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An expanded view of energy homeostasis: Neural integration of metabolic, cognitive, and emotional drives to eat

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Abstract

The traditional view of neural regulation of body energy homeostasis focuses on internal feedback signals integrated in the hypothalamus and brainstem and in turn leading to balanced activation of behavioral, autonomic, and endocrine effector pathways leading to changes in food intake and energy expenditure. Recent observations have demonstrated that many of these internal signals encoding energy status have much wider effects on the brain, particularly sensory and cortico-limbic systems that process information from the outside world by detecting and interpreting food cues, forming, storing, and recalling representations of experience with food, and assigning hedonic and motivational value to conditioned and unconditioned food stimuli. Thus, part of the metabolic feedback from the internal milieu regulates food intake and energy balance by acting on extrahypothalamic structures, leading to an expanded view of neural control of energy homeostasis taking into account the need to adapt to changing conditions in the environment. The realization that metabolic signals act directly on these non-traditional targets of body energy homeostasis brings opportunities for novel drug targets for the fight against obesity and eating disorders.

Keywords

appetite; obesity; hypothalamus; food reward; food hedonics; motivation; gut hormones

1. Introduction

Given the commercialization of the food supply in the modern world, it has become increasingly difficult to make adequate qualitative and quantitative nutritional choices, and for a large segment of the population, the economically most feasible choices are energy dense foods with inadequate nutritional value. Combined with sedentary behavior, these poor nutritional choices are the main causes of the obesity pandemic, with no clear concepts for prevention or treatment in sight. Major research efforts are underway to make changes to the toxic environment, educate vulnerable populations to healthier lifestyles, and find potential drug targets by understanding how energy balance is biologically regulated. Regarding the latter, early discoveries around the mid 20th century pointed strongly to the hypothalamus as the key area for the physiological controls of appetite and energy balance, and this view was

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initially enforced by the discovery of leptin. Since then, an impressive amount of knowledge has accumulated concerning these hypothalamic neural pathways and signaling mechanisms, typically referred to as the homeostatic regulator of body energy balance. However, it was also realized that the controls of appetite are not limited to the hypothalamus, but engage most other parts of the brain, in particular the caudal brainstem, the senses, and cortico-limbic systems. This led to the distinction between homeostatic and non-homeostatic controls of appetite and body weight regulation. Here we argue that this distinction may have been premature, as the latest insights from animal experiments and human functional neuroimaging studies suggest that the systems interact intimately to serve one overarching purpose – to maintain an optimal internal millieu in harmony with the external world.

2. Traditional view of homeostatic controls and their neural representation

Adult body weight is remarkably constant

In a given environment, body weight is kept remarkably constant during most of adult human life in spite of a large total calorie turnover. A cumulative error in the adjustment of food intake to energy expenditure of only 1%, or about 20 kcal/day, would lead to a body weight gain of about 1 kg/year, or >50 kg over the adult lifespan. That a majority of the population keeps body weight gain well within these limits suggests the existence of active regulation or defense. This is further demonstrated by the fact that weight loss and weight gain induced by under- and over-feeding are rapidly corrected by compensatory increases and decreases of calorie intake, respectively, in both rodents and humans [1–5].

Regulation of target body weight: sliding set point

The body weight set point theory suggests that, like temperature in a room regulated by a thermostat, body weight (or body fat) is regulated by a device in the brain, which compares actual values of the regulated parameter with a reference value and makes adjustments by controlling energy intake and/or energy expenditure. The existence and layout of an adipostat has been hotly debated ever since its inception [6], with one camp quite literally applying the “thermostat principle” to body energy balance regulation, with a specified regulated parameter and a reference value as set point [7–12], and another camp, realizing that body energy fluxes are much more complex, so that the combined regulation of many parameters achieves equilibrium at a preferred body weight/adiposity level (settling point), merely giving the impression of a set point regulation [13–17]. At the neurological level, one camp reduced the “regulator” to a circuit of two types of leptin-sensitive neurons in the arcuate nucleus of the hypothalamus [18–20], and the other camp suggested it to be a widely distributed system [21,22]. However, there is general agreement that the system consists of three basic components, (1) a nutrient sensing system providing feedback for the regulated parameters, (2) an integrator making sense of all the internal signals in a given environment, and (3) behavioral, autonomic, and endocrine effector pathways leading to changes in energy intake, efficiency, and expenditure. These components of the traditionally-called homeostatic regulator of body weight/adiposity are briefly summarized before we will examine their relationship with the so-called non-homeostatic systems.

Feedback signals

Different components of ingested foods interact with mechano- and chemo-sensors all along the alimentary canal that send neural signals via sensory nerves and/or hormonal signals via the bloodstream to the brain [for a detailed review see [23]]. Once absorbed, macronutrients and their metabolites are partitioned into either storage or immediate metabolism in various tissues, including the brain. Important nutrient sensors with vagal afferent connections to the brain are located in the hepatic portal vein, as it collects all the hormones and metabolites from the gut [24,25]. The pancreas plays a special role in that circulating fuels and certain

gastrointestinal hormones, the incretins, determine the release of the pancreatic hormones insulin, glucagon, amylin, and pancreatic polypeptide, all signaling to brain [26–28]. Similarly, adipose tissue is another key organ sending hormonal signals to the brain and other organs [29], although the stimuli and mechanisms determining the release of leptin, adiponectin, resistin, and other adipose tissue derived cytokines are less clear. It is also likely that the other major metabolically active tissues, muscle and liver, produce hormonal signals used for energy balance regulation and these are just starting to be explored [30,31].

Neural integration

Clearly, the hypothalamus is the most crucial player in the control of food intake and energy balance. The arcuate nucleus in particular, is a major hub for integrating nutritionally relevant information originating from all peripheral organs and mediated through circulating hormones and metabolites and/or neural pathways mainly from the brainstem. Nutritional information is then further integrated with other important information from the internal and external world, such as the diurnal clock and the presence of predators. Nutritional information also competes with other motivated behaviors such as thermoregulatory, fluid homeostatic, reproductive, and aggressive/defensive behaviors represented in the hypothalamus. Finally, the resulting optimal adaptive responses chosen are executed through behavioral, autonomic, and endocrine output pathways. Some of the key neuronal populations have been identified in the arcuate nucleus and much of the molecular mechanisms of intracellular integration of various hormonal and nutrient signals are currently under intensive investigation. The neuroanatomical layout [32, 33], molecular machinery [34,35], and genes (Lenard and Berthoud, 2008, in press) constituting the hypothalamic energy balance regulator have been reviewed extensively in the past, and here we will draw attention to only a few important unsolved questions.

If we accept that body energy homeostasis is achieved by regulating not one single, but a number of parameters whose combined equilibria determine a settling point, the question arises: what are the critical parameters and what are their feedback signals? As the name implies, at least two adiposity signals, leptin and insulin, have been proposed to track fat mass [18,36], with the important corollary that only long-term averages of circulating but not acute levels of these hormones reliably track fat mass [17]. However, besides these two key hormones, many other hormones and metabolites representing metabolism of the three macronutrients (see above) provide additional important information regarding fuel storage, mobilization, and oxidation in many metabolically active organs. For each of these signals, it will have to be demonstrated (1) what metabolic parameter it represents, (2) with what other signal(s) it cooperates or competes on a neuronal level, and (3) where in the neural hierarchy described below it acts.

To accommodate the fact that body weight/adiposity is regulated at different levels under different environmental conditions, it is now generally agreed that the regulator has no fixed set point or reference value. However, the conditions necessary and sufficient to induce a change in settling point and the neurological/molecular mechanism(s) involved are not known. It appears that exposure to high-energy diet is sufficient for a portion of animals and humans to gain fat mass and regulate at a progressively higher set point.

Effector pathways

The homeostatic regulator in the hypothalamus and brainstem has three effector arms available to influence energy balance, behavior, autonomic, and endocrine outflow. Besides the arcuate nucleus, the paraventricular nucleus of the hypothalamus and lateral hypothalamus serve as major integration and output hubs. Neurons within the LHA/perifornical area contain several food regulatory neuropeptides (hypocretin/orexin, melanin concentrating hormone, neurotensin, and histamine), and many of these neurons receive direct input from ARC NPY/

AgRP and POMC neurons. In addition to metabolic information from the mediobasal hypothalamus, the LHA also receives information from brain areas associated with (1) reward, motivation, learning and memory (orbitofrontal cortex, nucleus accumbens, amygdala, ventral tegmental area), (2) from areas associated with sensory input (insular and olfactory cortex) and (3) from brainstem areas associated with vagal and visceral sensory input, sensory motor coordination, and arousal (NTS, parabrachial nucleus, locus coeruleus). In turn, the LHA projects widely through the entire brain, from cortex to spinal cord [21]. Consequently, information processed within the LHA has the capacity to impact nearly every neural activity.

The paraventricular nucleus of the hypothalamus is another key downstream structure receiving integrated metabolic information generated in the arcuate nucleus. The paraventricular nucleus is classically associated with neuroendocrine function via the hypothalamic pituitary axis, as well as regulation of both arms of the autonomic nervous system. For example arcuate NPY/AGRP and POMC/CART neurons coordinately control thyrotropin releasing hormone (TRH)-expressing neurons in the PVH which in turn control the thyroid axis, an important modulator of overall metabolic efficiency [37].

In contrast to the central organization of autonomic and endocrine outflow, our understanding of the neural pathways leading to ingestive behavior is much less clear, because behavioral activation typically requires more or less involvement of extrahypothalamic structures. Although there are some evolutionarily conserved pathways linking hypothalamus directly to brainstem and spinal cord responsible for fight and flight and primitive ingestive behaviors, an eating episode in humans typically engages the limbic system, thalamus, and cortex, with their complex loops and interactions. This makes it extremely difficult to point to the exact path of neural signaling for a given eating episode. Some of these extrahypothalamic pathways involved in the typical expression of ingestive behavior are introduced in the next section.

3. Neural systems and mechanisms termed “non-homeostatic”

Food reward: the basic drive to eat

It is thought that emotions evolved as a mechanism to reinforce beneficial and suppress potentially harmful stimuli and behaviors. For example, the sweet taste of certain foods is associated with positive emotions that augment the motivational drive to obtain such foods – in brief, it is said to be rewarding. The reward value of a particular food is bundled with other attributes into stored representations. Thus, life is all about learning how specific behavioral responses or actions lead to positive emotions or reward in the future.

That food is more rewarding in the hungry compared to the satiated state is a well known fact [38–41], but the underlying neural mechanisms are far from being clearly understood. The main reason for this is that although several specific brain areas have been implicated in the reward process, we still have no clear understanding of how these areas work together and how they are embedded in overall behavioral control. The traditional view of homeostatic regulation originating from centers in the hypothalamus assumed that the attribution of incentive value happened within this area, specifically in the lateral hypothalamus. Eating elicited by electrical stimulation of the lateral hypothalamus was shown to be modulated by metabolic signals such as leptin, insulin, cytoglucopeonia, and gastric fill [42–44]. However, the mechanisms by which these disparate metabolic signals modulate lateral hypothalamic activity was not revealed by these studies. Because NPY/AGRP and POMC/CART neurons in the arcuate nucleus are thought to provide an integrated readout of many internal metabolic state signals, output from this area to the lateral hypothalamus may be important. However, in a direct test of this hypothesis, locally administered NPY was unable to change LH eating thresholds [45]. However, it is possible that arcuate nucleus nutrient sensor output is affecting the LH via melanocortin (α-MSH, AGRP) and/or CART signaling.

The 'Motivator' (Matching objects to internal values triggers option reevaluations) model suggests that attribution of value occurs in nutrient-sensitive lateral hypothalamic neurons [46]. LH neurons are excited by both deprivation and the taste of a particular metabolite such as glucose and specific amino acids [47–51] and some of them project to the amygdala, orbitofrontal cortex, and ventral striatum [46]. By responding the same way to the taste of a specific metabolite and the conditioned stimuli that predict it in a deprivation-dependent manner, the LH-amygdala circuitry would thus be able to compute the net subjective outcome associated with a consummatory act [46].

During the last two decades, great progress has been made in identifying the neural pathways and mechanisms involved in reward behavior. Specifically, it has been proposed that reward can be parsed into liking, wanting, and learning, each representing separate but interlinked psychological processes with at least partially distinguishable underlying neurological substrates [52–56]. Together with the advent of functional neuroimaging in humans and an explosion of research on the mechanisms of drug addiction, a general working blueprint for a new functional anatomy of reward has emerged. Like all behavioral control systems, reward has sensory, integrative, and motor components, and as for most systems, the least understood is the integrative component.

Recent studies have demonstrated that metabolic state signals can modulate many brain areas involved in the processing of external food cues and reward functions, including the sensory input channels of most modalities, polymodal association cortices such as the orbitofrontal cortex, the hippocampal complex, the mesolimbic dopamine system, nucleus accumbens (ventral striatum), dorsal striatum, and prefrontal cortex. These areas are all involved in using reward to guide behavior. Thus, it appears that attribution of value may not be limited to the hypothalamus, but can occur at every level of processing from sensory input to motor output.

Metabolic signals modulate sensory processing and integration

Metabolic state signals can modulate the various steps of processing food-relevant sensory stimuli, from primary afferents to multimodal association cortex. For example, leptin can modulate detection thresholds of olfactory and gustatory stimuli [57–59]. Remarkably, leptin-(ob/ob) and leptin receptor-deficient (db/db) mice can smell and find buried food ten times faster than wildtype mice, a phenomenon readily reversed in ob/ob mice by leptin administration [59]. Because leptin receptors are expressed on taste receptor and olfactory mucosal cells, modulation can occur at the earliest sensory processing steps [59,60]. Leptin action at progressively higher processing steps for both modalities is indicated by presence of leptin receptors and leptin-induced Fos expression in the nucleus of the solitary tract, parabrachial nucleus, olfactory bulb, and insular and piriform cortices of rodents [61–65].

Electrophysiological studies in behaving monkeys have revealed individual neurons in the orbitofrontal cortex and amygdala that are responsive to the taste of specific nutrients such as glucose, amino acids, and fat, as well as texture of foods and the burning sensation of pepper [66–68]. The response magnitude of these neurons is modulated by hunger in a sensory specific manner [69].

The functional magnetic resonance imaging (fMRI) response to olfactory, gustatory, and visual food stimuli is now widely used to demonstrate human brain function as modulated by the metabolic state in lean and obese women and men. It was shown that taste-induced changes in neuronal activity occurred within several areas of the human insular and orbitofrontal cortex and preferentially in the right hemisphere [70], and that taste and olfactory inputs converge within areas of the orbitofrontal cortex to provide representations of flavor [71].

Comparing the food-deprived vs. satiated state, it was found that food deprivation increased activity of visual (occipito-temporal cortex) and gustatory (insular cortex) sensory processing areas by the sight and taste of food, respectively [72]. In another study, pictures of food with high hedonic value that elicited strong activation of visual and premotor cortex, hippocampus, and hypothalamus under eucaloric conditions, elicited much weaker responses after 2 days of overfeeding [73]. In a recent study exploring the functional neurological consequences of dieting in obese humans, it was found that after a diet-induced 10% body weight loss, the response to visual food cues was significantly enhanced in several brain areas dealing with higher-order sensory perception and working memory formation, including an area in the middle temporal gyrus involved in higher-order visual processing [74]. Both of these responses were reversed after leptin treatment, suggesting that low leptin sensitizes brain areas responding to food cues.

Ghrelin, so far the only gut hormone found to stimulate appetite and food intake, profoundly changes neural activity induced by visual food cues in a number of cortico-limbic brain areas as measured by fMRI in human subjects [75]. Specifically, intravenous ghrelin administration increased the response to food pictures in the left pulvinar, fusiform, and occipital gyrus, areas involved in visual processing, attention, and memory [75,76].

It thus appears that signals reflecting energy status can modulate the sensitivity of both exteroceptive and interoceptive mechanisms participating in the control of appetitive and consummatory behaviors. In particular, low energy status enhances sensitivity of the visual and olfactory systems to detect and interpret external cues indicating impending feeding opportunities.

Metabolic signals modulate mechanisms of learning and spatial orientation important for foraging behavior

We remember past experiences with foods, particularly if the experience was out of the ordinary. Experiences that evoked either extreme pleasure or complete disgust generate the most salient memories. Thus, we remember the restaurant and everything in and around it very well, where we had that extraordinary dish, and we remember even an average dish when we fell in love at that occasion. On the other hand, we immediately recognize and avoid a food that made us sick. A growing number of studies suggest that representations of experience with foods are generated in the orbitofrontal cortex, an area in the prefrontal cortex that receives converging information through all sensory modalities[77]. Therefore, representations contain a number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, social context, cost, and reward expectation [77,78].

It is not clear how and where exactly such representations are stored. The orbitofrontal cortex is in intimate contact with other cortical areas, particularly the anterior cingulate, perirhinal and entorhinal cortices, as well as with the hippocampal formation and the amygdala, often collectively referred to as paralimbic cortex [for review see [77]]. It is within these areas that polymodal representations are thought to be available as working memory for constant updating. Recent findings suggest that the hippocampus encodes episodic memories comprising not just spatial information where the episode occurred, but contextual information such as time of occurrence and any other details [79–81].

Ghrelin receptors are highly expressed throughout the rodent hippocampus [82], and peripheral ghrelin passively crosses the blood-brain barrier [83]. In slice preparations, ghrelin significantly enhanced long term potentiation (LTP) in hippocampal neurons, and systemic ghrelin administration enhanced performance in the elevated plus maze [82]. Wildtype mice readily learned to recognize novel objects while ghrelin-deficient mice learned the novel object recognition task only after ghrelin replacement [82]. The possible underlying mechanism for

these electrophysiological and behavioral changes is ghrelin-induced increased spine synapse density in the stratum radiatum of the CA1 subfield [82]. In other studies, ghrelin administered directly to the hippocampus increased food intake and memory retention [84], and systemic ghrelin administration rescued decreased memory for novel objects induced by chronic food restriction in mice [85], and increased foraging behavior in Siberian hamsters [86].

There is a considerable literature also demonstrating memory-enhancing effects of leptin and memory deficits in leptin signaling-deficient mouse and rat models [87–89]. It is not clear why ghrelin and leptin, two signals with opposing effects on appetite and energy balance, should have similar effects on memory. One possible explanation is specificity in memory enhancing effects, with ghrelin enhancing memory functions selectively used for foraging behavior, while leptin enhancing those for reproductive behaviors.

Neuroimaging (fMRI) studies in humans also report effects of ghrelin on hippocampal activity. One recent study found strong enhancement by ghrelin administration of hippocampal activity induced by visual food cues[75]. Because similar findings were reported earlier in food-deprived subjects, and ghrelin levels are elevated after food deprivation, it is possible that ghrelin is the interoceptive depletion signal modulating formation and recall of spatial memories in the hippocampus elicited by relevant visual cues [90,91]. Such an interpretation is further supported by a report in humans that ghrelin administration elicited a vivid, plastic image of their preferred meal [92].

Metabolic signals modulate hedonic evaluation ('liking')

In its most primitive form of expression, the hedonic value or 'liking' of a food stimulus is the characteristic "happy face" expressed by rodents, monkeys, and humans when tasting sweets. Current knowledge suggests that liking is neurologically organized by a widely distributed system with the mu-opioid and perhaps the cannabinoid receptor systems playing common denominators [93,94]. In animals, only the subconscious components of pleasure and aversion (also termed core 'liking') are experimentally accessible, and one of the few specific test paradigms is measurement of tongue protrusions and orofacial expressions when tasting pleasurable (typically sweet) or aversive stimuli [95]. Because the "happy face" is observed in decerebrate rats and anencephalic human infants, neural circuits in the hindbrain appear to be sufficient for the basic (subconscious) expression of liking [96,97]. In addition, areas in the ventral striatum (nucleus accumbens and ventral pallidum) and the amygdala are undoubtedly part of this distributed neural network of liking. To consciously experience and give subjective ratings of pleasure from palatable foods (liking), humans appear to also use areas in the prefrontal and cingulate cortex [98].

In rats, it was shown that the number of positive hedonic reactions to sucrose was reduced by caloric satiety and sensory-specific satiety, but enhanced by 48h of food deprivation [99]. Because affective taste reactivity is also observed in decerebrate rats, its basic mechanism is thought to reside within brainstem structures such as the nucleus of the solitary tract and the parabrachial nucleus [96].

Hedonic hotspots (anatomical sites that yield increased 'liking' when chemically activated) have also been identified in the nucleus accumbens shell and ventral pallidum of rats [100, 101]. Little is known about modulation of activity in these hot spots by metabolic signals. In one study, direct nucleus accumbens shell administration of amylin, the satiety hormone co-secreted with insulin from pancreatic beta cells, suppressed food intake and locomotor activity in food-deprived rats [102]. In sodium-depleted rats, neurons in the ventral pallidal hotspot are as vigorously activated by an intensely salty taste as they are by sweetness, and while such high-salt concentrations are normally 'disliked', they are suddenly 'liked' [103].

Results from human neuroimaging studies suggest strong modulation of areas involved in reward processing by nutritional depletion and repletion signals. Neural activity in the nucleus accumbens elicited by visual food stimuli is very high in genetically leptin-deficient adolescents and promptly returns to normal levels upon leptin administration [104]. In the leptin-deficient state, nucleus accumbens activation was positively correlated with ratings of liking for the food images in both the fasted and fed state - even bland foods were highly rated in the satiated state. After leptin treatment and in normal subjects nucleus accumbens activation was only correlated with ratings of liking in the fasted state [104].

Humans can subjectively experience pleasure and disgust. It has been suggested that conscious pleasure feelings are generated from core 'liking' reactions by additional cognitive brain mechanisms that underlie subjective awareness [54]. From neuroimaging studies in humans, it appears that parts of the orbitofrontal cortex are an important key node of pleasure representation and may be involved in the generation of subjective awareness [54]. Subjective pleasantness in humans was coded by neural activity in the medial orbitofrontal cortex and was subject to sensory-specific satiety, a form of reinforcer devaluation [71,105–107]. This cortical area appears to be equivalent to the area showing sensory-specific satiety at the single neuron level in behaving monkeys discussed above [69].

Thus, it is quite clear that processes of subconscious hedonic evaluation and subjective experience of pleasantness in animals and humans are modulated by the internal state. However, except for the possible role of amylin in rats and leptin in genetically leptin-deficient humans, the involvement of other metabolic signals has not yet been explored.

Metabolic signals modulate the mesolimbic dopamine system ('wanting')

Wanting, or incentive salience, is another component of reward as proposed by Berridge [52, 55]. It usually, but not always, follows liking. While liking is closer to sensory processes, wanting is closer to motor action. Neurologically, wanting is intimately linked to the mesolimbic dopamine system, which is crucial for the orchestration of motor behavior to obtain rewards. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens, prefrontal cortex, and amygdala, are the most important component of the implicit or unconscious 'wanting' system [108–110]. Manipulation of this dopamine system powerfully influences 'wanting' (instrumental performance for and consumption of) drugs or food, but not 'liking', as determined in the taste reactivity test measuring orofacial expressions [52, 111–113].

Leptin and insulin can act directly on mesolimbic dopamine neurons to modulate 'wanting' of food[114–116]. The long form leptin receptor is expressed in dopamine neurons of the mouse VTA (H. Munzberg, personal communication), and leptin administration induces phosphorylation of STAT3, one of the leptin receptor-linked intracellular signaling pathways responsible for leptin's effects on energy balance [115,116]. Leptin administration directly to the VTA decreased firing rate of dopamine neurons and food intake, while silencing of leptin receptor signaling by local administration of viral siRNA increased total food intake and preference for sucrose and high-fat diet compared with control virus injection [115].

In contrast to leptin, the gut hormone ghrelin secreted from an empty stomach stimulates the mesolimbic dopamine system [117,118]. In rats and mice, ghrelin triggered dopamine neuronal activity, synapse formation, and dopamine turnover in the nucleus accumbens in a ghrelin receptor-dependent manner [117], effects that appear to depend on intact cholinergic inputs from the midbrain tegmental area to the VTA and nicotinic cholinergic receptors [118]. Ghrelin receptors are highly expressed in dopamine neurons of the VTA[119]. Because direct administration of ghrelin into the VTA stimulates food intake [117], and ICV administration in rats increases progressive ratio performance to obtain food reward [120], these observations

strongly suggest that ghrelin specifically enhances 'wanting' through the mesolimbic dopamine system. This conclusion is supported by an fMRI study in humans, demonstrating that ghrelin-induced enhancement of visual food cue-induced neural activity in the VTA correlated with subjective reports of hunger [75].

Lateral hypothalamic electrodes that maintained vigorous self-stimulation and elicited eating, drinking, or sexual arousal were termed pleasure electrodes, but a recent reappraisal has made it clear that they do not elicit feelings of pleasure ('liking'), but rather 'wanting' more of the same, whether it is pleasurable or not [54]. Recent studies have strongly implicated lateral hypothalamic orexin neurons with projections to the VTA in reward seeking ('wanting"), drug relapse, and addiction [121,122]. Hypothalamic orexin neurons send axonal projections to the VTA[123], including dopaminergic neurons [124,125], and dopaminergic neurons are excited by orexins [126,127]. Direct chemical activation of lateral hypothalamic orexin neurons leads to strong preference of cues associated with food and drug reward [121], and indirect activation by opioid receptor stimulation in the nucleus accumbens leads to voracious intake of palatable high-fat food in rats [128]. Both effects are blocked by orexin receptor antagonist administration into the VTA [121,128]. In addition to orexin neurons, another population of lateral hypothalamic neurons with projections to the VTA has recently been demonstrated to express leptin receptor and neurotensin [129]. Together, these findings suggest that orexin and possibly other LH neurons could play an important role in the modulation of the mesolimbic 'wanting' system by internal state signals.

Because the nucleus accumbens appears to play a dual role in both 'liking' and 'wanting', metabolic signals acting on this structure could affect either one selectively or both. Thus, the above mentioned effects of intra-accumbens amylin on food intake and locomotor activity in the rat [102], and leptin replacement on visual food cue-induced neuronal activity in the nucleus accumbens of leptin-deficient humans [104] could affect 'wanting', 'liking', or both. However, it is more likely that the systemically administered leptin changed nucleus accumbens activity via its effects on the VTA. This may also be the case for PYY(3–36), shown to modulate neural activity in the ventral tegmental area and ventral striatum [130]. This lower gut hormone has now been convincingly demonstrated to suppress food intake in humans and rodents [130, 131] and is thought to be important for decreased food intake after Roux-en-Y gastric bypass surgery [132,133].

The mesolimbic dopamine system is not only involved in food reward but considered key for addictive behavior [134]. It is well established that food deprivation can enhance drug reward [135], but the mechanism(s) are not clear. Acute or chronic leptin administration in chronically food-restricted rats (amounting to leptin replacement therapy) did not reverse the enhanced behavioral sensitivity to psychostimulant challenge [136,137]. Therefore, another metabolic depletion signal, perhaps increased ghrelin, must be responsible. This may be surprising in light of the findings by Hommel et al. that direct leptin administration to the ventral tegmental area of rats suppresses food reward (as indicated by decreased activity of dopamine neurons and food intake), while silencing leptin receptor signaling appears to enhance food reward (as indicated by increased food intake and preference for palatable foods) [115].

Whatever the starvation signal might be, neuroadaptations at the level of postsynaptic D1 and D2 dopamine receptor-bearing cells in ventral and dorsal striatum appear to be responsible for enhanced drug reward [138]. Reduced striatal D2 dopamine receptor availability and signaling is at the core of the reward-deficiency hypothesis as an explanation of heightened susceptibility for obesity and drug abuse [116,134,139].

Direct vs. indirect modulation

While many of the above-cited demonstrations in animals use targeted administration of hormones and metabolites and/or find relevant receptors within the area of interest, this is not the case for the human neuroimaging studies. In the latter, changes in neuronal activity in a given brain area may not be the result of direct receptor stimulation within that area. The peripherally administered hormone (or metabolite or drug) could interact with receptors anywhere else in the periphery or CNS, with propagation of the signal by neural pathways to the site(s) of detection by fMRI. This limitation is particularly evident if the site of initial receptor interaction is outside the "easily" accessible part of the brain, in "deeper" structures such as the brainstem and hypothalamus. The problem can be addressed only by using additional techniques such as PET scanning, which allows visualization of specific ligand-receptor interactions [e.g. [134]], and by complementary animal *in vivo* and *in vitro* studies.

The downstream signaling mechanisms triggered after a hormone binds to its receptor are not well understood, except for leptin and insulin acting on arcuate nucleus neurons. In cortico-limbic structures specifically discussed here, signaling cascades may be different, and involve local interneurons and nerve terminals releasing classical neurotransmitters such as GABA and glutamate and neuromodulators such as opioid and other peptides as well as endocannabinoids [140,141]. Given the current limits of its anatomical resolution, fMRI is not suited to answer such questions.

Depletion signals produce more powerful effects than repletion signals

The strongest, most compelling behavioral and neuronal activity changes were observed with powerful metabolic depletion signals such as leptin deficiency, food deprivation/restriction, or ghrelin administration [e.g. [59,74,82,104]]. Decreased leptin signaling as in leptin deficiency or 2-deoxy-D-glucose-induced reductions in metabolizable glucose stimulates food intake much more than leptin or glucose administration inhibits food intake. The fact that the response to weight loss is inherently more vigorous than the response to weight gain and its implications has been discussed [142]. When metabolic repletion signals are merely added to an animal already in energy balance (eucaloric state), the effects are often small or absent. For example, peripheral or central leptin injections at physiological doses have very little effects on food intake, unless they act as replacement therapy in a leptin-deficiency model. Similarly, leptin administration in a leptin-deficient ob/ob mouse restores food-finding time in the buried food paradigm, but even high doses of leptin do not increase food-finding time above the level of wildtype mice [59], suggesting that leptin is most powerful at low levels, but once reaching "normal" levels there is no further biological effect [35]. Although this could be interpreted as *de facto* leptin-resistance, there is no need to assume that this resistance is pathological. Rather, it suggests that the biological purpose of leptin is not to curb excessive food intake, at least not in the short term [143].

An explanation of this asymmetrical response pattern may be found in theories of evolutionary selection pressures. One theory suggests that the frequent exposure to famines led to the selection of fuel-efficiency genes (thrifty genes) [144]. Evolutionary pressure has also existed to defend the upper limits of adiposity and, perhaps more likely, body weight [145]. Disadvantages of elevated body weight are evident in the relationship between prey and predator – a heavier rodent is more likely to become prey of a weasel or bird compared to a lean rodent. Humans too, were prey of larger predators, but this selection pressure for leanness decreased with the use of weapons, fire, and shelter. This theory suggests that the loss of selection pressure allowed the upper boundaries of adiposity and body weight to drift upwards by random genetic mutations over the last 2 million years or so [12,145,146]. These two theories are not mutually exclusive and any given individual genetic predisposition could result from a contribution of both mechanisms. One such hypothetical gene could favor the role of

negative regulators of leptin receptor signaling such as SOCS3 or PTP1B [147,148], thereby shifting the set point of leptin action upward [18].

4. Conclusions: An expanded view of homeostatic control and implications for the development of obesity and eating disorders

This brief review of the literature finds strong evidence that internal state signals modulate reward and cognitive functions important for the control of food intake and the regulation of energy balance. Despite the significant limitations of the fMRI approach, on which almost all human studies are based, existing data collectively suggest that several internal state signals achieve this modulation by directly affecting key areas of reward and cognitive processing. Thus, metabolic feedback signals involved in body weight homeostasis do not act exclusively on targets in the hypothalamus, but also on sensory pathways and cortico-limbic structures. They include (1) sensory processing channels allowing detection and interpretation of food cues (visual, olfactory, and gustatory systems), (2) cognitive systems allowing the formation, storage, and recall of food representations (orbitofrontal cortex, amygdala, and hippocampal complex), (3) the distributed neural circuitry encoding ‘core liking’ and subjective pleasure of food and food cues (areas in brainstem, hedonic hotspots in the ventral striatum, orbitofrontal and prefrontal cortex), and (4) the mesolimbic dopamine system attributing incentive salience or motivation to obtain food (ventral tegmental area, nucleus accumbens, frontal cortex). When considering homeostatic control of food intake and regulation of energy balance, these extrahypothalamic systems need to be included.

In distinction to the homeostatic controls residing in the hypothalamus, the term “non-homeostatic” has recently made its way into the vocabulary. This label implies that these additional controls of food intake have little or nothing to do with the homeostatic controls. In the past, we have ourselves used the term (Zheng and Berthoud), but given the intimate interactions between the two systems as highlighted here, this categorical distinction seems premature. Corwin and Hajnal have provided an operational definition of non-homeostatic appetitive behavior as consuming too much or too little food relative to what is biologically required (as defined by homeostatic needs) [149].

Eating in the absence of metabolic hunger may seem incompatible with the traditional, rigid view of homeostatic energy balance regulation. However, energy homeostasis should take into account the need to adapt to changing conditions in the environment. The proactive aspect of food supply is important in restrictive environments as during most of our evolutionary history with uncertain and unpredictable food availability. Food hoarding is one way to smooth fluctuations in supply and demand, but eating beyond the immediate metabolic needs is an even safer strategy. It seems natural that seeing, smelling, and tasting food elicits both so-called cephalic responses affecting autonomic functions and triggers the recall of memories of reward and satisfaction that can lead to eating even in the absence of immediate metabolic need.

The implications of this expanded view of body energy homeostasis for obesity and eating disorders are quite obvious. The realization that metabolic signals act directly on these non-traditional targets of body energy homeostasis brings opportunities for novel drug targets for the fight against obesity and eating disorders. The new insights gained from studying the effects of natural hormones on cortico-limbic structures involved in cognition, reward, attention, emotion, and decision-making will be very valuable for drug development. In most cases, the targeted neurons, ligand-receptor interactions, and downstream signaling cascades have not yet been explored. The main cause of the obesity epidemic lies in the ability of environmental and lifestyle changes to exploit individual predisposition. Therefore, the focus shifts on interactions between the environment and the brain, specifically the cortico-limbic systems. Also, given that the primary defects in eating disorders such as anorexia nervosa and binge

eating are suspected to be within these systems, significant advances in understanding these diseases can be expected. Finally, studying the effects of natural hormones and metabolites on higher brain functions could also lead to new dietary and functional food strategies.

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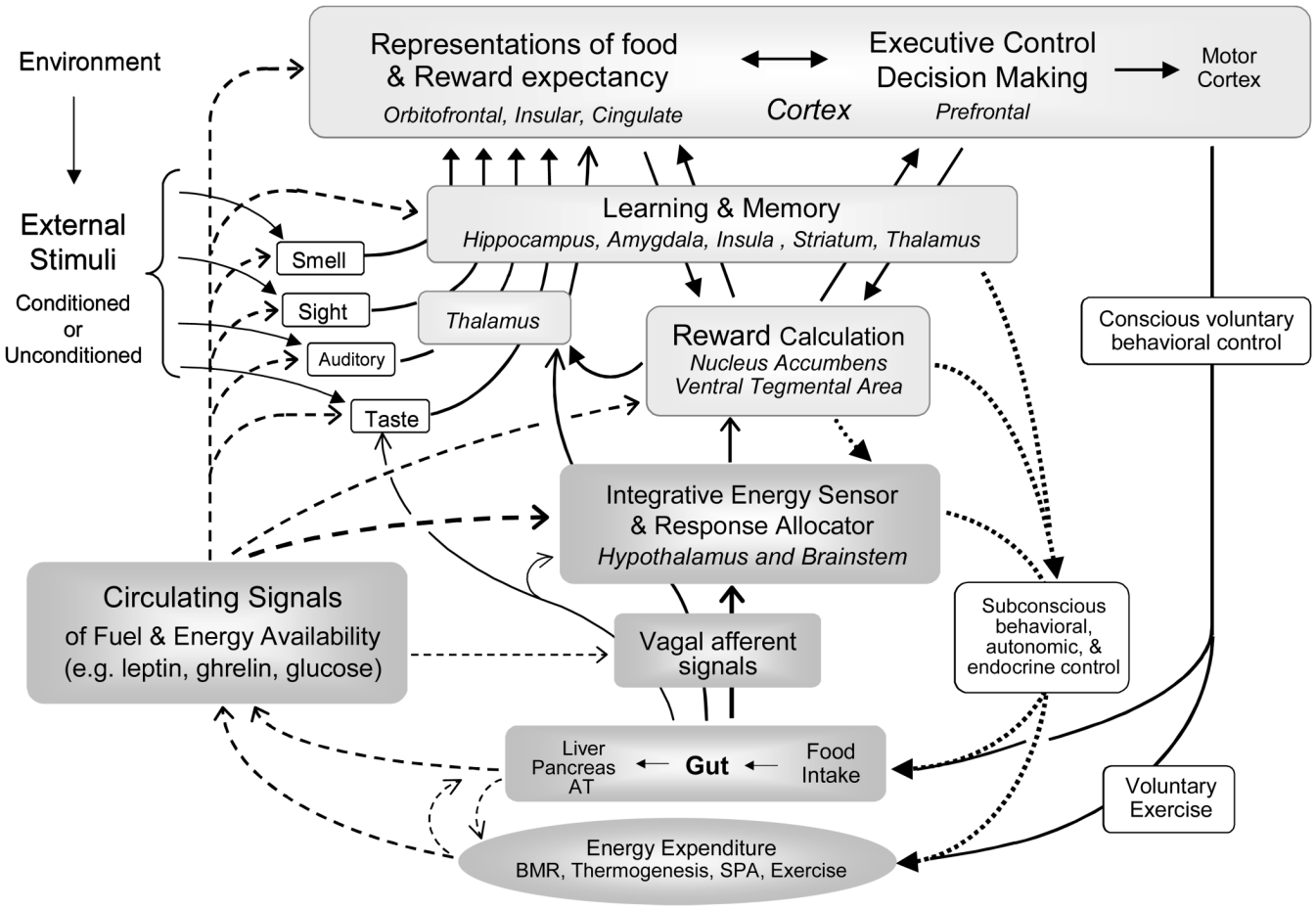

Fig. 1.

Highly schematic diagram showing neural systems and flow of information involved in the control of food intake and regulation of energy balance. The traditional regulatory circuitry using neural and hormonal feedback from the internal milieu acting on hypothalamus and brainstem is shown on the bottom (dark grey boxes). Sensory and cortico-limbic brain areas used for processing information from the environment are shown in the upper half (light gray boxes). The extensive influence of circulating and neural internal feedback signals on sensory processing and cortico-limbic systems concerned with reward, emotion, learning and memory is emphasized (broken line open arrows).