 receptor subtypes, Y1 receptors may be especially important. Genetic deletion of Y1 receptors or the administration of Y1 receptor antagonists reduces NPY- and fasting-induced eating [190–194].

One function of the PVN apparently is to communicate with the caudal hindbrain areas involved in the control of eating. For example, POMC, OT and CRH neurons in the parvocellular subdivision of the PVN as well as GRP neurons in the magnocellular subdivision of the PVN project to the nucleus tractus solitarii (NTS) and dorsal motor nucleus of the vagus [158, 195–198]. The functions of these projections are discussed in the chapter by Blevins and Baskin [65] and Schwartz [49].

In the LHA, MCH- and ORX-expressing neurons receive synaptic inputs from Arc NPY-, AgRP- and α-MSH-expressing neurons [199–201]. Chronic central administration of MCH results in increased food intake and adiposity [202], whereas chronic administration of MCH-1 receptor antagonists inhibit eating and reduce body weight [203]. Additionally, transgenic mice overexpressing MCH are hyperphagic and obese, whereas MCH-null mice are hypophagic and lean [204]. MCH affects energy expenditure as well as eating. ORX A and B are 33 and 28 amino acid peptides, respectively, that increase arousal and stimulate eating [205, 206]. Finally, as discussed previously, the LHA also contains neurons that function as receptors for glucose and, perhaps, long chain fatty acids (fig. 8) [207, 208]. ORX may play a role in glucose-sensing because hypoglycemia induces increases in ORX mRNA and c-Fos expression in ORX neurons [209], and ORX-A excites LHA glucose-sensing neurons [210, 211]. Finally, LHA ORX neurons reciprocally innervate NPY- and POMC-producing neurons of the Arc [211].

Other Hypothalamic Areas. As suggested by figure 8, the Arc, PVN and LHA are by no means the only hypothalamic areas contributing to the control of eating. For example, direct injections of NPY into the perifornical area and ventromedial hypothalamus (VMH) stimulate eating similarly to PVN injections [179]. As well, NPY projections to the PVN from sites other than the Arc, such as the dorsomedial hypothalamus (DMH) have also been implicated in the control of eating. This DMH projection is especially interesting. DMH NPY neurons are under a tonic inhibitory influence of neuronal (not hormonal) CCK, such that rats with mutations of the CCK-1 receptor overexpress NPY in the DMH and are obese [63]. In addition, chronic increases in exercise seem to produce an independent tonic inhibition of DMH NPY [212].
The VMH also receives projections from Arc NPY/AgRP and POMC neurons, so has been regarded as another downstream site for signaling events initiated in the Arc. The VMH also contains LRb, so is a potential sensory site for adiposity signals. Dhillon et al. [213] recently provided support for this idea by demonstrating that leptin depolarizes and increases the firing rate of steroidogenic factor-1 (SF1)-positive neurons in the VMH and that transgenic mice lacking LRb on SF1-positive neurons became heavier than controls when fed an energy-dense diet. Brain-derived neurotrophic factor (BDNF) is another candidate mediator of the VMH’s effect on in eating. BDNF is abundantly expressed within the VMH, and mice with reductions in BDNF neuronal function increase food intake and body weight [214].

Caudal Brainstem

Eating is a rhythmic behavior produced by motor neurons of cranial nerves V, VII, IX, X and XII. These nerves are driven by central pattern generators, a variety of reflex-like sensory feedback signals, and more remote upstream neural networks, including the hypothalamic projections described above. The neural machinery for central pattern generators and sensory feedback signals are contained in the caudal brainstem. The caudal brainstem also receives the sensory inputs from all but the olfactory dimension of flavor and from a variety of interoceptive information. It also contains many of the same neuronal signaling sensitivities as found in the hypothalamus, including leptin, ghrelin, amylin, NPY, MC and estrogen receptors as well as POMC neurons [162, 168, 188, 215–217]. Some of this is depicted in figure 10.

Studies by Harvey Grill and his colleagues [127, 162, 218] of the chronic decerebrate (CD) rat, i.e. animals with midcollicular transections of the neuroaxis, and of direct administration of neuroactive substances into the caudal brainstem, indicate that the caudal brainstem is sufficient for nearly normal effects of taste and gastrointestinal feedback signals on meal size. For example, although CD rats do not initiate meals unless food is placed into the mouth, when this is done by intraoral infusion, they take well-defined meals terminated by passive refusal of more food. Furthermore, CD rats increase or decrease meal size in a normal way when sucrose concentration is varied [219] and have apparently normal sensitivity to peripheral CCK injection [220]. Although CD rats eat less after insulin or leptin administration [162], the caudal brainstem does not seem sufficient for regulation of energy homeostasis. That is because they do not increase meal size normally after food deprivation or when the number of daily opportunities to eat is reduced [221].

The structure in the caudal brainstem most investigated in relation to the control of eating is the NTS (fig. 10). It receives a wide variety of sensory information, has important integratory functions, and is a source of ascending projections to further integratory sites as well as descending projections that control behavioral and autonomic responses. Flavor-related information reaches the NTS directly via cranial
nerves V, VII, IX and X. Cranial nerves VII (the facial nerve), IX (glossopharyngeal) and X (vagus) innervate taste buds and mediate the primary tastes (sweet, bitter, sour, salt, protein or umami, and, in rats, apparently starch taste). Receptors for temperature, mechanical stimulation, and certain chemicals, such as capsaicin (chili) convey flavor information via cranial nerve V (trigeminal), which synapses in the sensory trigeminal nucleus prior to projecting to the NTS. In addition, a variety of interoceptive information reaches the caudal brainstem in part directly, via the transport of certain metabolites (glucose) and hormones (leptin), and indirectly, via neural projections from either the adjacent AP, which has a porous BBB, or from the gut. As described above, vagal and spinal visceral sensory nerves relay temperature, mechanical, osmotic and chemical (metabolite and hormone concentrations) information from the gut to the NTS.

The NTS is an integratory site, not a mere relay. For example, the electrophysiological responses of second order taste neurons are affected by a range of eating-related information, including plasma glucose levels and preference and aversion learning [222]. Immunochemical detection of the expression of c-Fos protein, a marker of neuronal activation, reveals an even wider range of integratory effects. For example, the increase in the satiating potency of CCK by estradiol described below is associated with an increase in CCK-induced c-Fos expression in NTS neurons expressing the estradiol receptor-alpha (ERα), strongly suggesting that the interaction arises in the NTS [223, 224]. Similarly, the functionally synergistic inhibition of eating produced by co-administration of leptin and CCK or CCK1R antagonists is mirrored by a similar increase in the number of NTS cells expressing c-Fos [142, 225]. This integrative function is the focus of the chapter by Schwartz [49].

Forebrain

The increased complexity of the forebrain, or telencephalon, is a hallmark of human evolution. As with other categories of information, eating-related information is represented and re-represented in telencephalic areas. Not surprisingly, therefore, the telencephalic contributions to eating-related associations, cognitions, emotions, and motives, both conscious and unconscious, are very poorly understood [168]. Nevertheless, substantial progress has been made in studies of the telencephalic contributions to some aspects of food reward.

As described above, orosensory pleasure is a powerful controller of eating. Analyses of the telencephalic contribution to this reward function support several generalizations: (1) Many reward-related behaviors are similar in animals and humans [8, 226]. (2) Partially homologous neural mechanisms mediate food reward in animals and humans [9, 227, 228]. (3) The neural networks mediating food reward and those mediating other natural (e.g. sex, water when thirsty) and unnatural (e.g. drugs of abuse) rewards overlap very heavily. (4) Neural networks mediating food
reward also overlap with the mechanisms regulating mood and affect. (5) These neural networks are extensively and reciprocally connected with the neural networks mediating the more regulatory and reflexive aspects of eating, discussed above, so that simple notions of parallel processing or ‘homeostatic vs. non-homeostatic’ controls are correct in only the most general, heuristic way. An example of this is that ventral forebrain manipulations that are linked to hedonic eating also activate Arc NPY neurons and inhibit Arc POMC/CART neurons, whose activity is, as explained above, usually interpreted in the context of homeostasis [229]. (6) At least partially independent neural substrates can be identified for different aspects of food reward [226, 230–233]. The outstanding example of the last point is the differentiation of the affective or emotional impetus to eat (implicit ‘liking’ and conscious pleasure) from the classical motivational impetus (implicit incentive salience ‘wanting’ and cognitive incentive goals [9, 227].

Some principal components of the telencephalic reward system are the nucleus accumbens (NAc), the amygdala, especially the central nucleus of the amygdala (CeA), and parts of the limbic, orbitofrontal, cingulate and insular cortical areas (fig. 11).
The NAc and the CeA, in particular, receive projections from a variety of hypothalamic areas and brainstem areas discussed above. In addition, most of the telencephalic reward system receives dopaminergic (from the ventral tegmental area and substantia nigra), noradrenergic (from the locus coeruleus) and serotonergic (from the rostral raphe nuclei) inputs. These ascending systems also provide important links among these areas and the brainstem and the hypothalamus, as exemplified by the recent report [172] that serotonin modulates the hypothalamic melanocortin pathway.

The NAc, and directly interconnected brain areas, have been intensely investigated in relation to food reward. Within the NAc, dopamine, opioid, cannabinoid, acetylcholine and GABA neurotransmission have all been implicated in processing food reward. Hajnal, Norgren and colleagues [234, 235] have verified the role of dopamine in orosensory food reward, which they isolated from post-oral food stimuli by testing sham-feeding rats. They demonstrated that for both sucrose solutions and corn oil emulsions, concentration-dependent increases in sham feeding were closely associated by the release of dopamine in the NAc. Note that these studies suggest that sensory information for two entirely different sensory pathways, i.e. relatively purely gustatory in the case of sucrose versus olfactory/trigeminal in the case of oil, converge in the NAc. Similarly, administration of mu-opioid agonists into the NAc preferentially stimulates ingestion of high-fat foods and sucrose solutions, whereas administration of opioid antagonists selectively reduces ingestion of palatable foods [236, 237]. Additionally, in man, opiate antagonists reduce food palatability, but not subjective hunger [238].

The endocannabinoid system also contributes to food reward circuitry. Endocannabinoids act at brain CB1 cannabinoid receptors in both the NAc and hypothalamus to stimulate eating, and endocannabinoid activity in these regions varies in relation to nutritional status and eating expression [239]. The powerful effects of manipulation of endocannabinoid function on mood, at least in susceptible individuals, exemplifies the overlap between neural mechanisms processing food reward and regulating emotion and affect [228].

Some aspects of the connectivity of the NAc, the amygdala, and other areas that mediate eating have emerged (fig. 11). For example, connections between the basolateral amygdala (BLA) and forebrain cortical regions appear crucial in determining food palatability [240]. A reciprocal connection between the CeA and the NAc is also involved in opioid-mediated eating [241], although whether this pathway is selectively involved in reward is not yet clear [242]. Another mechanism that may involve reciprocal projections from the NAc and ventral palladium to the LHA also appears to selectively stimulate consumption of palatable food to the LHA [243]. As previously discussed, the LHA contains MCH and orexin neurons, both of which stimulate food intake. Activation of opiate neurons in the NAc may stimulate eating by releasing these neurons from a tonic inhibition [244]. Similarly, the stimulation of eating caused by NAc administration of the GABA(A) agonist muscimol was
associated with increased activity in orexin neurons in the perifornical region of the hypothalamus [229].

Physiological Modulators of Eating and Body Weight

A number of physiological functions whose primary purpose is not the control of eating nevertheless powerfully affect eating. For example, thermoregulation, water balance, exercise, and stress (both physiological and psychological) can affect eating in the short term and, under certain circumstances, chronically affect eating and weight regulation in the long term. This section discusses two such physiological modulators.

Sex

In the physiology of eating and body weight regulation, as in other areas, sex is a fundamental biological variable [245]. In animals and humans, reproductive, or hypothalamic-pituitary-gonadal (HPG), axis function affects the controls of eating, growth, energy metabolism, nutrient partitioning, physical activity, adipose tissue distribution, etc. Research in these areas is complicated by several factors, ranging from the extensive developmental and species differences in HPG axis function to the marked interactions of culture and physiology in most human behaviors related to HPG axis function.

After puberty, most physiological sex differences are not directly controlled by sex chromosomes, but by activational effects of the gonadal steroid hormones, i.e. effects related to current circulating levels of androgens, estrogens, and progestins. The clearest activational effect on eating is the decrease in eating that occurs during the peri-ovulatory period of the ovarian cycle in women and animals. This is absent when estradiol secretion does not occur, and a physiological pattern of estradiol treatment is sufficient to reinstate it in ovariectomized rats [246]. Part of the mechanism involves an increase in the satiating potency of CCK mediated by ERα stimulation in the NTS [223, 224, 247, 248]. Estradiol also appears to reduce the eating-stimulatory action of ghrelin [249]. Brain serotonin appears to be crucially involved in the effects of estradiol on eating [250]. Estrogens also exert activational effects on energy homeostasis and regional adipose tissue distribution, at least in part via ERα stimulation in the hypothalamus [251–253]. Emerging data also link membrane ERs to energy homeostasis, although the physiological relevance of these effects is still unclear [254]. Finally, the relevance of these controls of eating to human weight regulation is underscored by reports that loss-of-function polymorphisms of the ERα gene are linked to increases in fat mass in girls [255]. Several recent reviews [247, 248, 252, 256, 257] discuss the current progress in this important area.

Overview
The Immune System and Eating

The loss of appetite during illness is a well-known phenomenon resulting from the effects of immune activation on eating. Acute infections and other immune challenges trigger a generalized host defense reaction, known as the acute-phase response (APR), which is comprised of several physiological and behavioral changes, including anorexia [258]. Illness anorexia appears to be beneficial for the host in the beginning [259], but becomes deleterious over time. Most current knowledge on the mechanisms of illness anorexia is derived from the model of acute microbial infections produced by administration of lipopolysaccharides (LPS), Gram-negative bacterial cell wall constituents that are released in natural infections during bacteriolysis or rapid bacterial proliferation [260]. LPS administration stimulates the immune system and mimics the APR including anorexia. It initiates a cascade of immune and neuroendocrine events that involve endogenous mediators, such as pro-inflammatory cytokines, most likely acting at the BBB, where they trigger from BBB endothelial cells the release of other downstream mediators, such as prostaglandin E₂ or nitric oxide, to ultimately modulate the activity of the neuronal network described in the previous sections that controls normal eating [261]. A more detailed appraisal of the recent developments concerning this aspect of the control of eating is given in several recent reviews [261–263]. Because immune mechanisms are also implicated in obesity and diabetes (see below), illness anorexia research is also relevant to the understanding of diabetes.

Eating, Obesity and Type 2 Diabetes Mellitus

The connection between eating and diabetes follows from the fact that overeating leads to overweight and obesity, which is the major risk factor for the development of insulin resistance and type 2 diabetes mellitus (T2DM). The relationship between eating and diabetes, however, is more complex than this simple unidirectional pathophysiological sequence. Instead, there appear to be positive-feedback links between increased eating, increased adiposity, and insulin resistance, thus setting up vicious cycles that exacerbate diabetes risk or diabetes per se. For example, as shown in figure 12, several vicious cycles apparently result from increased fat intake. (1) Animals with experimentally induced T1DM select and eat fat-containing food in order to obtain utilizable energy [264]. (2) Fat intake may result in brain insulin resistance, i.e. a reduced influence of insulin on eating, which would further increase eating [76]. (3) Increased fat intake per se may stimulate an immune response, which can lead to insulin resistance and thus set up another vicious cycle. Fat metabolism is thought to stimulate the immune system because saturated long-chain fatty acids are structurally similar to bacterial pathogens such as LPS and may therefore target innate immune receptors [265].
Although we have emphasized the relationships between increased ingestion of fat and obesity, it is important to note that causes of increased adiposity other than increased fat intake can set up similar vicious cycles. Finally, recent research increasingly indicates that there are important developmental aspects to these processes. Early development in particular appears to alter metabolic and neural mechanisms in ways that may last a lifetime. The chapters by Bouret [144] and Sullivan and Grove [145] describe some of this work.

**Genetics of Eating and Body Weight Phenotypes**

Body weight is a highly heritable, polygenetic trait, similar to height. Depending on the measurement method used, the heritability (h², the percent of variation in a population phenotype that is due to genetic variation) of body weight or BMI is generally between 0.65 and 0.85 [266]. For example, h² of BMI estimated from a comparison of monozygotic and dizygotic Danish male twins was 0.77–0.84, depending on the age at which BMIs were compared [267]. Similarly, adiposity in a group of adult Danes who had been adopted at an early age was strongly and significantly related to the adiposity of their biological parents, but was not significantly related to the adiposity of their adoptive parents [268]. Which genes contribute most to the heritability of obesity remains unclear. According to a recent large (>90,000 total subjects) genomewide association study, eight contributing genes have been identified [269].
It is often asked that if adiposity is highly heritable, how can the prevalence of obesity increase so rapidly without a change in our genome? Two points explain this apparent paradox. First, \( h^2 \) measures heritability in a single environment. If the environment changes, \( h^2 \) may as well. Thus, individual estimates of \( h^2 \) in the present high obesity-risk environment and in the former low obesity-risk environment might each be near 0.8, but this figure would be markedly reduced if \( h^2 \) were estimated in both environments simultaneously. Second, although the genome has not changed much in recent times, the particular genes that are expressed and their degree of expression probably have. That is, different genes are likely to effectively contribute to our phenotypes in the present environment more than in former environments. Genes related to the intake of sugar and fat, for example, are certainly more effective regulators of gene expression now than in former days when sugar and fat intakes were lower.

A more directly relevant question in the present context is, are food selection and amount eaten genetically determined traits that contribute to the risk of obesity or other disorders of eating? As recently reviewed by de Krom et al. [270], an increasing number of studies indicate that the answer is yes. Furthermore, allelic variants that contribute to this heritability have been identified. The earliest such reports were rare cases of single-gene mutations that produce dramatic hyperphagia and obesity syndromes in affected people, for example, in individuals lacking leptin due to null mutations in \( LEP \) [271] or lacking POMC-derived peptides due to null mutations in \( pomp \) [272].

More interesting are reports of altered eating in relatively more common allelic variants. So far, most is known about the melanocortin-4 receptor gene \( MC4R \) [266, 269, 273, 274]. The role of MC4R in the control of eating was reviewed above. About 100 \( MC4R \) variants have been associated with obesity and occur in about 2–6% of obese people, depending on the population sampled. In one study of 17 children with \( MC4R \) mutations and severe early onset obesity, the degree of impairment in MC4R signaling in vitro was associated with amount eaten during an ad libitum meal, with the energy intake of the most affected children about four times that of controls [275]. A recent analysis of semiquantitative eating questionnaires taken during a longitudinal study of >5,000 US nurses, all American women of European ancestry, revealed that the single-nucleotide polymorphism (SNP) rs17782313 near \( MC4R \) was significantly associated with increased intakes of energy, fat and protein [276]. This SNP was also associated with BMI, weight gain between ages 44 and 54 years, and T2DM risk in these women. As this SNP was quite common (minor allele frequency of about 25% in this sample), its potential role in human obesity deserves further analysis. Further associations of variants in obesity-related genes and measures of eating behavior and food reward are described in the chapters by Hetherington and Cecil [277], which includes a discussion of the eating effects of variants in the FTO gene, and by Stice and Dagher [4], who focus on genetic variations in dopaminergic food reward.
Finally, an interesting alternative method, the extreme discordant phenotype approach, deserves mention. Beginning with a sample of >17,000 Dutch women, de Krom et al. [278] first identified women who were both obese and in the top 5% of either meal frequency (n = 60) or meal size (n = 72), estimated by questionnaires and the use of photos of food portions, respectively, and then searched for the presence of known SNP in cck, LEP or LR. Women with LEP SNP rs4731413 had markedly increased risk for extremely frequent meals, whereas those with CCK SNP rs6801844 had increased risk for extremely large meals. Furthermore, the prevalences of these eating-related SNP were remarkably high in both control and affected women, 58 and 68%, respectively, in the case of the LEP SNP. These data indicate not only that specific high-risk eating traits have genetic bases but also that the genes conferring such risks are surprisingly common.

Conclusion

This chapter has presented an overview of the present status of the physiology of eating, in particular as it relates to body weight regulation and the pathophysiology of obesity. As mentioned at the beginning, it also serves as an introduction to the chapters describing specific research frontiers in the physiology of eating.

Dealing with the current obesity epidemic is a major societal problem, and responses at all levels are being sought to reduce the incidence of obesity and to treat obese persons. Overeating and lack of physical activity are recognized as the main causes of this problem. It is increasingly apparent that a multifaceted approach is required to reverse the obesity epidemic, involving numerous adjustments in our culture as well as improved medical approaches. As part of the latter, a better understanding of the physiological controls of eating, in particular as they interrelate to the regulation of body weight and adiposity, would facilitate development of more effective treatments for obesity. As emphasized by De Kloet and Woods [279], at present only two prescription medications are available for the treatment of obesity, but their efficacies are very modest and patients’ perception of the quality of life benefit they yield is minimal. Gastric-bypass bariatric surgery is certainly much more effective than any currently available medication, but because of its drawbacks and risks, it is presently considered appropriate for only the persons at the highest risk. From a basic research perspective, the marked decrease in eating after bariatric surgery poses a problem and, perhaps, an opportunity. That is, could the physiological mechanisms that bring about the decreases in eating after bariatric surgery be harnessed in non-surgical ways to develop new treatments? Finally, bariatric surgery also exemplifies the often overlooked point that translational research means not only translating basic research into clinical practice, but also translating clinical experience back into new directions in basic research.
References


56 Ballinger AB, Clark ML: L-Phenylalanine releases cholecystokinin (CCK) and is associated with reduced food-intake in humans: evidence for a physiological role of CCK in control of eating. Metab Clin Exp 1994;43:735–738.


Levin BE: Metabolic sensing neurons and the control of energy homeostasis. Physiol Behav 2006;89:486–489.

128 Malik KF, Young WS: Localization of binding sites in the central nervous system for leptin (OB protein) in normal, obese (ob/ob), and diabetic (db/db) C57BL/6j mice. Endocrinology 1996;137:1497–1500.
177 Broberger C, Landry M, Wong H, Walsh GN, Hokfelt T: Subtypes Y1 and Y2 of the neuropeptide Y receptor are respectively expressed in pro-opiomelanocortin- and neuropeptide-Y-containing neurons of the rat hypothalamic arcuate nucleus. Neuroendocrinology 1997;66:393–408.


188 Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD: Localization of the melanocortin-4 receptor (MCR-4) in neuroendocrine and autonomic control-circuits in the brain. Mol Endocrinol 1994; 8:1298–1308.


204 Marsh DJ, Weingarth DT, Novi DE, et al: Melanin-concentrating hormone 1 receptor-deficient mice are lean, hyperactive, and hyperphagic and have altered metabolism. Proc Natl Acad Sci USA 2002; 99:3240–3245.

208 Routh VH: Glucose-sensing neurons: are they physiologically relevant? Physiol Behav 2002;76:403–413.


