Three Pillars for the Neural Control of Appetite

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appetite, satiety, reward, brain, hypothalamus, eating, feeding behavior, motivation

Abstract

The neural control of appetite is important for understanding motivated behavior as well as the present rising prevalence of obesity. Over the past several years, new tools for cell type-specific neuron activity monitoring and perturbation have enabled increasingly detailed analyses of the mechanisms underlying appetite-control systems. Three major neural circuits strongly and acutely influence appetite but with notably different characteristics. Although these circuits interact, they have distinct properties and thus appear to contribute to separate but interlinked processes influencing appetite, thereby forming three pillars of appetite control. Here, we summarize some of the key characteristics of appetite circuits that are emerging from recent work and synthesize the findings into a provisional framework that can guide future studies.

INTRODUCTION

The neural processes that control appetite offer insight into basic motivated behaviors along with factors contributing to a rising incidence of obesity (1). Obesity and its associated health problems result from overeating and the difficulty of losing excess weight once it has been gained. Conversely, undereating is associated with life-threatening conditions, such as anorexia and cachexia. Due to the central role of eating in society and the major health effects associated with both overeating and undereating disorders, a considerable amount of attention is directed to the control of appetite and body weight. This problem involves the intersection of environmental, physiological, and genetic factors, which are largely integrated by neural circuits in the brain. Moreover, human genetic studies of obesity indicate an outsized role for neuronal function (2). Because of the nervous system's privileged role for controlling behavior, the neurobiology of appetite is key for understanding how procurement and ingestion of food is regulated.

In the central nervous system, numerous neuronal populations and circuits control appetite (reviewed in 3, 4). Discrete appetite circuits can serve as entry points for investigating the processes that control food intake, and these have revealed distinct components of appetitive control. Although multiple circuits influence food intake, in-depth analyses have revealed disparate characteristics, which have also led to some confusion about the neural processes underlying appetite. A major limitation is that the complexity of appetite control is obscured by the simplicity of its most basic measure, food intake. Moreover, there is a divide in appetite research between automatic or instinctive mechanisms (5, 6) and the learning-based mechanisms emphasized in behavioral psychology (7, 8). The literature describing various hormones and brain regions that influence motivation and appetite were previously reviewed (9–11). However, over the past several years, new tools for cell type-specific neuron activity monitoring and perturbation have enabled more detailed analysis of the mechanisms underlying individual appetite-control systems. Here, we summarize some of the key characteristics of appetite circuits that are emerging from this recent work and synthesize these findings into a provisional framework that can guide future studies.

Three major neural circuits robustly and acutely influence appetite but with notably different characteristics. Although these circuits interact, they have distinct properties and thus appear to contribute to separate but interlinked processes influencing appetite, thereby forming three pillars of appetite control (**Figure 1**).

1. The first pillar involves the Agouti-related protein (AGRP)-expressing neurons in the hypothalamic arcuate nucleus (ARC). These neurons elicit food intake, and when activated, they also transmit a negative valence signal that may correspond to the unpleasant feelings attributed to hunger. AGRP neurons increase their activity during energy deficit, and a reduction of AGRP neuron firing is reinforcing. Although external optogenetic or chemogenetic activation of these neurons drives food intake, they are normally rapidly suppressed just as food consumption commences. Therefore, they are primarily involved in food seeking but are less likely to normally drive food consumption.
2. The second pillar is consists of circuits involving the lateral hypothalamus (LH), a brain region that is tied to consummatory behaviors and also mediates positive reinforcement. Thus, these circuits drive food consumption and are rewarding. Recordings from the neurons in the LH show diverse activity patterns that encompass multiple phases of food seeking and consumption.
3. The third pillar involves calcitonin gene-related peptide (CGRP) neurons in the parabrachial nucleus (PBN) that potently suppress eating when activated, but these neurons do not increase food intake when inhibited. PBN^{CGRP} neurons are activated by signals associated with food intake, and they provide a signal of satiety that has negative valence when strongly activated.

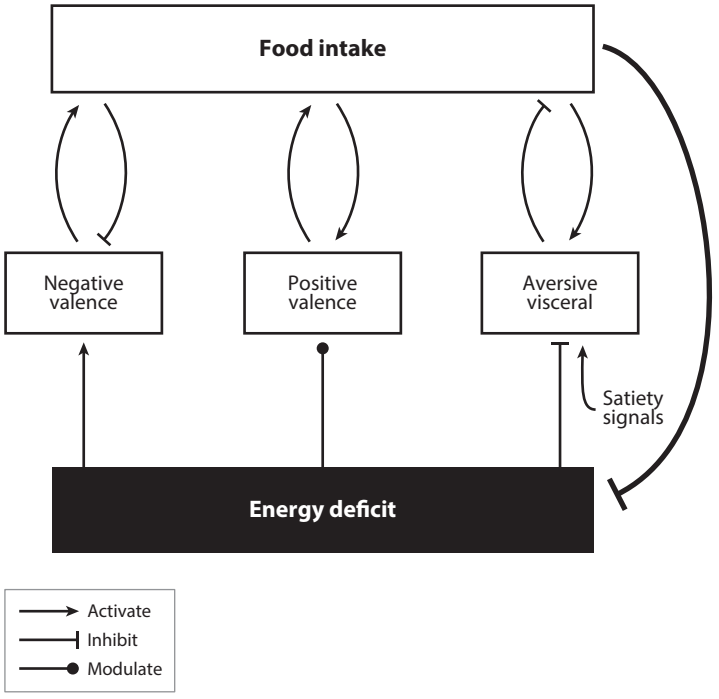

Figure 1

Three pillars of appetite control: regulation of food intake by negative valence and positive valence appetitive systems, visceral aversive pathways, and the relationship with homeostatic deficit. First, negative valence appetitive systems [e.g., Agouti-related protein (AGRP) neurons] are under homeostatic control, but AGRP neurons are rapidly inhibited by food-predictive cues. Second, positive valence-driven eating (e.g., via the lateral hypothalamus) is modulated by energy deficit but also maintains appetite irrespective of a homeostatic need state. Third, aversive visceral signals, with different motivational properties than negative valence AGRP neurons from parabrachial nucleus calcitonin gene-related peptide (PBN^{CGRP}) neurons, are activated by visceral and hormonal satiety signals and lead to cessation of food consumption. Interactions between these systems exist but are not shown here. Adapted from Reference 12.

How do these three systems fit together? A popular dichotomy divides appetite into homeostatic and hedonic systems (9). This reflects the observation that eating is observed reliably when most organisms are in a state of homeostatic energy deficit, but eating is also observed in the absence of an energetic need state, especially when highly palatable (hedonically pleasurable) food is present. However, this distinction can be misleading because it is also well established that each of these systems is influenced by signals of homeostatic state. Based on recent experiments, it was proposed that these three systems fit together in a roughly sequential manner (12). The AGRP neuron system is activated by hormonal signals of energy deficit that produce a state of negative valence and lead to food-seeking behaviors. The activity of these neurons is immediately reduced upon access to food, which reinforces an approach to environmental features that are associated with food, thereby increasing the likelihood of food cue-approach responses in a state of high AGRP neuron activity (normally a state of energy deficit). Eating commences and is driven by the circuits associated with the lateral hypothalamus. This is a positive feedback process in which the rewarding aspect of palatable nutritive food drives more consumption (13) and is further modulated by signals of energy deficit. Positive feedback is eventually counteracted by circuits involving PBN^{CGRP}

neurons, which increase their activity during food intake due to stomach distension and hormones that signal the presence of food in the gut. These core processes involve sequential engagement of these three circuits, which also interact with one another. Here, we review the background for this framework, with a focus on recent experiments.

AGOUTI-RELATED PROTEIN NEURON CIRCUITS

Food Consumption

Circuits involving neurons in the medial portion of the hypothalamus are closely associated with homeostatic control of body weight. One aspect of this homeostatic system is mediated by AGRP neurons in the ARC. AGRP neurons are activated both directly and synaptically by circulating cues of energetic deficit, such as the gut-derived hormone ghrelin (14–17) and the fat-derived hormone leptin (15). These neurons release the neurotransmitter GABA (gamma-aminobutyric acid) (18, 19) as well as the neuromodulators AGRP and neuropeptide Y (NPY) that increase feeding when injected into the brain (20, 21). Optogenetic (22) and chemogenetic (23) induction of electrical activity in AGRP neurons is sufficient to rapidly evoke voracious feeding behavior within minutes, even at times when mice normally do not eat. Oppositely, chemogenetic inhibition of AGRP neurons reduces food intake during energy deficit or during the dark period, when mice usually eat (23, 24). This acute food intake response is mediated by the release of NPY and GABA (25, 26) but not AGRP (22), which appears to increase appetite on a longer time frame of hours (26). The magnitude of AGRP neuron-evoked feeding is nearly as great for mice that are food deprived for 24 h, even on the first exposure to exogenous AGRP neuron stimulation (22). Moreover, AGRP neuron activation experiments showed that the magnitude of food consumption was an increasing function of both the number of photoexcitable neurons and the photostimulation frequency (22). Thus, cell type-specific AGRP neuron activation behaves as a "gas pedal" for feeding, meaning that the magnitude of the behavioral response is sensitive to the level of engagement of AGRP neurons.

The influence of AGRP neuron activity on behavior also leads to a dramatic increase in the motivation to work for food (23–25). This indicates that AGRP neurons do not directly control the motor actions of ingestion but instead influence a motivated process to seek and obtain food.

Influence on Learning

The processes underlying motivated behavior associated with AGRP neurons were investigated using cell type-specific perturbations. Optogenetic activation showed that AGRP neurons transmit a signal with negative valence, such that mice learn to avoid a flavor or a place in which AGRP neuron activity was high, and this may serve as a motive for mice to consume food (24). Similarly, intracranial NPY administration elicits flavor aversion (27). Conversely, food-deprived mice preferred cues associated with a reduction of AGRP neuron activity (24). This indicates an important role for AGRP neurons to influence learning about the value of environmental cues that are associated with reducing an unpleasant energy deficit state.

Although this property of AGRP neurons is consistent with human self-reporting about the unpleasantness of hunger (28–30), it is also seemingly paradoxical that a neuron population that elicits intensive food consumption would also lead to avoidance responses. After all, it would not be adaptive for an animal to avoid environmental cues that predict food. Importantly though, imaging, electrophysiology, and population activity measurements all showed that, in food-deprived mice, food intake reduces AGRP neuron activity within seconds, even before food is consumed (24, 31–33). Based on measurements made using in vivo deep-brain calcium imaging, 96% of AGRP neurons rapidly reduced activity upon just the sight of food or a food-predictive auditory

cue (24), such that nearly all of the neurons have low activity during food consumption (only 1 out of 110 imaged neurons was found to increase activity during eating). This indicates that AGRP neurons are primarily involved in food seeking but not food consumption. Interestingly, intracranial injection of NPY does not increase consumption of a sucrose solution via oral cannula (34). In contrast, food deprivation doubled intake, which is further consistent with the idea that this signaling system is less involved in the consummatory aspect of feeding behavior (34) but instead mediates food seeking.

The rapid reduction in AGRP neuron activity upon food presentation also involves learning such that initially neutral cues reduce AGRP neuron activity after they have come to be associated with food delivery (24). Moreover, sustained reduction of AGRP neuron activity requires food consumption, which is consistent with homeostatic control over these neurons (**Figure 2**) (24). Thus, there is a major role for learning in both the activity patterns of AGRP neurons and their behavioral consequences. This may also explain why mice eat in response to exogenous AGRP neuron activation, even though most AGRP neurons normally show reduced firing during eating. AGRP neuron activation presumably engages circuits that both motivate behavior and signal the identity of the need (i.e., energy deficit). Thus, eating behaviors result, in part, because these were previously learned to be effective for shutting off negative valence AGRP neuron activity. Consistent with this, for AGRP neuron-evoked food seeking, sustained AGRP neuron activation led to a reduced willingness to work for food on high reinforcement schedules over multiple sessions (24). Therefore, high effort food-seeking behaviors in response to AGRP neuron activation are greatly diminished when they do not result in the sustained inhibition of these homeostatically sensitive negative valence neurons.

Taken together, deep-brain imaging and electrical perturbation experiments indicate a learning rule for homeostatic need, where some physiological state-sensitive neurons, such as AGRP neurons, motivate behavior by a negative valence signal, which reinforces preference for items that return an animal to homeostasis (**Figure 3**). Thus, AGRP neurons are activated by weight loss, and because they are normally suppressed by food, food seeking will be selectively reinforced. Furthermore, the unpleasant motivational properties of AGRP neurons indicate that they mediate some of the negative emotional qualities of weight-loss diets.

Feeding Behavior Without AGRP Neurons

Ablation of AGRP neurons is also consistent with a role in modulating food preference and food procurement primarily in energy deficit states. Diphtheria toxin-induced killing of AGRP neurons in adult mice leads to short-term anorexia (35) due to visceral malaise resulting from loss of a key AGRP neuron circuit connection suppressing an aversive visceral circuit in the parabrachial nucleus (36). When AGRP neurons are ablated in neonatal mice, they grow up to have normal body weight as a result of compensatory circuits (35, 36). However, detailed analysis of mice that lack AGRP neurons showed altered food consumption characteristics (37).

Mice with neonatal AGRP neuron ablation, after developing to adulthood, displayed an enhanced reliance on incentive-driven appetite. After food deprivation, AGRP neuron-ablated mice showed a blunted refeeding response with grain-based chow, which is a moderately rewarding food, but they ate as much of a palatable high-fat, high-sugar (HFHS) diet as intact mice. Similarly, the homeostatic hormone ghrelin did not elicit feeding with grain-based food in AGRP neuron-ablated mice (as it does in intact mice), but ghrelin was effective at increasing HFHS diet consumption. Furthermore, elevated dopamine signaling resulted in increased grain food consumption only in AGRP neuron-ablated mice, presumably due to a greater reliance on dopamine release for appetite regulation. In the absence of AGRP neurons, appetite is faulty with a moderately palatable

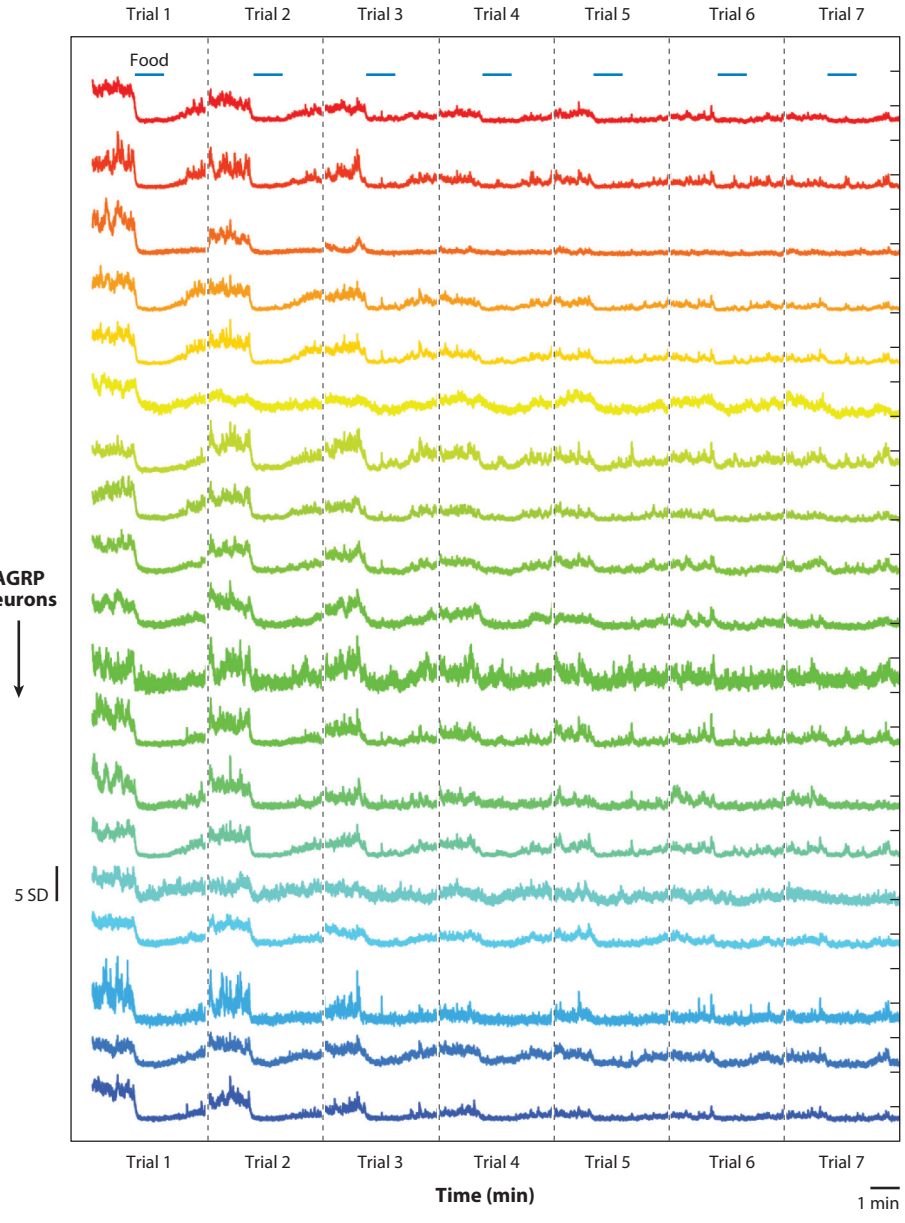

Figure 2

Each row presents an example of the calcium dynamics of individual AGRP neurons during multiple brief trials of food consumption. AGRP neurons rapidly transition from high activity to low activity upon food delivery, and then activity increases slowly after food is removed. Each trial is separated by a 6-min interval (*vertical gray lines*) several minutes after food removal. AGRP neuron activity is elevated but below the prefood level from the preceding trial. Each subsequent round of food intake leads to a progressive reduction in the prefood AGRP neuron activity for each trial. After sufficient food is consumed, the prefood activity level is similar to that in the presence of food. This reduction in basal calcium activity occurs at different rates for distinct AGRP neurons in the same mouse. Figure based on data from Reference 24; figure courtesy of Shengjin Xu. Abbreviations: AGRP, Agouti-related protein; SD, standard deviation.

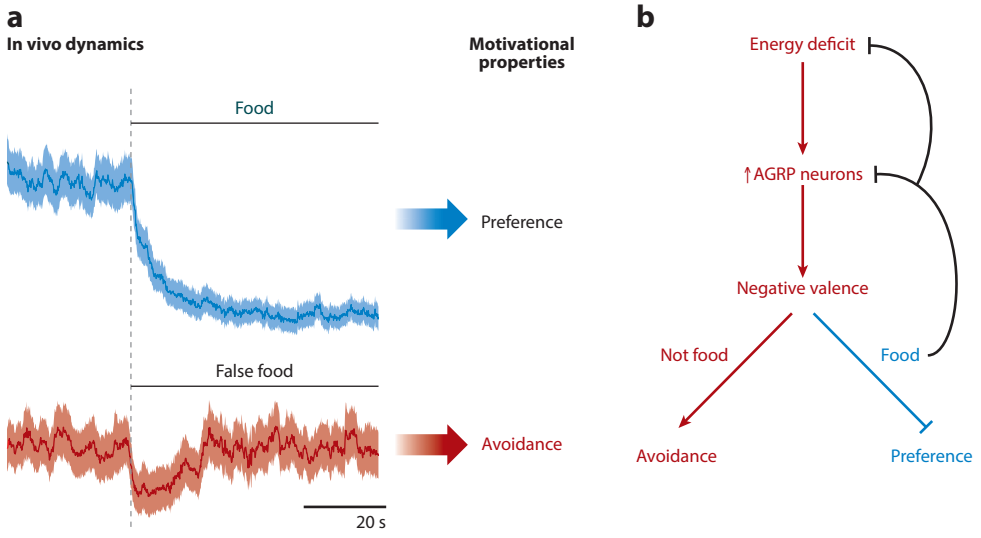

Figure 3

A motivational mechanism for Agouti-related protein (AGRP) neurons. (*a*) Deep-brain calcium imaging shows that AGRP neurons reduce activity upon the presentation of food, and this corresponds to motivational properties measured in chemogenetic AGRP neuron inhibition experiments (not shown), which were found to be rewarding (i.e., it induces preference learning). In contrast, AGRP neuron activity is only very briefly suppressed by the presentation of nonfood items, and high AGRP neuron activity was shown to be unpleasant (i.e., it leads to avoidance). Figure based on data from Reference 24. (*b*) This illustrates a learning rule in which an energy deficit state increases AGRP neuron activity, which leads to learned avoidance for nonfood items (*red lines*). Inhibition of this negative valence signal induces (disinhibits) preference learning for items that return an animal to homeostasis, typically food (*black lines*). Thus, AGRP neuron activation elicits eating because mice have previously learned that food intake is a response that reduces the negative valence signal.

grain-based diet, but this is normalized by excess dopamine or by feeding a HFHS diet, which can even lead to overeating in AGRP neuron-ablated mice (37). Thus, AGRP neurons are important for motivating the consumption of less palatable food during energy deficit, but with sufficiently palatable foods, other systems are able to respond to the homeostatic need state by increasing food intake.

AGRP Neuron Circuits

AGRP neurons target a variety of downstream brain regions (38), subsets of which are also sufficient to induce food consumption behaviors. These include the paraventricular hypothalamic nucleus (PVH), the bed nucleus of the stria terminalis (BNST), the LH, and to a lesser extent, the paraventricular thalamus (PVT) (**Figure 4**) (39). AGRP neuron projections potently silence a subset of PVH neurons through the release of GABA (25). Correspondingly, inhibition of the PVH increases food intake (25, 40) nearly to the same degree as AGRP neuron activation. Synaptic silencing of PVH projections in the vicinity of the ventrolateral periaqueductal gray (vlPAG) recapitulates the elevated food intake associated with PVH neuron silencing (41). Silencing melanocortin receptor 4 (Mc4r)-expressing neurons in the PVH, a subset of the cells in this brain area, also increases appetite but to a lesser extent (42). Activation of PVH^{MC4R} neuron projections to the nearby PBN reduced food intake in food-deprived mice (42). Interestingly, this $PVH^{MC4R} \rightarrow$ PBN

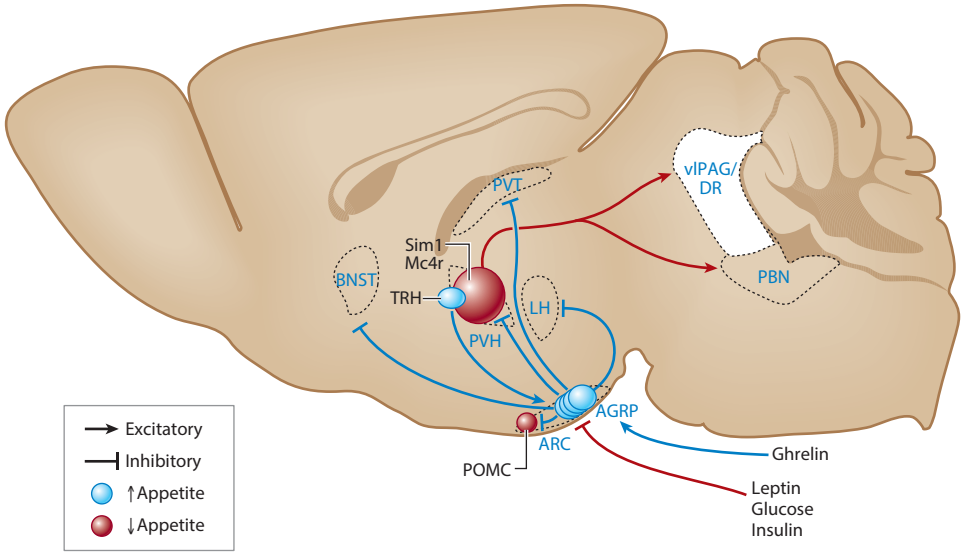

Figure 4

Summary diagram illustrating AGRP neuron circuits that influence food consumption. Inhibitory AGRP neuron projection fields whose activation is sufficient to induce food consumption behaviors: the PVH, BNST, LH, and to a lesser extent, the PVT. A reciprocal projection from thyrotropin releasing hormone-expressing neurons in the PVH can increase food intake by activating AGRP neurons. Activation of most neurons in the PVH expressing Sim1 or a subset of these that express Mc4r can suppress food intake, which involves a projection to the PBN. Synaptic silencing of PVH^{SIM1} neurons in the vicinity of the vlPAG or DR elicits robust food intake. Based on anatomical studies, AGRP neurons are shown as separate subpopulations defined by their axon projection sites. Abbreviations: AGRP, Agouti-related protein; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe nucleus; LH, lateral hypothalamus; Mc4r, melanocortin receptor 4; PBN, parabrachial nucleus; POMC, proopiomelanocortin; PVH, paraventricular hypothalamic nucleus; PVT, paraventricular thalamus; Sim1, single-minded 1 transcription factor; TRH, thyrotropin-releasing hormone; vlPAG, ventrolateral periaqueductal gray.

projection showed rewarding characteristics in a real-time place preference assay only in mice that were in a state of energy deficit (42). This manipulation is analogous to the disinhibition of PVH neurons during energy deficit that is expected to result from suppressing the activity of AGRP neurons (24), although somewhat different assays were used in the two studies. Although the motivational properties of AGRP→LH circuits have not been studied directly, administration of small amounts of NPY to the perifornical region of the LH increased feeding in rats, but the same rats showed place avoidance for NPY in a separate assay (43). Thus, the motivational properties of different nodes in the AGRP neuron circuit appear to be associated with reinforcement processes that result from reducing a negative valence signal in a state of energy deficit.

The examination of motivational properties of AGRP neurons and other nodes in this circuit have primarily focused on the acute effects on feeding behavior. Nevertheless, AGRP neurons are also involved in long-term energy homeostasis, and release of the neuropeptide AGRP from these neurons appears to specifically influence feeding over longer timescales (26). This is analogous to the opposite effects of activating the intermingled ARC neuron population and proopiomelanocortin (POMC)-expressing neurons, which suppress food intake and body weight (44), also over timescales of hours to days through engagement of the melanocortin receptors (22, 45). Notably, AGRP administration to the third ventricle suppresses conditioned place preference to

sucrose consumption (46), indicating that AGRP may potentially have similar negative valence properties resulting from acute AGRP neuron activation.

Summary and Recent Results

Experiments using cell type-specific manipulations of AGRP neuron activity support a role for influencing feeding behavior that is associated with learning to suppress a negative valence output. This is supported by observations that NPY elicits feeding but also conditions flavor and place avoidance. This negative valence signal may motivate behavior, and it also conditions approach to environmental cues that lead to prolonged reduction of AGRP neuron activity. In vivo imaging shows that this involves ingestion of food, whereas sensory cues that represent food transiently suppress AGRP neuron activity. The demonstration of reduced AGRP neuron activity during food consumption is surprising in light of optogenetic and chemogenetic experiments showing that activation of these neurons promotes food intake. Thus, AGRP neuron photostimulation-evoked eating may be due to actions previously learned to reduce AGRP neuron activity.

A new study (47) reports several additional findings relevant to the motivational characteristics of AGRP neuron-mediated appetite. First, optogenetic activation of AGRP neurons before food delivery elicited eating after cessation of photostimulation. Additionally, preference conditioning was reported for flavors consumed after AGRP neuron photostimulation was stopped. Finally, mice could be trained to lever press at a low reinforcement ratio to self-administer AGRP neuron photostimulation in the presence of food but not in the absence of food (unless the lever was previously associated with food delivery). Based on this result, the authors concluded that AGRP neurons transmit a sustained positive reinforcement signal that selectively enhances food reward.

In these studies using AGRP neuron silencing during food deprivation (24) or the cessation of AGRP neuron photostimulation in well-fed mice, (47) AGRP neurons condition preference learning after a transition from high to low activity. This could be related to offset of a negative valence signal and/or the selective enhancement of food reward by a signal that persists after the offset of AGRP neuron activity.

AGRP neuron activation and induction of a virtual hunger state are useful for examining the circuit and motivational processes by which this population elicits appetite. However, it is important to consider the relevance to the natural hunger state associated with energy deficit, which is the primary condition in which AGRP neuron activity is elevated. AGRP neuron silencing during food deprivation reduces food consumption (23, 24), whereas cessation of AGRP neuron stimulation in the absence of food followed by food delivery leads to robust food-seeking and consumption (47). This discrepancy between AGRP neuron silencing in hunger and the elevated feeding following optogentic stimulation in the absence of food may indicate some limitations of the photostimulation model to track the contribution of AGRP neurons to natural energy deficit, possibly due to the buildup of neuropeptides.

Nevertheless, the finding that AGRP neuron activity is reduced during food consumption and that eating during AGRP neuron activation leads to flavor and place avoidance indicate that these neurons are unlikely to drive food consumption during physiological energy deficit. To maintain the consumption of food, an important role must be contributed by other neural circuits, such as those associated with the lateral hypothalamus.

CIRCUITS INVOLVING THE LATERAL HYPOTHALAMUS

Electrical Activity Perturbations of Lateral Hypothalamus Neurons

The LH has long been studied as a feeding center based on the observation that electrical stimulation in this area elicits avid food consumption (48, 49), whereas lesions to this area reduce food

intake (50). One interpretion is that the hypothalamus acts as a behavioral controller containing neurons that would control the motor patterns associated with basic survival behaviors, such as jaw movements relevant for eating (51–53). However, there are indications based on electrical activity manipulations that the behavioral effects associated with LH manipulations might not be specific for appetite. Some animals with stimulating electrodes targeted to the LH selectively consume food (48) in response to electrical stimulation, whereas other subjects perform different behaviors, such as drinking (54, 55), predatory attack (56), gnawing (57, 58), or sexual activity (59). Moreover, the magnitude of these behavioral responses was often modest upon initial exposure to brain stimulation but increased to voracious eating with successive exposure to the stimulation (60, 61). Although these disparate behavioral outputs were initially attributed to slight variation in stimulating electrode placement (62, 63), when rats that showed selective electrical stimulus-bound eating were stimulated in the absence of food but in the presence of these other potential consumable items, they switched their preference to that item, such as drinking water, which then persisted even when food was reintroduced (58). This is in contrast to feeding evoked by photostimulation of AGRP neurons in the ARC, which have consistent food intake responses across trials and are selective for food over water (22). An important clue for this lack of behavioral specificity is found in another major property of the LH, which is that electrical stimulation is reinforcing. Animals reliably perform instrumental responses, such as lever pressing, to deliver electrical stimulation to the lateral hypothalamus in the same sites that elicit robust feeding responses (64). Based on these studies, one role of the LH and its circuits is influencing the reward value of food (65, 66).

More recent studies have refined this classic body of work by applying new cell type-specific tools for manipulating neuronal activity in LH circuits (4). Optogenetic activation of LH inhibitory neurons, marked by the vesicular GABA transporter (*Vgat*, *Slc32a1*), elicited feeding, and these manipulations were also rewarding (67, 68). In contrast, activation of excitatory LH neurons expressing the vesicular glutamate transporter type 2 (*Vglut2*, *Slc17a6*) suppressed feeding and led to avoidance responses, whereas photoinhibition of these neurons was rewarding and led to food consumption (67). These experiments revealed a subdivision, albeit a broad one, of cell populations in the lateral hypothalamus with opposite effects on feeding and reward.

Lateral Hypothalamus Neuronal Dynamics

Electrical activity recordings of LH neurons in primates and rodents show the involvement of this brain area in representing information about food seeking, taste, and food-predictive cues (69–72). Recordings and lesion studies also indicate that LH activity modulates the hedonic quality of gustatory stimuli (73) and impacts conditioned taste preference and aversion (74–76), implicating the LH in palatability processing (77–79). Moreover, gustatory sensory information enters the brain via the nucleus of the solitary tract (NTS) and is routed through the PBN to the LH (80, 81). This sensitivity to food palatability, coupled to the reinforcing qualities of LH perturbations, suggests a role for the LH in promoting the consumption of palatable foods (13).

In vivo recordings from neurons in the LH without regard to molecularly defined cell type show heterogeneous responses to food. Food consumption in energy deficit is associated with rapid modulation of activity in LH neurons, and some of these responses are sensitive to the energetic or satiety state of the animal (69, 71, 82). Recent in vivo imaging experiments show that LH^{VGAT} neurons, which as a population promote feeding, display heterogeneous response types in a food-seeking task. Some members of the LH^{VGAT} subpopulation are excited in a nose poking food-seeking task, and a mostly separate ensemble are excited during consumption of food. In

addition, a subset of LH neurons that project to the ventral tegmental area (VTA), which are not otherwise distinguished by molecular markers, were found to modulate activity in a conditioned feeding task during the conditioned response of entering a food delivery area but not during the consumption of food (83). A separate LH subpopulation responded to food-predictive cues, which required neural activity in the VTA and were consistent with reward prediction error signaling (83). The dynamics of LH neurons before and during food intake indicates that these neurons participate in both preparatory and consummatory aspects of feeding behavior. Presently, cell type-manipulation experiments have not precisely defined the role of particular neuronal populations that represent these different dynamic responses. In the case of $LH^{VGAT} \rightarrow$ VTA projecting neurons, photostimulation led to poorly directed consummatory responses that involved licking and gnawing of the floor or empty space (83). Similarly, activation of the entire population did not elicit food-seeking behavior in a nose poke task, but mice extensively licked the unrewarded food delivery spout (68). To understand the disparate response types found in this brain area, further delineation of cell populations in the LH based on their response properties during well-structured feeding behavior tasks, along with their causal roles, will be needed.

In addition to these broadly defined subgroups of LH neurons, two small subpopulations of molecularly defined cell populations in the LH have received extensive consideration for their role in increasing appetite: those expressing hypocretin (Hcrt, also called orexin) and a separate population expressing melanin concentrating hormone (MCH) appetite (84–86). LH^{HCRT} neuron dynamics indicate that they are active in a range of behavioral states not limited to eating and were interpreted as responding to changes in sensory stimulation (87). In vivo electrophysiology experiments showed that these neurons were maximally active during exploratory behavior and equally active during food consumption and grooming (87), which are two different behavioral states. Recently, measurement of population calcium dynamics in LH^{HCRT} neurons found a reduction in neuronal calcium levels during food intake (88). Resolution of the discrepancy between these two studies requires further measurements of single LH^{HCRT} neuron dynamics. LH^{MCH} neurons discharge in a reciprocal manner to LH^{HCRT} neurons in the sleep-wake cycle (primarily during REM sleep) (89, 90). In population activity measurements, they are activated by novel stimuli and suppressed by restraint stress (91), but little is known about their endogenous activity in during feeding. However, optogenetic activation of LH^{MCH} neurons promotes flavor conditioning, and ablation of MCH neurons (including both DMH^{MCH} and LH^{MCH} neurons) blocks nutrient-mediated flavor conditioning, indicating a role for nutrient reinforcement (92). Thus, LH^{HCRT} neurons and LH^{MCH} neurons appear to play an important role in arousal and nutrient conditioning, respectively, but further evaluation of in vivo neuronal dynamics is needed to better understand their relationship to appetite and food ingestion.

Overall, existing data on the role of the LH indicate participation during all of phases of food-seeking and consumption behavior. However, cell type-specific activity manipulations reveal a robust role in driving food consumption. Nevertheless, major gaps remain regarding the identity and causal role of distinctive neuronal subpopulations that modulate their firing in specific phases of feeding behavior. Better delineation of cell types in the LH and well-structured behavioral tasks are needed to advance understanding of the division of labor within the LH.

Lateral Hypothalamus Circuit Connections

The LH^{VGAT} and LH^{VGLUT2} subpopulations appear to engage overlapping but also somewhat different neural circuits, receiving diverse inputs from multiple brain areas conveying sensory, homeostatic, as well as reward information (**Figure 5**). Inhibitory projections from the BNST

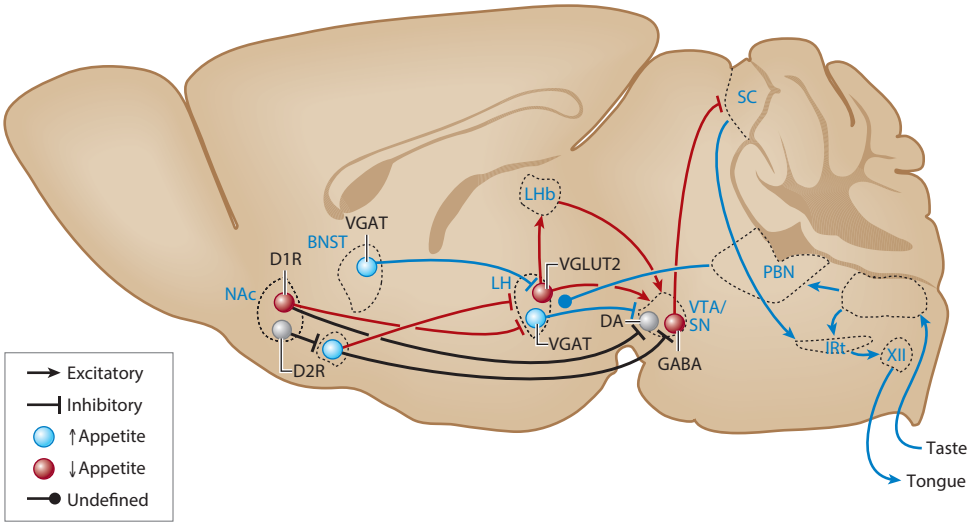

Figure 5

Summary diagram illustrating a subset of LH neuron circuits that influence food consumption. Activation of LH^{VGAT} neurons and inhibition of LH^{VGLUT2} neurons increase food consumption. This involves inhibitory circuits from BNST and D1R neurons of the NAc to LH neurons. LH neurons are activated by gustatory (taste) information transmitted from the NTS and PBN. LH neural circuits promote reward and motor actions, in part through projections to the VTA and SN, which contain neuron populations that release dopamine (projections of DA neurons to NAc and VP are prominent but not shown) or GABA. Inhibition of GABA-releasing SN projections to the SC activates licking central pattern generators in the IRt, which activate motor neurons in the XII that control licking. Abbreviations: BNST, bed nucleus of the stria terminalis; DA, dopaminergic; D1R, dopamine 1 receptor; D2R, dopamine 2 receptor; GABA, gamma-aminobutyric acid; IRt, intermediate reticular formation; LH, lateral hypothalamus; LHb, lateral habenula; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; SC, superior colliculus; SN, substantia nigra; VGAT, vesicular GABA transporter; VGLUT2, vesicular glutamate transporter 2; VP, ventral pallidum; VTA, ventral tegmental area; XII, hypoglossal nucleus.

to the LH elicit eating and reward when activated, which are due to preferential inhibition of LH^{VGLUT2} neurons (67). Conversely, neurons in the nucleus accumbens (NAc), a brain region implicated in reward processing, pause firing during reward consumption and increase food intake when inhibited (93–97). Neurons in the NAc receive dopaminergic inputs from the VTA, and reduced dopaminergic transmission in the NAc reduces the motivation for food and drugs (98–100). The NAc contains two major subpopulations of neurons that express either dopamine D1 or D2 receptors. Most projections from the NAc to the LH originate from D1R-expressing neurons (101). Activation of NAc^{D1R} but not NAc^{D2R} neurons selectively inhibits LH^{VGAT} neurons and reduces food consumption (101). NAc^{D1R} neurons play a role of "sensory sentinel" (95) to rapidly veto feeding in hungry mice, whereas inhibiting D1R-expressing NAc neurons prolongs consumption, even in well-fed mice (101). Correspondingly, in vivo recordings show that NAc^{D1R} neurons pause their firing during consumption, whereas NAc^{D2R} neurons do not (101). Although NAc^{D2R} neuron activation did not reliably affect feeding, NAc^{D2R} neurons project to the ventral pallidum (VP), which is involved in processing taste palatability (102), and VP activation increases feeding via the LH (103).

The midbrain dopamine system in the VTA and substantia nigra (SN) is critical for reinforcement learning, including lateral hypothalamus self-stimulation (104–107). The VTA receives GABAergic input from LH neurons, and activating these projections induces feeding and gnawing (83). Ex vivo functional circuit mapping showed synaptic connections of $LH^{VGAT} \rightarrow$ VTA onto both dopamine and GABA-releasing VTA neurons (83). The functional significance of this circuit is not yet well established. Dopamine neurons in the VTA respond to cues that predict reward (106), and the amplitude of this reward prediction error signal is sensitive to satiety state and leptin (108). Therefore, inputs that precede feeding appear to be most important for controlling the activity of these neurons. However, LH → VTA-projecting neurons were associated with conditioned responding, which occurs after the food-predictive cues that are associated with dopamine neuron activation. The activity of GABA-releasing neurons in the SN is sensitive to satiety state (109). These neurons provide a link to motor behavior, and inhibitory SN neurons project to the superior colliculus (SC). A pause in SN → SC activity is important for releasing motor actions (97, 110), and activation of SN → SC projections can suppress licking for liquid food (111). Neurons in the SC project to the medullary reticular formation (RT), which contains premotor neurons that generate motor patterns for chewing and licking by output to orofacial motor neuron pools, such as the hypoglossal nucleus (112). LH → VTA projections that lead to the inhibition of SN → SC neurons could contribute to the increased conditioned responding, such as undirected licking or food port entry, that was observed with LH → VTA and LH^{VGAT} neuron activation (68, 83).

Aversive behavioral responses were also sometimes observed in early electrical stimulation experiments, although these studies lacked cell type resolution (113–115). One explanation is that LH^{VGLUT2} neurons, which suppress eating when activated en masse, have a prominent excitatory projection to the lateral habenula (LHb), a brain region known to mediate the emotional qualities and learning of aversive stimuli (116) via inhibitory influences on the VTA (117, 118). Optogenetic inhibition of $LH^{VGLUT2} \rightarrow$ LHb projections selectively increases palatable food intake and causes place preference (119), suggesting its involvement in the regulation of feeding and reward.

Hormones and peptides associated with energy homeostasis interact with LH neurons and their downstream targets in the VTA (120, 121). Hormones that signal energy surfeit, such as leptin, reduce food intake, the preference for sucrose, and LH self-stimulation (122–125). This may be one component in reducing the effectiveness of the reward value of food under states of normal or excess energy stores. Overall, the LH circuit appears to be under homeostatic control and can be modulated by hormones and peptides that signal energy deficit or energy surfeit, which will increase or reduce the rate of consumption, respectively.

Summary

Multiple studies show that the LH plays a crucial role in appetite. Because activation of the LH is rewarding, elicits appetite, and is modulated by food consumption, food intake appears to be propagated by the continued activation (or inhibition) of the appropriate LH neuron population during progressive consumption of food. These neurons receive diverse inputs from regions that are under direct homeostatic control and from areas that are associated with hedonic or environmental feeding situations (103, 126). In most studies, evoked eating is closely connected to the reward characteristics of LH stimulation. Homeostatic control appears to act on this reward property whereby the threshold for self-stimulation is lowered by food restriction (127), indicating that homeostatic need modulates the reward characteristics of the LH. However, LH neurons also influence motor actions associated with ingestive behaviors, such as through SN → SC → RT → motor nuclei circuits.This represents another area that deserves further investigation.

CIRCUITS INVOLVING PARABRACHIAL NUCLEUS CALCITONIN GENE-RELATED PEPTIDE NEURONS

If food intake is driven via LH circuits by a self-sustaining relationship between nutrient detection and reward processes, then another process is needed to terminate eating. Satiety is a distinct concept from a reduction in appetite (13, 128). Satiety is associated with a range of gut-derived hormonal signals, such as cholecystokinin (CCK) (129, 130) and glucagon-like peptide-1 (GLP1) (131), as well as characteristic behavioral readouts (132, 133). In addition, a reduction of activity in satiety systems does not always lead to a large rise in appetite. This is exemplified by neurons in the PBN, which is a relay for taste and visceral sensory information. Using lesion studies and expression of the immediate early gene *Fos*, studies show that activated neurons of the PBN are associated with aversive visceral states mediated by nausea (reviewed in 134), hormones that elicit satiety (135, 136), and stomach distention (137, 138).

Recent work has focused on a subpopulation of excitatory neurons in the PBN that express the neuropeptide CGRP. These neurons represent a considerable fraction of the neurons expressing *Fos* in response to induction of nausea by lithium chloride or illness by lipopolysaccharide (139). They appear to be distinct from the PBN neurons that mediate the transmission of gustatory information (139). Optogenetic activation of CGRP neurons powerfully reduces food intake (139). Importantly, inhibition of these neurons does not directly increase appetite, but inhibition does increase food intake under conditions of nausea or exogenous administration of satiety-related hormones (139). In fact, PBN^{CGRP} neurons are broadly tuned to a wide variety of aversive visceral signals, including pain-related signals (139, 140). Activating PBN^{CGRP} neurons is aversive and leads to avoidance learning of cues that are paired with their elevated activity (141). Silencing PBN^{CGRP} neurons reduces the effective responses to painful stimuli (140). In addition, PBN^{CGRP} neuron inhibition increases the duration of a meal without increasing the total amount of food consumed (142). Therefore, within a fixed amount of time, the number of food consumption bouts decreases while the amount of food consumed within a bout increases. Thus, PBN^{CGRP} neurons mediate the physiological effects of satiety.

PBN^{CGRP} Neuron Circuits

The PBN^{CGRP} neurons are part of a circuit that transmits visceral peripheral information to the forebrain (**Figure 6**). PBN^{CGRP} neurons receive projections from excitatory *Vglut2*-expressing neurons from the NTS, which is a major entry point for visceral, taste, hormonal, and metabolic information into the brain (143, 144). These NTS^{VGLUT2} neurons are in turn regulated by serotonergic inputs from neurons in the raphe magnus and raphe obscurus (143). PBN^{CGRP} neurons also project to the central nucleus of the amygdala (CeA) (139). The CeA is a brain area associated with aversive emotional responses, such as fear and anxiety (145), although a role in appetitive behavior is also established (146, 147). PBN^{CGRP} neurons activate a subpopulation of protein kinase C δ (PKCδ)-expressing neurons in the CeA that potently suppress food intake (148). In addition, silencing $CeA^{PKC\delta+}$ neurons leads to a slight increase in food consumption in well-fed mice and decreases the anorexic effects of CCK and lithium chloride in food-deprived mice (148). This is due to an increase in feeding bouts (148), not bout size, unlike in the case of PBN^{CGRP} neuron silencing (142).

The visceral circuit involving PBN^{CGRP} neurons projecting to the CeA appears to play a key role in mediating satiety and operates in opposition to LH-driven food consumption to diminish food intake. The output of the CeA that controls food intake remains to be determined. However, this circuit reveals the neural underpinnings of the relationship between meal size, satiety, and the aversive properties of nausea and pain.

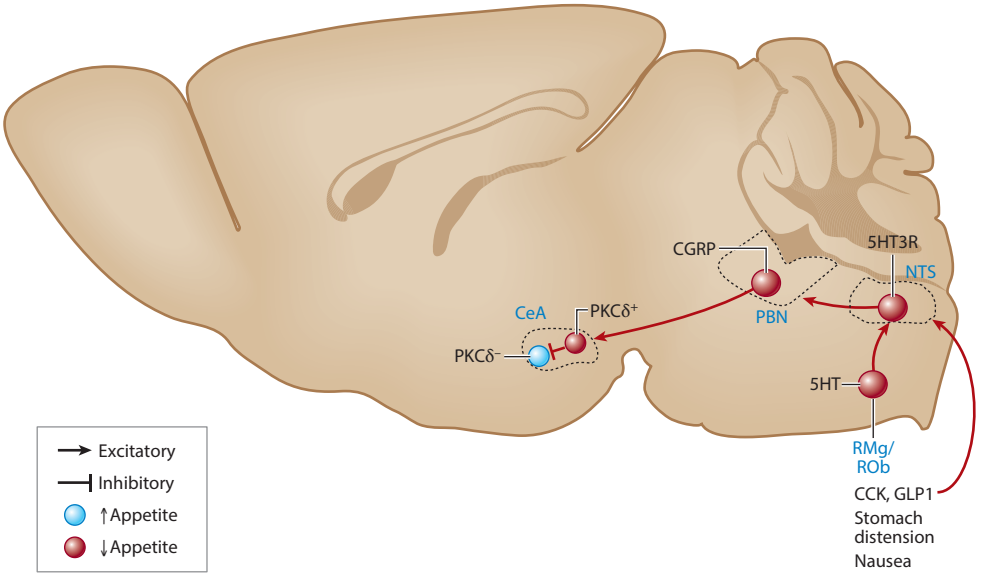

Figure 6

Summary diagram illustrating PBN^{CGRP} neuron circuits that influence satiety. Visceral and hormonal cues are received by the NTS and activate PBN^{CGRP} neurons to suppress feeding by projections to the $PKC\delta^{+}$ neurons in the CeA. These neurons inhibit intermingled $CeA^{PKC\delta-}$ neurons to influence food intake in the presence of the anorectic hormone CCK. Abbreviations: 5HT, serotonin; 5HT3R, serotonin receptor 3; CCK, cholecystokinin; CeA, central nucleus of the amygdala; CGRP, calcitonin gene-related peptide; GLP1, glucagon-like peptide-1; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; PKCδ, protein kinase C δ; RMg, raphe magnus nucleus; ROb, raphe obscurus.

SUMMARY OF THREE DISTINCT CIRCUIT PROCESSES

Here, we propose a framework, based on recent studies, of the processes by which multiple neuron populations influence food intake. We use three criteria to argue that circuits involving AGRP neurons, LH neurons, and PBN^{CGRP} neurons mediate different behavioral processes.

The first criterion is the timing of neuronal activity modulation in response to food. Evidence that AGRP neurons are active during energy deficit before a meal and are rapidly suppressed during eating indicate that they likely play a role in the preparatory aspects of feeding. LH neurons appear to be involved at multiple stages of the behavior and influence different aspects of eating: reward, approach, and palatability encoding. Precise PBN^{CGRP} neuron dynamics during food intake are not yet known, but *Fos*-expression analysis indicates that they encode visceral responses to satiety cues, and neurons in the PBN show stomach distension thresholds for activation (137).

The second criterion that we use to distinguish the circuits is their effect on food intake. AGRP neurons promote instrumental food seeking but LH^{VGAT} neurons do not. AGRP, LH^{VGLUT2}, and LH^{VGAT} neuron circuits bidirectionally influence food consumption, but LH^{VGAT} neurons also induce undirected licking and gnawing behaviors. PBN^{CGRP} neurons suppress food intake when activated but do not lead to an increase in food intake when silenced. However, they do lead to an increase in meal size, which is compensated by a reduction in meal number, consistent with a role primarily in satiety (142).

The third distinguishing category is the behavioral valence of the output of different circuits. AGRP neurons increase food seeking but have a negative valence output. AGRP neuron silencing during food restriction (when AGRP neurons have high basal activity) is reinforcing. PVH neurons, which are inhibited by AGRP neurons, have a positive valence output in food-restricted mice. LH^{VGLUT2} neurons show negative valence, but they decrease eating, whereas LH^{VGAT} neurons increase eating and have positive valence. Therefore, AGRP neuron circuits appear to reinforce environmental cues associated with offset of the physiological need state, whereas LH neuron circuits participate in reinforcing specific cues and actions associated with rewarding aspects of food consumption. PBN^{CGRP} neurons decrease food intake and have negative valence when strongly activated. The processes mediated by these three pillars of appetite control correspond to classic descriptions of feeding behavior phases: appetitive food seeking, consummatory food intake, and satiety processes (132, 149).

In light of the apparent diversity of responses mediated by the LH, why do we need an AGRP system? Alternatively, why are there both negative and positive valence systems that promote feeding behavior? Several authors have outlined reasoning that a negative valence system in hunger is not necessary given the homeostatic sensitivity and behavioral flexibility of the positive valence system involving the NAc, LH, and VTA/SN (7, 8). However, experiments looking at the feeding behavior of mice lacking AGRP neurons provide some insight here (37). Mice and people have for most of their history often lacked easy access to highly palatable foods. Therefore, many animals have to make do with whatever can be found. The LH is especially sensitive to palatable food sources, but when delectable morsels are not present, organisms depend on the AGRP neuron system in times of metabolic challenge. The AGRP neuron negative valence signal is activated by energy deficit and suppressed by nutritive food consumption, so mice learn to eat when they get hungry to minimize this unpleasant state (24). This is complemented by the neurons in the LH that are both homeostatically sensitive and also mediate rewarding responses to palatable food. Thus, the negative valence output of AGRP neurons acts to impose a cost on an animal during a state of energy deficit, such that it must search for food. It also provides a component of reinforcement for consuming food, even if it is not very palatable, as long as this unpleasant physiological state is relieved.

Caveats

One limitation of the divisions emphasized in this framework is that they may artificially imply that each of these processes operates independently, but there is clearly a great deal of interaction between these systems. AGRP neurons project to the lateral hypothalamus, and this projection increases food intake (39). AGRP neurons also participate in additional interactions such as a projection to the PBN, and activating this circuit does not increase food intake (25, 39), but this projection does increase meal size in hungry mice (142). This is consistent with effects from inhibiting PBN^{CGRP} neurons (142). AGRP neurons also project to the CeA (the target of the PBN^{CGRP} projection), and although this projection does not increase food intake (39), the possibility for an effect on meal size remains to be examined. Interestingly, AGRP neurons also appear to influence dopamine neuron functions developmentally, although there is no direct axonal connection in adult mice (150). LH neurons are so diverse in their response types that they could potentially be involved at many stages of feeding behavior. Interestingly, some LH^{VGAT} neurons project to the PVH, and optogenetic stimulation of these fibers increases food intake, providing a potentially important connection between these two pathways (151). LH neurons also have bidirectional interactions with the PBN (78, 152), although only a few PBN^{CGRP} neurons are reported to project there (139). Notably, inhibition of PBN^{VGLUT2} neurons promotes food intake, and the PBN

receives glutamatergic input from Mc4r-expressing neurons within the PVH (153), which were found to suppress food intake (42). Thus, these three pillars of appetite control have distinctive characteristics, but there is clear evidence for extensive interactions between these systems.

It should also be noted that the manipulation and monitoring of very broad categories of neurons in the LH, coupled with the extensive LH interactions with AGRP, PVH, BNST, amygdala, and PBN circuits, still leave open the possibility for a dissociation of the rewarding characteristics of the stimulation in the LH and the ability of neuronal activation to elicit feeding (154). Moreover, following cessation of AGRP neuron photostimulation in the absence of food, subsequent food intake is reinforced. This could reflect offset of a prolonged negative valence signal (24), prolonged effects of AGRP neuron output to prime positive valence processes selectively in conjunction with eating (47), or a combination of these processes. Thus, further refinement of the cell types involved in each brain region associated with appetite is essential for a clearer understanding of the degree to which separate processes controlling appetite are mediated by these different circuits.

CONCLUSION

Modern changes in our food environment have posed challenges for human health due to the conserved neural circuits that regulate appetite. These circuits are specialized for responding to nutrients and hormones that are associated with organismal energetic state, and they also influence learning in a distinct fashion. In our current food environment, an overabundance of highly palatable food might frequently engage LH circuitry that reinforces consumption, thus favoring overeating. The difficulty of losing excess weight is likely related to the function of AGRP neuron circuits, which are activated when body weight falls below an individual's energy balance set point. It is the interaction of these three pathways that drives the initiation, maintenance, and termination of food consumption. With improved understanding of the cell types, connections, and dynamics within and between these pathways, principles can emerge explaining how appetite can be altered by diet, plasticity, early development, or pathophysiology to give rise to overeating and undereating behaviors.

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