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Homeostatic and non-homeostatic controls of feeding behavior: Distinct vs. common neural systems

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ABSTRACT

Understanding the neurobiological controls of feeding behavior is critical in light of the growing obesity pandemic, a phenomenon largely based on excessive caloric consumption. Feeding behavior and its underlying biological substrates are frequently divided in the literature into two separate categories: [1] homeostatic processes involving energy intake based on caloric and other metabolic deficits, and [2] non-homeostatic processes that involve feeding driven by environmental and cognitive factors. The present review summarizes both historic and recent research examining the homeostatic regulation of feeding with specific emphasis on hypothalamic and hindbrain circuitry that monitor and regulate various metabolic signals. Regarding non-homeostatic controls, we highlight higher-order brain structures that integrate feeding-relevant external, interoceptive, and cognitive factors, including sensory cortical processing, learned associations in the hippocampus, and reward-based processing in the nucleus accumbens and interconnected mesolimbic circuitry. Finally, the current review focuses on recent evidence that challenges the traditional view that distinct neural systems regulate homeostatic vs. non-homeostatic controls of feeding behavior. Specifically, we highlight several feeding-related endocrine systems that act on both lower- and higher-order substrates, present evidence for the modulation of learned and cognitive feeding-relevant behaviors by lower-order brain regions, and highlight data showing that apparent homeostatic-based feeding behavior is modulated by higher-order brain regions. Our concluding perspective is that the classic dissociation between homeostatic and non-homeostatic constructs in relation to feeding behavior is limited with regards to understanding the complex integrated neurobiological systems that control energy balance.

1. Introduction

The regulation of feeding behavior is often divided into two separate categories: homeostatic and non-homeostatic controls. Homeostatic mechanisms control feeding in response to general energy deficit or other types of metabolic need, whereas non-homeostatic mechanisms include learning, memory, and cognitive processes that can affect feeding based on previous learned experiences and hedonic aspects of food. The latter, of course, is of more relevance to the excessive food intake that is driving up obesity rates in the U.S. and other modern Westernized countries, as cognitive and hedonic factors are thought to override inhibitory mechanisms regulating caloric intake. Much progress has been made in the past several decades with regards to identifying the neural substrates and biological pathways that control feeding behavior. While the control of homeostatic and non-homeostatic aspects of ingestive behavior has traditionally been attributed to distinct neural pathways, a number of recent findings suggest that the neural substrates involved in these two putative distinct domains of feeding behavior are not entirely dissociable. Here, we describe a classic model whereby hindbrain and ventromedial hypothalamic circuits primarily regulate homeostatic controls of feeding behavior, whereas non-homeostatic substrates include brain regions involved in memory, cognition, and reward (e.G. *hippocampus*, cortical, and mesolimbic dopamine circuitry). Finally, we present evidence that challenges the notion that these two feeding behavior constructs can be dissociated as being regulated by fundamentally distinct neural systems.

2. Homeostatic control of energy balance

In the 1850s, Claude Bernard proposed the concept of the milieu intérieur, the internal environment that is maintained stable independent of the external environment [1]. Approximately 80 years later, Walter Cannon expanded on this idea and popularized the

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concept of homeostasis. He defined it as “a fairly constant or steady state, maintained in many aspects of the bodily economy even when they are beset by conditions tending to disturb them” [2,3]. His work in defining homeostasis as the maintenance of a specific “set point” shifted focus towards identifying the specific control factors that maintain a steady internal environment. Core body temperature regulation is perhaps the most classic biological system considered to operate in a homeostatic manner, with a clear negative feedback system in place to preserve a set point (i.e., approximately 37 °C). Energy balance (energy intake vs. energy expenditure) involves a system that, while often described as being regulated by homeostatic processes (hence the common phrase “energy homeostasis”), does not necessarily fit neatly within the Cannon model of homeostatic systems. For example, while mammals are quite effective in defending against lower limits of energy reserves via alterations in behavior (e.g., food seeking, foraging, elevated energy intake) and metabolism (e.g., ketogenesis, gluconeogenesis), defense against the upper limits of adiposity are clearly poorly controlled in light of the pandemic of obesity and its related negative health co-morbidities. According to Speakman's “drifty gene” hypothesis, body adiposity as humans evolved was regulated by a system that involves lower (risk of starvation) and upper (risk of predation) intervention limits [4]. The genes defining the upper intervention point, however, have been subject to random mutation and “genetic drift” over the past 2 million years based on advances such as social behavior, weapons, and fire that minimize excess adiposity as risk for predation. Thus, unlike other biological systems that revolve around the maintenance of a specific ‘set point’, energy balance control has likely evolved with limited control for defending against excessive caloric intake and adiposity.

2.1. Hindbrain controls

The hindbrain plays an important role in processing and integrating energy balance-relevant information, particularly with regards to meal size regulation and thermogenesis. The caudal brainstem integrates direct inputs from vagally-mediated gastrointestinal satiation signals, alterations in glucose and other circulating metabolites, and descending neural, neuroendocrine, and neuropeptidergic signals from the midbrain and forebrain. These energy status cues are subsequently relayed to other ascending neural sites to control behavior, autonomic, and endocrine responses [5]. A powerful illustration of the importance of brainstem circuitry in controlling fundamental feeding behavior comes from seminal chronic decerebrate rat studies from Grill, Norgren, and colleagues, revealing that decerebrate rats show relatively normal satiation processing (demonstrated via orofacial rejection of orally infused nutrients) in the absence of forebrain neural processing [6,7]. Specifically, taste reactivity responses following intraoral sucrose stimuli were examined under deprived and non-deprived conditions, and satiation was marked by termination of ingestion through the active or passive removal of the sucrose stimulus. This classic study revealed that both groups demonstrated similar intake in the sated condition, and most often satiation was characterized by a quinine-like rejection sequence [7].

Levels of circulating blood glucose and other feeding-related peripherally-derived hormones, such as ghrelin and leptin, are thought to be closely monitored for the central control of energy homeostasis. Consistent with the hindbrain being a critical neural substrate for homeostatic aspects of energy balance, Ritter, Slusser, and Stone [8] conducted an important study revealing that obstruction of the cerebral aqueduct and subsequent infusion of 5-thioglucose, an antimetabolic glucose analogue, to the fourth ventricle (restricted to hindbrain), but not the lateral ventricle (restricted to forebrain with aqueduct obstruction) effectively increased food intake and hyperglycemia via acute glucoprivation. They concluded that glucoreceptors that respond to cerebral glucoprivation are located in the caudal brainstem. In addition to blood-borne information, the medial nucleus tractus solitarius (mNTS) of the caudal brainstem also receives direct input from the vagus nerve that conveys information from the gastrointestinal tract about the nutritive, osmotic, and volumetric properties of food [9,10]. For example, the vagus nerve sends information about the volumetric-mechanical distension of the stomach, and stretch and tension of the stomach are communicated via vagal afferent pathways projecting to the NTS. Physiological levels of gastric distension prompt the vascular release of serotonin (5-HT), which results in neural activation (detected via c-Fos expression) in the NTS. Furthermore, distension-induced c-Fos expression in the NTS is completely blocked by truncal vagotomy or perivagal capsaicin treatment [11], thereby highlighting a critical interaction between peripheral vagal nerve signaling and hindbrain regulation of feeding and metabolism. In summary, the hindbrain responds to circulating nutrients, hunger- and satiation-related hormones, and volumetric properties of food in order to control feeding and energy homeostasis.

In addition to integrating energy status information, the NTS also produces outputs to the dorsal motor nucleus of the vagus (DMX) to control parasympathetic gastrointestinal responses, such as insulin secretion and gastric emptying [12–15]. Additionally, the DMX is central to ingestive consummatory behaviors, such as movements of the tongue, jaw, pharynx, and facial muscles, as well as oral motor behaviors that include licking, chewing, swallowing, and food rejection [16]. The NTS also projects to forebrain regions affecting appetite and food reward [17–19] and to the paraventricular nucleus of the hypothalamus (PVH) to influence neuroendocrine responses [20–22].

2.2. Hypothalamic controls

An important forebrain substrate that is critically involved in maintaining energy homeostasis is the ventromedial region of the hypothalamus, particularly the arcuate nucleus of the hypothalamus (ARH). Within the ARH, the most attention with regards to energy balance has been given to leptin signaling and its integration with the central melanocortin system. The ARH contains two antagonistic cell groups: the anorexigenic propiomelanocortin (POMC)-expressing neurons and the orexigenic agouti-related protein (AgRP)/neuropeptide Y (NPY)-coexpressing neurons. POMC is cleaved into alpha-melanocyte stimulating hormone (alpha-MSH) which binds to and activates melanocortin-4 receptors (MC4R) expressed in the PVH and other regions, thereby decreasing food intake and increasing energy expenditure [23–25]. In support of this ARH system being critical for energy balance, genetic mutations in the POMC gene or disruption of the melanocortin-4 receptor yields an obese phenotype in both humans and experimental rodent models [26,27]. In contrast, NPY is released by AgRP/NPY neurons and binds to NPY receptors to increase appetite and feeding [28]. Furthermore, AgRP directly blocks alpha-MSH activation of the MC4R, thereby inhibiting the anorexigenic effect of POMC neurons. In mice, acute ablation using diptheria toxin of AgRP/NPY neurons blunts appetite and leads to starvation [29–31].

The POMC and AgRP/NPY neurons within the ARH express receptors for and are modulated by various hunger and satiety hormones important in the regulation of homeostasis, including leptin, insulin, peptide YY (PYY), and ghrelin [32–36]. Theoretically, modulation by these hormones allow for appropriate changes in feeding behavior for the maintenance of energy homeostasis. In addition to hunger and satiety hormones, specific nutrients have also been found to modulate hypothalamic control of energy homeostasis and influence appetite based on the composition of a diet. For example, the hypothalamus senses changes in levels of plasma fatty acids, which subsequently affects hepatic gluconeogenesis and glucose homeostasis [37,38].

AgRP neurons have been shown to integrate complex nutritional, hormonal, and neuronal signals, in order to modulate gamma-aminobutyric acid (GABA)-ergic signaling in the pontine parabrachial nucleus (PBN) to stimulate feeding [39]. Conversely, POMC neurons that co-express oxytocin receptor regulate glutamate signaling in MC4R-

expressing neurons in the PVH to rapidly trigger satiation and satiety [40]. These data provide further evidence that the ARH possesses bi-directional control of fundamental feeding behavior. Indeed, the ARH has historically received more attention than any other brain region with regards to the regulation of food intake and body weight, and generally speaking ARH circuits are thought to integrate rapid nutrient sensing with endocrine signals related to energy reserves (e.g., leptin) to control homeostatic aspects of energy balance [41–43].

3. Learned and cognitive controls of feeding behavior

In contrast with classic homeostatic-regulated metabolic systems, like core body temperature and plasma calcium regulation, energy balance explicitly and constantly requires complex goal-directed and consummatory behaviors. Immediately prior to, during, and after feeding-relevant behavioral experiences, animals integrate the sensory processing of ingestion (taste, prandial gastrointestinal signaling) with interoceptive (hunger, satiety, and other metabolic states) and external cues (spatial location, social cues) to form learned associations that influence future behaviors relevant to food procurement and consumption. In the modern obesogenic environment, conditioned food cues associated with consumption of highly palatable and calorically dense foods are particularly prevalent, and can trigger eating in the absence of energy or metabolic deficits [44–46]. Various forebrain regions and networks, some of which are discussed below, are implicated in encoding rewarding, learned, and contextual information to influence feeding behavior.

3.1. Cortical regulation

The prefrontal cortex (PFC) is implicated in inhibitory control mechanisms related to food intake. For example, individuals with binge-eating disorder and some forms of obesity have decreased baseline activity in the PFC [47,48]. Moreover, in obese patients with congenital leptin deficiency, leptin treatments enhance activation of the PFC in response to exposure to food stimuli [49]. Rodent model studies also provide data consistent with the notion that the PFC influences feeding by inhibiting impulsive responding for palatable food [50–52], as well through the inhibition of environmental cue-driven eating [46,53,54].

The insular cortex has been shown to contain taste-responsive neurons that project to the orbitofrontal cortex (OFC) where there are ‘secondary taste neurons’. This pathway is implicated in the integration of taste, olfactory, visual, and cognitive inputs [55], all of which are modulated by hunger [56–58]. The secondary taste neurons of the OFC encode the predictive reward value of palatable foods to influence motivational aspects of feeding [59,60]. Additionally, the insular cortex encodes the perceived pleasantness of taste [61] and internal state [62–64], thereby modulating food value through manipulation of expectations [65,66]. These findings indicate that the primary taste cortex responds to homeostatic signals to reduce pleasantness or value of food and promote meal termination [67].

The OFC is also implicated in sensory-specific satiety, the behavioral phenomenon whereby an animal's satisfaction for a specific food declines with consumption of that food, but rebounds when other foods are presented that have not been eaten within that eating episode. A functional magnetic resonance imaging (fMRI) study showed decreased cerebral blood flow in the OFC in response to presentation of an odor of a food already eaten to satiety, yet no similar decrease in cerebral blood flow was observed for an odor of a different food not eaten in the meal [68]. Additionally, neural activity of the OFC in humans is related to reward value and pleasantness of taste stimuli [69,70], supporting the notion that the OFC is involved in the hedonic regulation of feeding.

3.2. Mesolimbic dopamine pathway

“Reward systems” that influence motivational processes are thought to override physiological hunger and satiety cues to influence feeding behavior. Dopaminergic input to the nucleus accumbens (ACB) from the ventral tegmental area (VTA) is involved in encoding the rewarding properties of food, and consumption of palatable food can cause an increase in extracellular dopamine (DA) levels in the ACB [71]. In vivo brain microdialysis studies indicate that DA release significantly increases in the ACB during consumption of a palatable meal, and 20 h food deprivation further enhances the magnitude of this increase [72]. In addition to these feeding-based effects, DA is involved in the control of conditioned incentive motivation, as conditioned cues associated with food reward can evoke ACB DA release [73–77]. Pecina and Berridge also revealed that both DA and opioid signaling in the core and medial shell of the ACB amplify the reactivity of mesocorticolimbic circuits, and enhance the incentive salience or “wanting” of a reinforced conditioned stimulus [78]. The increased rewarding aspects of food, as well as the increased incentive salience, both augment motivation to work for food. For example, pharmacological increases in DA signaling in the ACB increase the extent to which an animal will work for food in an operant lever pressing procedure, and increases sensitivity to high ratio (i.e., high demand) operant requirements [79–82]. Overall, these studies show that VTA dopaminergic input to the ACB encode conditioned rewarding properties of food, and that these rewarding aspects further enhance incentive salience and motivation to acquire palatable foods.

Both orexigenic (ghrelin) and anorexigenic (glucagon-like peptide 1 [GLP-1], leptin) peptides modulate cue-induced dopaminergic signaling from VTA to the ACB under conditions of food-restriction, where leptin and GLP-1 inhibit firing and ghrelin increases firing rate [83,84]. While ghrelin signaling in the hypothalamic ARH is implicated in metabolic deficit-based feeding behavior, ghrelin signaling in the VTA is involved in hedonic aspects of feeding behavior. For example, ghrelin injections in the VTA and ACB cause a dose-dependent increase in food intake [85]. Further, ghrelin signaling in the VTA increases food motivation and intake of rewarding “palatable” food in rodents [86–88]. Such effects are further modulated by hunger and satiety states, as DA spikes in the VTA (measured via fast-scan cyclic voltammetry) under conditions of food restriction increase in response to feeding [89]. These ghrelin-mediated ACB DA spikes are also engaged by learned food-predictive cues, as ghrelin modulates phasic DA fluctuations in response to a reinforced conditioned stimulus (but not in response to a non-reinforced conditioned stimulus) [90]. These findings indicate that ghrelin signaling in the ACB is critical in the modulation of learned aspects of food reward.

Conversely, GLP-1 receptor signaling in the VTA and ACB suppresses food intake and motivation to work for food [91–94], and the adipocyte hormone leptin also acts in the VTA and ACB to decrease feeding behaviors. VTA DA neurons express the leptin receptor (*LepRb*), and direct administration of leptin to the VTA activates the JAK-STAT intracellular signaling pathway resulting in phosphorylation of STAT3 and a decrease in DA neuron firing rate. Furthermore, activation of VTA *LepRb* decreases food intake and RNAi-mediated genetic knockdown of the *LepRb* in the VTA increases food intake. These findings implicate a role for VTA *LepRb* in the regulation of rewarding aspects of feeding behavior [95,96].

Apart from VTA dopaminergic input to the ACB, GABA- and glutamate-conveying information from corticolimbic and thalamic afferents act directly within the ACB to cause changes in feeding behavior and learning. Classic experiments conducted by Ann Kelley and colleagues revealed that GABA agonists applied directly to the ACB medium spiny neurons increase feeding even in sated animals [97]. Furthermore, application of a glutamate antagonist also induces voracious feeding [98]. These GABAergic and glutamatergic inputs may also act synergistically with VTA dopaminergic input for learned responses. For example, coincident activation of dopaminergic and glutamatergic receptors in the ACB core have been shown to mediate appetitive response learning [99]. Thus, the mesolimbic DA circuit combined with

input from various corticolimbic and thalamic afferents modulate rewarding and conditioned properties of feeding that can often override homeostatic signals.

3.3. Hippocampus

The hippocampus has recently been identified as a food intake control center that integrates [1] the external visuospatial environment, [2] the internal context (interoceptive cues that inform about energy status), and [3] previous learned experience in the regulation of feeding behavior [100]. Among its various mnemonic control processes, the hippocampus encodes episodic meal-related memories that are strongly impacted by both interoceptive and external environmental factors and can potently modulate feeding behavior. For example, amnesic patients with bilateral hippocampal damage who show deficits in episodic meal-related memory formation will consume second and third meals only minutes after the first [101–103]. In non-amnesic subjects, memories related to a recent eating occasion is a powerful factor with regards to making decisions about subsequent food intake (e.g., when to eat) and the amount consumed [104]. In an elegant study, human volunteers were shown two different amounts of soup, while actual portions of soup were manipulated with a computer-controlled peristaltic pump designed to withdraw or refill soup in a covert manner. When subjects were later asked to rate hunger level, independent of the actual amount of soup consumed, subjects rated hunger based on the amount of soup they perceived to have consumed [105]. In addition to manipulating meal-related sensory information, distracted eating also distorts perceptions of the amount of food consumed. For example, Higgs and Woodward [106] discovered that subjects who watched television while eating lunch were also more likely to eat more cookies later on in comparison to subjects who were not distracted while eating lunch. Thus, appetite and consumption are influenced by hippocampal-dependent episodic meal-related memories that are subject to an individual's visual and other sensory perception during the eating occasion.

While episodic memory is not directly accessible to study in animal models, pharmacological manipulations that disrupt memory consolidation of an eating episode reduce the subsequent latency to feed and increase the size of the next meal [107]. Other research in rodents reveals that the hippocampus is important for conditional learned associations between food-related external and interoceptive stimuli, and hippocampal mechanisms are thought to be involved in utilizing energy balance signals to modulate feeding behavior [108]. Recent evidence converges on the idea that one of the critical roles of the hippocampus is to resolve 'predictable ambiguities,' where a stimulus predict different outcomes depending on the presence or absence of another cue or context [109]. Consistent with this perspective, rodents with complete hippocampal lesions are impaired in learning a negative occasion setting task, where a conditioned stimulus is reinforced only when presented in the absence of a different cue (i.e. negative occasion setter). Instead, rats with hippocampal lesions respond to the conditioned stimulus to a similar amount whether or not the negative occasion setter is present [110]. This hippocampal-dependent modulatory learning procedure can be considered analogous to interoceptive state cues (e.g., satiety) informing about when eating in response to ambiguous food cues will be followed by reduced postingestive reinforcement (as compared to eating in the absence of satiety [108,111]).

The ventral subregion of the hippocampus (vHP) in rodents has been shown to process endocrine feeding-related signals to regulate food intake and conditioned aspects of feeding. For example, the vHP densely expresses the ghrelin receptor (growth hormone secretagogue receptor 1-A [GHSR1A]), and administration of ghrelin to the vHP, but not the dorsal hippocampus, increases food intake via an increase in both meal frequency and size [112]. Additionally, activation of vHP GHSR1A also increases the frequency of meal initiation in response to conditioned discrete auditory cues [112]. Subsequent research identified neurons in the lateral hypothalamic area (LHA) that produce the neuropeptide, orexin, as being a functionally-relevant downstream target of vHP ghrelin signaling [113].

In addition to the LHA, the vHP's role in integrating and consolidating feeding-relevant learned associations and endocrine signals involves downstream engagement of additional forebrain areas, including the lateral septum and the medial PFC. For example, using either chemogenetic or optogenetic activation of targeted pathways, Sweeney and Yang identified an excitatory vHP (field CA3) to lateral septum circuit that when activated leads to suppression of feeding [114]. Similarly, we've shown that GLP-1 receptor signaling in the vHP (field CA1) potently reduces food intake and meal size, and these effects are blocked following chemogenetic synaptic silencing of vHP projections to the medial PFC [115]. Collectively these findings identify the hippocampus as a critical substrate that integrates learned experiences with endocrine signaling to modulate conditioned aspects of feeding behavior, and that these effects involve via downstream communication with both hypothalamic (LHA) and telencephalic (medial PFC, lateral septum) regions associated with food intake control.

4. Interactions and dissociations between homeostatic and cognitive substrates

Separating the neurobiology underlying the homeostatic and non-homeostatic mechanisms controlling feeding behavior into separate nodes is a convenient heuristic for understanding the diversity of energy balance-related behaviors. However, the reality is that these psychological and biological constructs are not composed of fundamentally distinct neurobiological systems. Rather, the complexity of feeding behavior requires reciprocal communication between various "lower-order" and "higher-order" brain regions to integrate diverse feeding-relevant information to ultimately guide complex, goal-directed behavior. In this section, we provide an overview of recent literature highlighting the inherent complexity of separating homeostatic and non-homeostatic mechanisms controlling feeding into distinct neural pathways.

4.1. Gastrointestinal and vagus nerve modulation of cognition

Vagal afferents innervate the gastrointestinal (GI) tract, including the pancreas, liver, stomach, and intestines, where energy balance relevant signals are detected and transmitted to the brain [12]. GI signals can activate vagal nerve signaling through specialized ionotropic and G protein-coupled receptors that are expressed on terminals of the vagus nerve and in the nodose ganglia (cell bodies of the afferent vagal fibers). The vagus nerve provides direct sensory input to the NTS in the hindbrain to influence satiation processing [5]. Several gut peptides communicate with the brain to affect food intake and regulate short- and long-term energy homeostasis, in part, through paracrine signaling to the vagal afferent terminals [12,116]. In addition to potently regulating the fundamental control of meal size, GI signaling (both vagally- and nonvagally-mediated) has recently been shown to affect higher-order brain functions. For example, Roux-en-Y gastric bypass surgery in obese patients, which yields partial GI vagal denervation [117], led to improved hippocampal-dependent memory and other cognitive functions, including attention, executive function, memory (verbal list learning), and language, up to 36-months post-operatively [118,119]. Furthermore, intragastric nutrient infusion (mimicking the rate of intake and emptying of a liquid meal) and gastric distension (a vagally-mediated satiation signal) in rats each induce changes in blood-oxygen-level dependent (BOLD) fMRI signal intensity in brain regions linked with limbic and cognitive control (hippocampus, caudate putamen, cerebral cortex) [120,121]. Additionally, vagal nerve stimulation in the rat increases hippocampal dentate gyrus BrdU-mediated neurogenesis by 50% [122], and increases extracellular concentrations of norepinephrine in both the cortex and hippocampus [123]. Consistent with

these studies, vagotomy decreases BrdU incorporation in the hilus and capsaicin-mediated vagal deafferentation decreases BrdU incorporation in the granular cell layer of the hippocampus [124]. Additionally, subdiaphragmatic vagal deafferentation in rats reduces anxiety-like behavior and facilitates discrimination reversal learning [125,126]. Further work is needed to determine the exact mechanisms and neurobiological pathways through which GI-derived vagus nerve signaling affects higher-order brain substrates.

4.2. Endocrine signals influence both homeostatic and higher-order aspects of feeding behavior

In addition to vagally-mediated signaling, circulating endocrine signals are transmitted across the blood-brain barrier (BBB) and act on various brain regions. In particular, two peripherally-derived signals highlighted in this review, ghrelin and leptin, communicate via humoral pathways from the vasculature to the brain and directly modulate both homeostatic and non-homeostatic-related processes to control food intake. GLP-1 will also be discussed, which influences both homeostatic and non-homeostatic feeding processes via both peripheral- and/or central-derived signaling pathways, as GLP-1 is produced both in the distal intestines and in the mNTS.

Often referred to as a "hunger hormone," ghrelin is a peptide hormone secreted from the stomach and binds to the GHSR, which is densely expressed throughout the neuraxis. Among the various regions that express GHSR, ghrelin acts in the ARH to stimulate food intake in a dose-dependent manner, an effect that is 55–60% reduced by NPY receptor blockade [127–129]. Furthermore, intraperitoneal injection of peripheral ghrelin increases c-Fos expression in NPY-synthesizing neurons in the mouse ARH, and this effect is significantly greater in fasted than in fed rats [130,131]. Additionally, ghrelin also acts in the hindbrain to control feeding, as unilateral administration of ghrelin in the dorsal vagal complex significantly increases food intake in rats and subdiaphragmatic vagotomy completely blocks deprivation-induced ghrelin rise [132,133]. These data collectively suggest that ghrelin acts to increase feeding behaviors by acting directly in brain regions (ARH, caudal brainstem) that are traditionally associated with homeostatic control of energy balance.

Recent literature indicates that ghrelin also acts to control learned/conditioned aspects of feeding behavior, acting as an anticipatory signal for meal initiation whose secretion is stimulated by circadian and external conditioned cues associated with meal access [134]. For example, Cummings and colleagues [135] observed a robust increase in circulating ghrelin levels immediately before each scheduled meal in humans fixed on an eating schedule, which was followed by a suppression 1-h after each meal. Additionally, food-related orosensory stimulation can affect circulating ghrelin levels, even in the absence postingestive nutritive consequences [112,136,137]. Evidence from our laboratory revealed that pharmacological blockade of vHP GHSRs (via pharmacological GHSR blockade) prior to 4-h food consumption in meal entrained animals reduced food intake, yet the same dose had no effect on food intake in rats that were not meal entrained [113]. In addition to the vHP, GHSR expression is also found in various limbic and mesolimbic reward systems, such as the VTA, ACB, amygdala, and medial PFC [35,138]. Importantly, GHSR action in the VTA has potent effects on stimulating feeding – not just food intake in the home cage – but also conditioned food reward-motivated behaviors [see Skibicka and Dickson [139] for review].

Another peripherally-derived endocrine signal that potently regulates feeding primarily via CNS action is leptin. Produced and secreted by white adipocytes, leptin acts, in part, as a satiation signal to reduce meal size. Work by Morton and colleagues indicates that leptin acts in the ARH to reduce food intake and body weight. Using Koletsky (fa^k/fa^k) rats, which develop severe obesity due to a LepRb mutation, they found that the mutated rats demonstrated significantly increased meal size and reduced satiety in response to the gut peptide cholecystokinin (CCK), and that restoration of LepRb in the ARH via gene therapy normalized this response [140]. LepRb-expressing neurons in the mNTS, which directly receives vagal afferent signaling from the GI tract, are activated by gastric distension [141]. Using an RNA-interference approach to knockdown LepRb specifically in the mNTS and area postrema (AP), Hayes, Grill, and colleagues revealed that mNTS/AP LepRb signaling is physiologically relevant for food intake and body weight regulation, in part by reducing meal size and enhancing the effectiveness of GI-related satiation signals [142,143]. Collectively, these data indicate that leptin potently regulates feeding behavior via action in brain regions traditionally associated with the homeostatic control of energy balance.

While the mNTS is thought to be fundamental hub for basic satiation and meal size control, leptin action in this site has also been shown to affect conditioned aspects of feeding behavior. Leptin administration to the mNTS reduced operant lever pressing for palatable sucrose under increasing work demands (progressive ratio schedule of reinforcement), as well as conditioned food-seeking behavior in the conditioned place preference procedure [144]. Thus, these findings indicate a novel role for hindbrain leptin in conditioned appetitive and motivational aspects of feeding. Moreover, in addition to ARH and the mNTS, LepRb relevance to feeding has been shown in various other forebrain sites associated with non-homeostatic energy balance control. For example, bilateral leptin administration in the vHP suppresses food intake and body weight, blocks expression of conditioned place preference for food, and increases latency to search for food in an operant runway paradigm [145]. Additional forebrain sites for leptin action include the VTA and substantia nigra, both part of the midbrain DA pathway that mediate reward-seeking behavior [146–149]. Leptin action in the LHA also reduces feeding via interaction with the mesolimbic DA system [150]. Overall these findings show that leptin not only acts in regions associated with both homeostatic (ARH, mNTS) and non-homeostatic (vHP, VTA) feeding processes, but also can signal in the mNTS, a brain region traditionally associated with basic meal size control, to influence learned and motivational aspects of appetitive behavior.

GLP-1 is primarily produced and secreted by intestinal enteroendocrine L-cells and by neurons in the mNTS. The GLP-1 analog, liraglutide (tradename Victoza or Saxenda), is used for Type 2 diabetes and weight loss treatment in humans. Endogenous mNTS GLP-1 receptor activation suppresses food intake by enhancing gastric satiation signaling via activation of PKA and MAPK activity [151,152]. Consistent with a role for GLP-1 in satiation processing, the feeding effects of peripheral GLP-1 require the vagal-brainstem-hypothalamic pathway, as subdiaphragmatic vagal afferent signaling is required for meal size reduction by peripheral GLP-1 injections [153], and peripheral GLP-1-mediated food intake suppression is abolished following brainstem-hypothalamic transections in rodents [154].

GLP-1 also acts in forebrain regions associated with cognitive and reward-related processes. GLP-1 neurons in the NTS project directly to the VTA and ACB and GLP-1 receptor activation in these regions reduces food intake (especially for highly-palatable foods) and reduces motivated responding for palatable food [91,155,156]. In humans, administration of a GLP-1 analog acutely decreased fMRI brain responses to food pictures in appetite- and reward-related brain regions, specifically the insula, amygdala, putamen, and orbitofrontal cortex [157]. GLP-1 also acts in the vHP, where it engages glutamatergic signaling to medial prefrontal cortex to control motivated operant responding for palatable food [115]. Together, these results indicate that GLP-1 acts in various brain regions that are traditionally involved in both homeostatic (mNTS) and non-homeostatic (vHP, VTA, ACB) aspects of food intake control. As was previously discussed for leptin, GLP-1R activation in the mNTS not only reduces food intake by augmenting the effectiveness of GI-derived satiation signals, but also reduces conditioned appetitive behaviors related to obtaining palatable food, including operant responding for sucrose and expression of conditioned place preference for palatable food [158].

4.3. Arcuate nucleus signaling mediates conditioned aspects of appetite

The ARH, primarily considered a homeostatic feeding substrate, has also been recently shown to have a fundamental role in conditioned aspects of appetite. The ARH receives information regarding nutritional and hunger state to motivate feeding behaviors and regulate overall energy balance. However, the ARH is also modulated by sensory and hedonic information to mediate conditioned aspects of appetite, as evident by findings that activity of AgRP and POMC neurons are regulated not only by energy status, but also by food palatability [159]. In addition, in a recent paper by Betley, Sternson, and colleagues [160] it was shown that optogenetic-mediated inhibition of AgRP neurons conditioned a preference for both flavors and physical/external locations. Importantly, using deep-brain calcium imaging, this paper further revealed that activity of AgRP neurons not only rapidly reduced in response to feeding, but also following exposure to conditioned food-related cues. Thus, the ARH, which is classically linked with homeostatic food intake control, also plays an important role in conditioned and hedonic aspects of feeding behavior. More recent findings from Betley and colleagues extend this work by revealing that the maximal AgRP neural activity suppression occurs at a much slower rate after consuming novel foods (or after direct gastrointestinal infusion of nutrients) compared to the suppression rate observed when consuming a known, familiar caloric food [161]. Collectively these findings clearly indicate that the interplay between feeding and AgRP neural responding is potently modulated by both hedonic evaluation as well as previous learned experiences.

4.4. Mesolimbic reward signaling is modulated by energy and micronutrient deficiencies

Energy balance-related endocrine signals (i.e. leptin, insulin, and ghrelin) also modulate reward processing [162]. For example, brain stimulation reward (BSR), or the operant self-administration of electrical brain stimulation, has long been used to assess the reward properties of various experimental manipulations. In an elegant study conducted by Fulton and colleagues [163], rats were trained to self-stimulate by pressing a lever that triggered pulses to the lateral hypothalamus. They found that chronic food restriction enhanced the rewarding effect of BSR, and that and intracerebroventricular infusion of leptin attenuated this effect. Thus, chronic energy depletion engages reward processing in the lateral hypothalamus and interconnected circuitry to increase appetitive behavior, an effect modulated by leptin, a correlate of long-term energy sufficiency. Conversely, ghrelin, a correlate of short-term energy depletion, stimulates DA release from VTA neurons [164,165] and potentiates conditioned cue-evoked DA release in the ACB [90]. Cone, McCutcheon, and Roitman further discovered that ghrelin directly activates orexin receptors in the VTA to stimulate food-evoked DA release [89]. These studies suggest that both short- and long-term energy status cues engage the mesolimbic reward circuitry. Congruent with these studies, elevated DA signaling in rats is observed in response to sodium in a sodium deplete state [166]. Thus, in addition to being modulated by short- and long-term energy status, mesolimbic "reward" signaling appears to be modulated by micronutrient status as well. Collectively, these findings blur the distinction between homeostatic energy regulatory mechanisms (i.e., energy intake in direct response to energy restriction) and non-homeostatic mechanisms (i.e., modulation of feeding by incentive and reward), as in addition to learned and cognitive factors, energy and micronutrient status pull the proverbial puppet strings for the brain's mesolimbic reward circuitry.

5. Conclusions

Feeding behavior is controlled by a number of complex regulatory mechanisms involving both homeostatic (lower-order) and non-homeostatic (high-order) processes. Previous research has predominantly linked hypothalamic and caudal brainstem signaling in the control of homeostatic aspects of feeding behavior, particularly within the hypothalamic ARH (POMC and AgRP/NPY neurons) and caudal brainstem (GI meal-related vagal nerve signaling to the mNTS). In the literature [e.g., [167–169]], these homeostatic feeding circuits are often distinguished from brain substrates involved in the non-homeostatic (hedonic and learned) control of food intake, which include cortical, mesolimbic DA, and hippocampal circuits that mediate the integration of sensory and hedonic properties with previous learned experiences to regulate conditioned and motivated aspects of food intake control. However, in this review we have highlighted several recent findings suggesting that the homeostatic and non-homeostatic neural pathways regulating feeding behavior are not easily dissociable. First, traditional homeostatic neural substrates are also critical in the control of higher-order functions relevant to feeding, as evidenced by GI and vagus nerve modulation of cognition and memory, as well as by potent mNTS and ARH influences on conditioned appetitive aspects of feeding behavior. On the other hand, traditional non-homeostatic regions in the midbrain and forebrain (hippocampus, mesolimbic circuitry) have also been shown to be interact with hindbrain and hypothalamic circuitry to regulate meal size, and to be modulated by both overall energy and micronutrient deficiencies. Additionally, various endocrine signals modulate food intake control by acting in both classic homeostatic and non-homeostatic neural substrates, and in some cases, to subserve similar and seemingly redundant feeding-related behavioral outcomes via signaling across multiple levels of the neuraxis. These findings taken together with the hypothesis that humans did not evolve with effective mechanisms for defending against the upper limits of body weight (e.g., obesity) suggest that energy balance is not explicitly regulated by homeostatic mechanisms, and therefore the classic dissociation between homeostatic and non-homeostatic controls of feeding may not be a useful heuristic for understanding the complex neurobiological systems that interact for feeding control and the maintenance of energy balance.

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