Mind versus metabolism in the control of food intake and energy balance

Hans-Rudolf Berthoud*

Neurobiology of Nutrition Laboratory, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA 70808, USA

Abstract

In a restrictive food environment, the homeostatic control system regulates body weight and adiposity with remarkable precision. However, this regulation appears to break down in many genetically predisposed individuals under conditions prevailing in the modern era characterized by a sedentary lifestyle and easy availability of large portions of palatable and calorically dense food. The nervous system is the main interface by which food-related environmental factors influence the regulatory process. Thus, focusing on the neural systems located in the telencephalon dealing with environmental factors, and on their connections with the homeostatic regulatory system distributed mainly in the hypothalamus and brainstem, should result in new drug targets and behavioral strategies for prevention and therapy. The structures providing this interface with the environment are involved in the initiation, procurement, and appetitive phases of ingestive behavior and associative learning before, during, and after the consummatory phase. It is thought that learned and unlearned representations of foods and food cues in the orbitofrontal and other cortical areas are filtered for affective/emotional value in the amygdala and for motivational salience in the nucleus accumbens/ventral striatum to initiate goal-directed motor programs. Internal state signals generated by the metabolic sensing mechanisms in the hypothalamus interact with each of these corticolimbic structures through reciprocal connections. While many projections from the hypothalamus contain the various “feeding peptides,” the neurochemistry of projections to the hypothalamus has not been well characterized.

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1. Introduction

With obesity affecting as many as 30% of the adult population of the United States [60], and rapidly on the rise in many other countries, this modern disease has reached epidemic proportions and produces a heavy financial burden on health care systems. Governments are trying to stem this tide by increased funding for research on prevention and treatment of obesity and the pharmaceutical industry is in hot pursuit of “magic bullet” drugs that will curb appetite and decrease body weight. However, to cure a disease, it is important to know what its cause is. In the case of Type-1 diabetes, replacement of insulin is essentially all that is necessary to cure the disease, because this hormone is no longer produced. Similarly, obesity in the case of inherited deletion of the leptin gene can be cured with leptin treatment [29], and there are other single gene mutations causing obesity [73]. However, the large majority of obesity, referred to here as “common obesity,” has a much more complex etiology. Genes are ultimately involved in any disease, just as they are involved in any structure and physiological function, but in common obesity, this involvement is complex, weak, and not easily demonstrable.

Just 50 years ago, obesity was a rare disease, but it has been steadily growing. It is impossible that the human genetic pool has changed in such a short period of time and all fingers point to changes in the environment and lifestyle as the real cause of common obesity [46,72]. In most humans, genes do not directly cause obesity but they predispose us to becoming obese in the changed environment of the modern world. Because it is clear that genes and their products ultimately control all bodily functions, including food intake, energy expenditure, and energy balance, it can be said that a fraction of the population is genetically prone to the environmental and lifestyle push towards obesity, while another fraction is resistant [34,63]. Thus, each of the many factors by which lifestyle and environment influence energy balance interacts with specific sets of susceptibility genes, the variations of which determine the physiological impact of the particular factor [8].
Consequently, some individuals respond strongly (prone) and others weakly or not at all (resistant) to a given factor. For example, resistant individuals may decrease meal size in response to increased caloric density, while prone individuals do not. Resistant individuals may increase physical activity in response to overeating a palatable meal while prone individuals do not.

In the more restrictive environment during most of human evolution, food came at a high cost of physical activity and the danger of tipping the energy balance towards excess was small. According to the “thrifty gene” hypothesis [63], genes that facilitated the procurement of food, allowed large meals, and made efficient use of ingested calories, were important for survival in a restricted environment. Energy reserves in the form of body fat must have been an advantage during long periods of famine, and this mechanism is preserved to this day in hibernating mammals. The main purpose of a system homeostatically regulating body adiposity and body weight was to make sure that enough food was ingested to keep up with energy requirements for growth, physical activity, and reproduction. With a much shorter life expectancy, the growth phase made up most of the life span of early humans. The development of obesity must have been extremely rare and mechanisms to prevent it had little survival value and hence did not evolve.

In the following, I will continue to develop the argument that pressures associated with the modern lifestyle simply overpower the relatively weak defense guarding the upper limit of adiposity (Fig. 1). I will briefly summarize the present knowledge regarding the homeostatic regulatory system as well as the nonhomeostatic cognitive and environmental factors and underlying neural systems, and briefly discuss possible interactions between the two systems.

2. Homeostatic regulation: powerful reaction to starvation but weak in defense of obesity

The relatively stable body weight during adulthood has led to the widely held view that body fat mass is tightly regulated by an adipostat mechanism functioning analogously to the temperature control of a room through a thermostat. Borrowing from the engineering vocabulary, this device receives feedback input from the controlled parameter (room temperature or body fat), and generates an error signal in a comparator if this feedback signal is deviating from a preset reference value (set point). The error signal is used to turn up or down any mechanisms that determine the level of the controlled parameter (heat production or dissipation in the case of room temperature, metabolizable energy-in or energy lost in the case of body weight/adiposity). The fact that adult body weight is relatively stable in many subjects although eating one additional potato chip each day would cumulatively lead to considerable weight gain and obesity over just a few years is often used to illustrate the amazing precision of the putative homeostatic regulatory system. Thus, when leptin and its receptors were discovered, it was declared the missing adiposity signal. Insulin, whose basal secretion rate is also positively correlated with body weight, had been advocated long before as an adiposity signal [105].

The discovery of leptin and its receptors was instrumental for the further characterization of the neural network involved in the control of energy balance [27,33,86]. Lack of leptin signaling very powerfully stimulates ingestive behavior and increases metabolic efficiency as shown in the ob/ob mouse, the leptin-receptor-deficient Zucker rat, and leptin-deficient humans [30]. Looking at where in the brain leptin receptor is expressed is very revealing. The hypothalamus is only one area showing leptin receptor expression. Leptin receptors are also expressed in various telencephalic structures, such as hippocampus and neocortex [36], the nucleus accumbens and ventral tegmental area [31], thalamus [28] in the caudal brainstem [42], in primary vagal afferent neurons [9], and even in taste receptor cells [53]. Thus, leptin signaling impinges on a variety of neural mechanisms involved in all aspects of ingestive behavior, such as taste perception, meal-related visceral feedback, brainstem satiety and oromotor functions, generation of motivational drive by hypothalamic metabolic sensors, and attribution of incentive salience (wanting) and hedonic value (liking) to direct and conditioned food cues. Leptin deficiency is also characterized by increased metabolic efficiency by conserving energy for metabolic processes and thermogenesis, but this effect is stronger in rodents than in humans [24,50,84]. In other words, the leptin-deficient brain is powerfully driven towards food and conservation of energy stores. The power of leptin is equally well revealed when it is replaced in the leptin-deficient state. Food intake and fat stores dramatically decrease, and energy efficiency is relaxed.

However, exogenous leptin rapidly loses its power to decrease food intake when “normal” levels of adiposity are reached [48,51]. The overwhelming majority of obese humans have paradoxically high circulating leptin levels, and very few respond favorably to exogenous leptin [44,49], suggesting a state of leptin resistance. In seasonal animals, leptin is only effective when endogenous leptin levels are already low during winter, but it is ineffective when leptin levels are high during summer [82]. The modern human environment could be regarded as the equivalent of continuous summer with natural leptin resistance in seasonal animals. Leptin treatment as an adjunct of moderate food intake restriction shows more promising effects, probably by counteracting the behavioral and metabolic adaptations that accompany weight loss attempts [32,81]. One thing is clear; leptin and all the other negative feedback signals are unable to prevent the development of obesity of many humans in the modern environment and in certain animal models using human-style cafeteria and highly palatable diets. A number of explanations have been offered for the
state of leptin resistance. There are two fundamentally opposing views. One view sees leptin resistance as a condition that naturally evolved [1], the other more like a pharmacologically treatable disease state brought about by either dietary [64], early life experience, and/or genetic factors [25].

The inability of leptin and insulin to prevent human and animal obesity has led to questioning the adiposity signal status of these two hormones. It has been suggested that the leptin-signaling-deficient mouse may not lack a signal telling them how fat they are, but rather, they lack a signal telling them they have not eaten food recently [95]. Leptin may not be an adiposity signal but rather a starvation signal. This argument is strengthened by the fact that common patterns of changes in body mass following a perturbation can be adequately explained without the need for an adipostat [95]. The extra potato chip every day is in fact a bad argument for the existence of a signal tightly regulating body adiposity in a set-point manner, because it can be shown that a small, constant bias to food intake is quickly compensated by the small but nonetheless significant increase in energy expenditure caused by the increased fat mass [95]. To end in significant body weight gain or obesity, food intake would have to progressively increase over a longer period of time, and a decrease in energy expenditure would synergize the effect. Such a progressive increase in food intake and decrease in physical activity was much less likely in the restrictive environment of the past, but appears to be exactly what happened for many of us during the last 20 years. Humans do not get obese because they eat one potato chip too many each day, but because they end up eating an extra whole bag of chips each day and give up physical activity.

Thus, the relatively constant body weight/adiposity of many adult humans and laboratory rats may give the illusion of a tight homeostatic regulatory system, when in fact, it simply reflects the safeguard of the lower end by the powerful reactions to relative leptin deficiency and the fact that body weight gain induced by increased food intake is limited naturally by the automatically increased metabolic rate caused by the added fat mass. This explanation together with the view that there was no evolutionary pressure to develop a mechanism to defend the upper level of body adiposity, seriously questions the validity of the homeostatic adipostat mechanism in the defense of obesity. Clearly, there is a very powerful homeostatic defense mechanism for the lower limit of adiposity, but apparently not for the upper limit.

Very similar arguments can be made regarding the other purported negative feedback signals controlling meal size. If the many candidate satiety signals, such as cholecystokinin (CCK), Polypeptide YY (PYY), glucagon-like peptide 1 (GLP-1), amylin, enterostatin, insulin, and apolipoprotein ApoAIV have any power, why is it that average meal size in
humans (as judged by portion size) has been steadily climbing in recent years? Again, the most parsimonious explanation is that there was little evolutionary pressure to make these signals strong, and the pressures of the modern food environment simply overpower all these satiety signals.

In summary, there are powerful homeostatic mechanisms that regulate energy balance and defend a certain level of adiposity. They are most powerful in defending a minimal level of adiposity, but are relatively weak in preventing obesity in the modern environment.

3. Environmental and cognitive factors acting in a nonhomeostatic fashion

Initiation and termination of food intake driven by cognitive and environmental factors are not part of this homeostatic system, and neither is the control of physical activity (Fig. 1). Perturbations to the energy balance produced by such factors are not compensated through this system’s own feedback signals and can only be compensated by the homeostatic regulatory system. de Castro and Plunkett [21] used computer simulation to show that food intake levels change depending not only on the internal milieu but also the external environment, that environmental changes result in new levels of intake, and that inherited individual differences in responsiveness to environmental factors can markedly influence the levels obtained.

With regard to food intake, the major components of this nonhomeostatic system are cephalic and intestinal feedforward mechanisms [62], the abundance of food cues in the modern environment, and the easy availability (low physical effort and cost) of palatable, energy-dense foods (snacks) in a socially enhanced environment [22,74,98,100].

Thus, it is not surprising that simply increasing the availability of food can have profound effects on intake and body weight both in rats and humans [74,98]. When rats were given access to five bottles of 32% sucrose in their home cage, they ingested significantly more calories from sucrose than control rats with only one bottle of sucrose and four bottles of water next to ad libitum chow [98]. Although this effect was greatest for the first few days, it lasted for more than 30 days, and the rats with the increased availability of sucrose gained significantly more weight over this period. Similarly, when rats that had a choice of protein, carbohydrate, and fat from separate cups were given access to one “extra” cup of either carbohydrate or fat, they increased intake of the highly available macronutrient and total caloric intake [98]. In experiments with human subjects eating a meal under laboratory conditions, subjects that were offered the largest portion size consumed 30% more energy regardless of serving method [75]. Doubling an age-appropriate portion of an entrée in children increased entrée and energy intake by increasing bite size [67]. Procurement cost is inversely related to availability of food. High procurement cost can substantially reduce intake in rats [12,13,61].

Palatability may be the single most important nonhomeostatic factor determining food intake. Enhancing the taste and flavor of food, as for example, in high-fat and sucrose-sweetened diets, can elicit further food intake in satiated rats, increase energy intake over the long term, and lead to obesity [87,88,102]. The choice of a variety of palatable foods, also known as cafeteria diet, is a particularly strong stimulator of food consumption in rats [89,94,99]. The power of variety to stimulate further food intake, the dessert phenomenon, has also been demonstrated by experiments looking at sensory-specific satiety in human subjects [76]. In addition, the social context, and conventional mealtime have been shown to influence energy intake in free-living humans [22].

All of these factors have changed dramatically in the modern time food supply over the last few decades. Many modern foods are flavor and color enhanced, high in energy density, easy available, and often cheap. Therefore, the modern environment encourages overeating and there does not seem to be a biological drive to increase voluntary physical activity [46,47]. In the modern world, overconsumption is driving a biological system that has been mainly designed to deal with energy depletion but not energy surplus, and the result is increased prevalence of overweight and obesity. These environmental pressures thus simply overpower the homeostatic regulatory capacity of the biological system. Because many of these environmental factors exert their biological effect mainly by interacting with cognitive, motivational, and emotional functions of the brain, it seems important to study how the cognitive brain talks to the autonomic–homeostatic brain.

4. Neural circuits and pathways relevant for energy balance in the modern world

The neural network controlling food intake and energy balance is hierarchically organized, comprising the brainstem, hypothalamus, and corticolimbic structures as major building blocks (Fig. 2). Circuits in the caudal brainstem are most basic, both in the phylogenetic and ontogenetic sense.

4.1. Direct controls of meal size and autonomic outflow in the brainstem

Caudal brainstem circuits have immediate access to the locomotor and oromotor apparatus enabling approach and ingestion of food. Caudal brainstem circuits talk back and forth to the alimentary canal and other organs involved in energy assimilation, from the taste buds to storage, and they control the organs involved in energy expenditure through the sympathetic nervous system. Thus, the brainstem harbors an impressive array of neurons and circuits directly involved in ingestion, digestion, and absorption of food, as well as in utilization of metabolites and fuels [6]. The brainstem contains the complete basic neural circuitry to
orchestrate ingestion of food and fluid placed into the oral cavity. It also generates most of the parasympathetic support accompanying the ingestive and digestive processes through the vagus nerve, and sympathetic responses related to severe energy depletion. Brainstem circuitry stops ingestion when the taste is aversive, when gastrointestinal feedback signals reach "satiety" levels, or when visceral sensors detect noxious or toxic stimuli. Clearly, ingestive behavior and regulation of energy balance cannot occur without this circuitry.

The neural circuits controlling most of these tasks are contained within the brainstem and do not require the forebrain for their execution [38,39]. Just as for respiration and circulation, other body functions essential for survival, the regulation of nutrient supply is to a large extent autonomically organized within the brainstem.

Based on experiments with the decerebrate rat, it appears that the isolated brainstem can terminate a meal and thus exhibit the basic behavior of satiety [40], but the specific neural pathways necessary for this response have not been identified. However, while intact rats respond to longer term food deprivation with a hyperphagic response, decerebrate rats are not able to increase meal size appropriately [90]. Thus, the brainstem in isolation is not able to respond to a long-term homeostatic challenge.

4.2. Sensing availability of fuels and activation of behavioral, endocrine, and autonomic outflow pathways in the hypothalamus

The role of hypothalamic circuits in the control of food intake and energy balance has been recently summarized in several excellent reviews [48,57,96,104,111], and will be only briefly summarized here.

It is now clear that internal state signals have access to various hypothalamic nuclei through multiple routes, including hormone receptors, metabolite sensors, and afferent neural pathways. It is also clear that such internal state information is further processed within the hypothalamus and then drives pituitary–endocrine and autonomic effectors through relatively well-defined output pathways. Modulation of these processes by behavioral state signals and other motivational systems, such as sleep/wake cycle, pregnancy, lactation via sex steroids, and alertness/stress level via corticosterone, also starts to become clearer.

Some of the key neurons responsive to circulating leptin, insulin, and other hormones are located in the arcuate nucleus of the hypothalamus. One group of neurons coexpressing neuropeptide Y (NPY) and agouti-related protein (AgRP) is activated, and another group of neurons coexpressing proopiomelanocortin (POMC) and cocaine- and

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**Fig. 2.** Neural network participating in modern world energy homeostasis. Schematic diagram of information flow involved in both internal homeostatic and external control of food intake and energy balance. Dotted lines/arrows indicate signaling from the internal milieu or external environment to the brain, either mediated by primary and higher order sensory neurons or hormones and substrates. Full lines/arrows indicate centrifugal signaling from the brain to the effector organs, either mediated by premotor and motor neurons or hormonally. Neural pathways involved in skeletal oro- and locomotor action are indicated by stippled lines. Abbreviations: ACB, nucleus accumbens; AIC, agranular insular cortex; AMY, amygdala; AP, area postrema; ARC, arcuate nucleus; dmX, dorsal motor nucleus of vagus; LH, lateral hypothalamus; HIP, hippocampus; MoN, motor nuclei for oromotor control; NTS, nucleus tractus solitarius; OLF, olfactory bulb; PFC, prefrontal cortex; PIR, piriform cortex; PIT, pituitary gland; POM, preoptic melonocort; PVN, paraventricular nucleus of the hypothalamus; RF, medullary reticular formation; RVL, rostroventrolateral medulla; SNS, sympathetic nervous system; V1/V4, visual processing areas 1,4; V, facial nerve; VII, trigeminal nerve; IX, glossopharyngeal nerve. (Modified after Ref. [6].)
amphetamine-regulated transcript (CART) is inhibited by low levels of leptin. These two groups of neurons have partially overlapping projection fields, with the paraventricular nucleus and perifornical and lateral hypothalamus playing a crucial role in translating the integrated metabolic sensor signal generated into autonomic, endocrine, and behavioral actions [14,15,96,111].

4.3. Acquisition, storage and recall of sensory representations in corticolimbic systems

Ingestive behavior is much more than swallowing food. Particularly the appetitive phase often demands complex cognitive processing. Procurement of food in a restrictive environment could be challenging and the use of higher neural functions was critical for survival. One of the crucial factors for human evolution was the tremendous expansion of the cerebral cortex. It allowed what is usually referred to as higher neural functions, such as cognition, language, planning, consciousness, and emotions, and as a consequence, a completely new way to guarantee and satisfy nutritional needs. In neurological terms, the huge, flexible, and multidimensional computational capability of the cerebral cortex allows primates and even lower vertebrates to generate the most complex sensory representations of nutrients and the nutrient-related environment. A myriad of sensory information pertaining to the physical attributes of potential nutrients, their relationship to the environment (where and how to find), and their physicochemical and neural interaction with the organism is collected through all senses and systematically refined and processed within specialized cortical areas (Fig. 2).

Considerable progress has been made recently in demonstrating cortical processing of food-related stimuli using lesioning techniques in rats, single-cell electrophysiological recording in behaving monkeys, and noninvasive functional magnetic resonance imaging (fMRI) in humans. These studies all point to a neural network, including the gustatory, visceral, olfactory, prefrontal, and orbitofrontal areas, as well as the amygdala and the hippocampal complex.

In the freely behaving monkey, single neurons have been identified in the orbitofrontal cortex encoding specific polymodal sensory representations of food and food-related stimuli [77,79,80,101]. Furthermore, taste-sensitive neurons in the orbitofrontal cortex can decrease firing rate to a particular taste targeted for devaluation, but keep firing to a closely related taste not targeted for devaluation [79]. Corresponding areas in the human orbitofrontal cortex show specific changes in neural activity in response to pleasant and aversive taste and odor stimuli [18–20,65,78] in a sensory-specific manner [66], and the degree of activation is correlated with its subjective pleasantness [56].

Furthermore, fMRI in humans identified small areas of the amygdala, insular, piriform, and orbitofrontal cortex in response to visual conditioned stimuli as part of learning a picture (CS)—odor (UCS) contingency in the food-deprived state [37]. Following devaluation of the odor by eating a satiating meal representing that odor, neural activity in the amygdala and orbitofrontal cortex decreased in parallel to decreased hunger level and pleasantness rating for the devalued odor. However, neural activity in these same areas did not change in response to another visual CS signaling another odor that was not devalued [37]. Neural activity in small parts of the ventral striatum and the insular and cingulate cortex changed in the opposite direction in response to the CS that indicated the nondevalued odor, suggesting a contrast effect reminiscent of the fact that a sweet dessert becomes more desirable after eating a steak [37]. Using lesions in rats, it was further shown that such encoding of predicted outcome and acquired value in the orbitofrontal cortex requires an intact basolateral amygdala [85].

These studies clearly show that a corticolimbic neural network is involved in learning and maintaining representations of predictive food-related reward. It is also clear that these brain areas are sensitive to metabolic status signals in a sensory-specific manner, but it is not clear how these signals are mediated. Assuming that the signal is generated by the metabolic sensors in the hypothalamus, the signal must be mediated by direct or indirect inputs from the hypothalamus. It has long been recognized that the entire cortical mantle receives significant inputs from the hypothalamus, particularly the lateral hypothalamus with its orexin/dynorphin, melanin-concentrating hormone (MCH), CART, and histamine-expressing neuron populations (Fig. 3). All the feeding-relevant areas in the cortex and limbic system as outlined above receive input from the hypothalamus, but the anatomical and neurochemical details and the type of information transmitted by these projections have not been explored. In addition to these direct hypothalamo—cortical inputs, there are a number of indirect projections, including those to the well-known noradrenergic, serotonergic, cholinergic, and dopaminergic systems in specific midbrain nuclei that in turn innervate the entire cortical mantle in a diffusible manner (Fig. 4). These systems are thought to be important in processes of arousal, attention, and behavioral selection, but their specific involvement in ingestive behavior is not well understood.

In addition to input from hypothalamic sensors of fuel availability, the corticolimbic areas are very likely to receive input from the gastrointestinal tract via the vagus nerve and nucleus of the solitary tract. Direct inputs from the NTS to the amygdala and insular cortex, and indirect connections via parabrachial region and midbrain arousal systems are well known. The observation that various stress-related diseases are associated with impaired functions in sensory vagal fibers and that vagal afferent stimulation hyperpolarizes cortical neurons and suppresses epileptic seizures has led to the suggestion that the “gut feeling” may be a sixth sense mediated by the vagus nerve [108].
Fig. 3. Efferent projections and afferent inputs of neuronal populations within the lateral hypothalamus. Note that not each neuronal group or population in the lateral hypothalamic area necessarily exhibits the complete projection and input pattern shown. Efferent projections are mainly based on retrograde tracing from respective targets as described by Simerly [92] and others and on more recent studies demonstrating the distribution of the “selective” lateral hypothalamic marker peptides orexin and MCH. Afferents are based on anterograde and retrograde tracing, and are thus less reliable, because of the problem with axons of passage (medial forebrain bundle) in the lateral hypothalamus. Bifurcations do not necessarily imply axon collaterals. Abbreviations: Acb, nucleus accumbens; ARC, arcuate nucleus; DMN, dorsomedial nucleus; DMV, dorsal motor nucleus of vagus; LC, locus coeruleus; MLR, midbrain locomotor region; NTS, nucleus tractus solitarius; PAG, periaqueductal gray; PBN, parabrachial nucleus; PVN, paraventricular nucleus hypothalamus; Sens. CTX, sensory cortex; SNC, substantia nigra pars compacta; Thal, thalamus; VMN, ventromedial nucleus; VTA, ventral tegmental area. (Modified after Ref. [7].)

Fig. 4. Cortical inputs to hypothalamic nuclei involved in the control of food intake and energy balance. Major inputs to the hypothalamus originate in the medial prefrontal, insular and olfactory cortices, the central and medial amygdala, and the entorhinal cortex and subiculum of the hippocampal complex. The lateral hypothalamus projects back to all of the cortical areas via direct orexin (ORX), MCH, and histaminergic (Hist) projections, and indirectly, via the mesocortical dopamine system (DA) and the noradrenergic (NA), serotonergic (5-HT), and cholinergic (ACh) “arousal and attention” systems with various involvement of certain thalamic nuclei. Note that all depicted cortical areas are also directly interconnected. Abbreviations: ARC, arcuate nucleus; BL, Ce, and Me, basolateral, central, and medial nuclei of amygdala; DG, dentate gyrus of hippocampus; DMH, dorsomedial hypothalamus; LC, locus coeruleus; LHA, lateral hypothalamic area; NTS, solitary nucleus; MPOA, medial preoptic area; Pa, paraventricular nucleus; PBN, parabrachial nucleus; PPT, pedunculopontine tegmental area; RF, reticular formation; SubPa, subparaventricular nucleus of hypothalamus; Tu mam, tuberal mammillary nucleus; VMN, ventromedial nucleus; VTA, ventral tegmental area. (Modified after Ref. [7].)
4.4. Food as a reward: learning, liking and wanting

Palatability and pleasantness are arguably the most powerful determinants of food intake. Experiencing or feeling pleasure is regarded as one of the human emotions that has been difficult to define both in psychological and neurological terms. Most researchers agree that emotions evolved from mechanisms that made animals engage in behaviors with a beneficial outcome [11]. Specifically applied to food intake, the positive emotion or pleasure of tasting sweet (sugars and certain amino acids) or creamy (fat-rich) foods may have evolved to guarantee sufficient intake of varied foods and high-energy foods [54]. Although we can follow gustatory processing from the brainstem through the secondary taste area in the insular cortex to a tertiary taste area in the orbitofrontal cortex, it is not well understood how the unconditioned or predicted reward value of pleasurable taste and flavor guides ingestive behavior. Berridge and Robinson [4] have outlined the potential psychological components that constitute reward into learning, liking, and wanting. The task of the neuroscientist will be to identify the underlying neurological substrates for each of these processes.

4.4.1. Learning

The basic components of sweet and bitter tastes are recognized at the level of the brainstem as demonstrated by typical orofacial expressions accompanying acceptance or rejection in anencephalic infants and decerebrate rats [41,97]. As these responses are already present in newborn human infants, no learning is necessary for their expression. However, later in life, most rewarding stimuli, such as specific tastes and flavors, have a learning component resulting in explicit and implicit knowledge through associative conditioning and cognitive processing [4]. As discussed above, such sensory representations are processed, stored, and recalled in specific areas of the cortex. Although not necessary for learning the basic Pavlovian association between a CS (e.g., a light) and a US (e.g., food availability), the basolateral amygdala is important for storing associations which allow the CS to retrieve the affective/emotional value of its particular US, a form of stimulus–outcome association [11]. Thus, if the particular food item was devalued, for example, by LiCl poisoning, the original light CS still elicits the same response (approach to the food cup) in rats with basolateral amygdala lesions [43]. The central nucleus of the amygdala (CeA) is not necessary for this retrieval, but it organizes the emotional experience through its direct connections to brainstem behavioral effectors and arousal systems (Fig. 5).

4.4.2. Liking

The characteristic orofacial expressions displayed by decerebrate rats [41] and anencephalic infants [97] in response to sweet taste strongly suggest that the forebrain is not necessary to experience the hedonic impact or liking of pleasant stimuli. Berridge and Robinson [4] refer to these expressions as objective affective reactions or implicit affect, and to the psychological process as ‘core hedonic impact’ or ‘liking.’ To distinguish this process from the conscious subjective experience of pleasure, they call it the human unconscious liking [4]. Because injection of benzodiazepine into the fourth ventricle [68] and directly into the parabrachial nucleus [45,93] enhanced positive affective reactions to sweet taste, the parabrachial complex in the rostral brainstem fulfills the criteria for mediation of core liking. In addition, circuits, including the NTS and reticular formation in the caudal medulla, are likely part of this brainstem system.

The other key components of the distributed core liking system are the nucleus accumbens and ventral pallidum (Fig. 5), with the μ-opioid receptor playing a crucial role. Local injection of the selective μ-opioid agonist DAMGO into the nucleus accumbens elicits voracious food intake, particularly of palatable sweet or high-fat foods [54,103,109]. This increased consumption of highly palatable foods appears to be due to increased liking, as morphine microinjections into this area increased the number of positive affective reactions [69], and microinjection of a selective μ-opioid antagonist reduced sucrose drinking [55]. Based on the resulting c-Fos plumes, the most sensitive area for this effect was the caudal shell of the nucleus accumbens, near the border with the adjacent core [69]. Contrary to the long held view, the mesolimbic dopamine system does not play any role in the affect or core liking of pleasurable stimuli (see below).

Berridge and Robinson [4] also suggested that neurons in the ventral pallidum are a necessary cause for positive affective reactions to sensory pleasure, because excitotoxic lesions in this area caused rats to respond to a sweet taste with aversion [16], and stimulation in humans induced bouts of affective mania [59]. As the ventral pallidum has strong direct reciprocal connections with the nucleus accumbens shell (and core) and descending projections to the hypothalamus, ventral tegmental area, pedunculopontine tegmental area, parabrachial complex, and dorsal vagal complex, as well as ascending projections via the mediiodorsal thalamus to the gustatory and orbitofrontal cortex, it may be in a central position to organize both the emotional reactions and conscious feelings associated with pleasurable sensations. To consciously experience and give subjective ratings of pleasure, areas in the prefrontal and cingulate cortex are thought to be necessary.

4.4.3. Wanting and working for food

The third fundamental and independent psychological process involved in reward is motivation, incentive salience, or ‘wanting,’ as termed by Berridge and Robinson [3,4]. Although liking a food is typically followed by wanting and eating it, wanting is a dissociable process that has a distinct underlying neural substrate. It grew mainly out of research on drug addiction, where stimuli that are often no longer ‘liked’ are still intensely ‘wanted.’ Just as learning and liking do, motivation has a conscious or explicit and an
unconscious or implicit aspect. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens (part of the mesolimbic dopamine system) are the most crucial component of the implicit or unconscious wanting system [17,52,107] (Fig. 5). Manipulation of this dopamine system powerfully influences wanting (instrumental performance for and consumption of) drugs or food, but not liking [4,10,70,106]. As stated by Berridge and Robinson [4], “wanting or incentive salience is a motivational, rather than an affective, component of reward. Its attribution transforms mere sensory information about rewards and their cues (sights, sounds and smells) into attractive, desired, riveting incentives” (p. 510).

The lateral hypothalamus is also involved in wanting as electrical stimulation of this area induces rats to vigorously self-stimulate and eat (want) food, although it does not make them like the food more [5].

4.5. Planning and execution of actions in the prefrontal cortex

In return, the corticolimbic structures involved in food intake also have strong projections to various hypothalamic areas, including the lateral hypothalamus, the arcuate, paraventricular, and dorsomedial nuclei [23,83,92], suggesting that some of them might be involved in the control of food intake (Fig. 4). As few details are known about these projections, a considerable task lies ahead to identify the exact connectivity and neurochemistry of feeding-relevant pathways. In a recent report, it was found that a Pavlovian conditioned stimulus predicting food while hungry significantly increased food intake in the satiated state, and that disconnection of amygdalo–lateral hypothalamic circuitry selectively abolished this response [71]. This suggests that such “descending” pathways may allow learned cues to interfere with the hypothalamic mechanisms signaling fuel sufficiency and thus to override satiety and promote eating. One of the mechanisms in the lateral hypothalamus targeted by such overriding input from cognitive processes might be melanocortin signaling, as learned meal initiation attenuates the anorexic effects of the melanocortin agonist MTII in rats [2].

4.6. Interactions between metabolic and nonmetabolic signals

Particularly in humans, the initiation of a meal often starts as a purely cognitive/executive decision from the cortex, in the absence of any depletion signal. Thus, even in the presence of satiety and replete energy stores, it
appears to be easy for the cortex and limbic system to overpower the hypothalamus into an ingestive mode, just as it is easy for the hypothalamus to overpower the cortex under severe depletion conditions, notwithstanding pathological conditions of anorexia.

There is evidence that metabolic and nonmetabolic signals are integrated within the nucleus accumbens, or within an extended loop also including the amygdala, frontal cortex, and ventral tegmental area. This is supported by recent findings, showing that conditioned place preference is modulated by nutritional state [31]. This modulation could result from hypothalamo–accumbens projections or through insulin and leptin receptors on neurons of the mesolimbic dopamine system gating accumbens function [31]. The integrated signal is then entering the behavioral selection pathways in the striatum and motor system as originally suggested by Mogenson. With respect to the extended loop, it is important to note that the activity of single neurons in the macaque orbitofrontal cortex activated by tasting sugar or fat is also modulated by the short-term nutritional state in a satiety-specific manner [37,79].

There is also evidence that integration of metabolic and nonmetabolic signals takes place in the hypothalamus, more specifically the lateral hypothalamus. Support for this view comes from the self-stimulation literature and the fact that the medial hypothalamic metabolic sensors directly connect to the lateral hypothalamus [26]. While self-stimulation behavior elicited by electrical stimulation within the lateral hypothalamus is considered to be rewarding and thresholds for LH self-stimulation can be lowered by food deprivation and elevated by ICV leptin [35,91], NPY does not seem to be involved in this modulation. Furthermore, food intake elicited by accumbens manipulation could be blocked by infusion of the GABA agonist muscimol [58], and Fos-expression was increased in hypothalamic neurons expressing orexigenic peptides orexin and NPY and decreased in neurons coexpressing the anorexigenic peptides α-MSH/CART [110]. It is not clear how feeding behavior is organized from the integrated signal in the lateral hypothalamus, but it is likely to involve the striatum. Thus, the flow of information might be looping from the accumbens to the hypothalamus and back to the accumbens.

Most likely, however, integration takes place in a more distributed network of reciprocally connected key areas, including the nucleus accumbens, hypothalamus, prefrontal cortex, amygdala, and areas in the brainstem [7] (Fig. 5). This is supported by the recent observation that GABA(A) agonism (inhibition) at several of these areas completely inhibited the robust feeding response following accumbens manipulation with the μ-opioid agonist DAMGO [103].

5. Conclusions

Besides the well-studied homeostatic regulatory system with its main components in the medial hypothalamus and caudal brainstem, there is an extensive other neural network involved in the control of ingestive behavior and ultimately also in energy balance. This corticolimbic system deals mainly with the cognitive, motivational, and emotional aspects of ingestive behavior and represents the main interface with environmental factors and stimuli. Because a changed lifestyle in the modern environment is clearly the primary cause of the current obesity epidemic, the brain systems processing these nonhomeostatic aspects of ingestive behavior are likely to play a crucial role in the development of obesity. With the focus on leptin and its targets in the hypothalamus, this other system has received much less attention.

It will be important to study the connectivity and neurochemistry of the relevant circuits within the corticolimbic structures and the pathways that connect these circuits with the homeostatic regulatory circuits in the hypothalamus and brainstem. Besides the mainly behavioral, anatomical, and functional neuroimaging approaches that are currently used, electrophysiological as well as genomic and proteomic approaches should be added. These studies will likely result in identifying new signaling systems and/or the specific mode and site of action of known signaling systems that could be the basis for new drug treatments for obesity and diabetes. It will also be important to study the kind of information that is exchanged between individual nuclei of the hypothalamus and the various corticolimbic forebrain players during different stages of ingestive behavior and under different internal and environmental conditions.

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