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Acts of appetite: neural circuits governing the appetitive, consummatory, and terminating phases of feeding

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Abstract

The overconsumption of highly caloric and palatable foods has caused a surge in obesity rates in the past half century, thereby posing a healthcare challenge due to the array of comorbidities linked to heightened body fat accrual. Developing treatments to manage body weight requires a grasp of the neurobiological basis of appetite. In this Review, we discuss advances in neuroscience that have identified brain regions and neural circuits that coordinate distinct phases of eating: food procurement, food consumption, and meal termination. While pioneering work identified several hypothalamic nuclei to be involved in feeding, more recent studies have explored how neuronal populations beyond the hypothalamus, such as the mesolimbic pathway and nodes in the hindbrain, interconnect to modulate appetite. We also examine how long-term exposure to a calorically dense diet rewires feeding circuits and alters the response of motivational systems to food. Understanding how the nervous system regulates eating behaviour will bolster the development of medical strategies that will help individuals to maintain a healthy body weight.

The term obesity is an absurdly monolithic label encompassing the many physiological and psychological consequences of a positive energy balance[1]. Myriad elements contribute to increased food intake, including genetics, socioeconomic status, food availability, aggressive marketing, engineered palatable products, stress, anxiety, appetitive cues, memories,

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Author contributions

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Competing interests

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medications, resistance to internal satiety signals, depression, and misinformation about health and nutrition. Because many of these societal influences cannot be faithfully replicated in a controlled laboratory setting, most work has instead focused on investigating the neurobiological underpinnings of eating to understand how individuals may develop obesity. Perhaps a common myth among the misinformed is that body weight regulation, largely driven by food consumption, is under strict volitional control, whereby one steadfastly determines what, when, and how much to eat. In reality, our neurobiology has evolved to ensure that we ingest the necessary calories to have a surplus, which is far more advantageous than a dearth of energy stores to meet everyday requirements. To efficiently and enduringly combat this evolutionary pressure to overconsume food, anti-obesity therapeutics should be designed to hijack the central mechanisms underlying eating at multiple loci. In this piece, we review the neural circuits underlying the phasic complexity and sequential nature of feeding, which can be summed up in a collection of behaviours and divided into three discrete acts[2]: (1) an appetitive step comprised of foraging and approaching food, (2) a consummatory stage, whereby a self-propagating feedback loop promotes ingestion, and (3) a termination phase, through which a host of mechanical and chemical signals act in concert to shut off feeding (Fig. 1).

The brain's role in shaping motivated behaviours was established over a century ago, with people with tumours, lesions, and additional pathologies exhibiting maladaptive feeding episodes. A high volume of these reports pinpointed the hypothalamus as a common target of these afflictions[3-19], as the lateral hypothalamus (LH), paraventricular hypothalamus (PVH), ventral medial hypothalamus (VMH), dorsal medial hypothalamus (DMH), and arcuate nucleus (ARC) were all shown to control eating to various degrees. Layered on top of hypothalamic gating of feeding was the emergence of the dopaminergic mesolimbic system's role in influencing motivational aspects of food substrates, including its rewarding properties, learnt responses towards acquisition probability, and the predictive and associative memories related to food procurement[20-24]. Although this groundbreaking work implicated distinct regions of the brain in appetite, or the desire to eat food, the techniques carried significant limitations, including a lack of anatomical precision, cell-type specificity, and targeted site of action. Additionally, many of the methods lacked reversibility, making it difficult to interpret direct versus indirect outcomes of the initial manipulation. These constraints were often a challenge to achieving reproducibility among participants or between laboratories, providing a broad and disjointed understanding of the central mechanisms underlying appetite.

This obstacle heralded a generation of genetically driven cell manipulations to globally knock out, selectively delete, or overexpress genes encoding critical peptides and receptors using transgenic mice. These strategies identified and validated many modulators of energy balance, including the adipocyte-derived hormone leptin and its cognate leptin receptor (LEPR)[25-27], the melanocortin system[28-32], and the gut-derived incretin glucagon-like peptide 1 (GLP1) and its targeted glucagon-like peptide 1 receptor (GLP1R)[33-35]. Although they significantly increased our understanding of the precise cell types and signalling schemes underlying feeding behaviours, these manipulations occur throughout development; thus, compensation for genetic perturbations is difficult to detect. Bypassing this drawback, several studies found that acute inactivation of hypothalamic neurons in adulthood using

diphtheria-toxin-mediated ablation approaches severely impacted feeding[36-40]. While this addresses developmental compensatory concerns, it raises additional issues, including the ill-defined temporal kinetics and permanent nature of the manipulation, as well as only testing for cell-type requirement, and not sufficiency, in mediating consummatory behaviours. Given these caveats, alternative techniques need to be employed for molecularly defined neural circuit analysis.

Recent breakthroughs in neuroscience allow for more targeted approaches to tackle these empirical questions. For the past two decades, researchers have used tools that grant both spatial and temporal precision of molecularly or behaviourally defined cell types to investigate their role in conducting food intake. Optogenetic and chemogenetic techniques allow scientists to explain behaviour through necessity and sufficiency claims, and in vivo optical imaging and electrical recordings are used to reinforce these findings by assessing endogenous, real-time neural activity in behaving animals. These approaches have been combined with cell-specific anterograde and retrograde tracing, ex vivo acute brain slice electrophysiology and imaging, single-cell RNA sequencing, upgraded (and often automated) equipment for more precise measurements and less experimenter intervention, innovative tracking solutions, and effective assay design to study the central mechanisms underlying feeding behaviours with an uncanny level of detail.

Prologue: appetite for calories

Appetite describes the desire to eat a specific food item regardless of the body's energy state, and hunger is a sensation that arises when the body is in need of caloric repletion following food deprivation and/or excess energy expenditure. This perception arises from multiple peripheral signals such as ghrelin, an orexigenic hormone released by the stomach[41,42] that increases during periods of fasting and quickly decreases on caloric consumption[43,44]. Ghrelin is transported from the periphery to the central nervous system, where it acts on multiple brain areas to guide food seeking and feeding behaviours. Furthermore, exogenous administration of ghrelin is sufficient to increase food intake, body weight, and adiposity in a dose-dependent manner[45-47].

To maintain proper energy balance and prevent overconsumption, anorexigenic hormones such as leptin help to promote satiety, the sensation of being sated or full in between meals, and satiation, the progressive sensation of fullness during a meal that eventually leads to meal termination. Leptin is produced mainly by adipose tissues; its circulating levels positively correlate with adipose tissue size and thus energy stores[48]. Similar to ghrelin, leptin encodes the body's current caloric state, but in the opposite way: leptin levels are low during fasting and increased following food consumption[49]. Mice lacking leptin show a drastic escalation in food intake and body weight[26]. Administration of leptin, in contrast, blunts appetite and can be used to reverse obesity in some people and rodent models[50,51].

Hunger states can therefore be viewed as the integration of orexigenic and anorexigenic peripheral signals that act on the central nervous system to restore energy homeostasis. Though several neurons expressing receptors for hunger and satiety signals are found throughout the brain, many of them are concentrated in the ARC. Often serving as an entry

point for humoral signals, the ARC is optimally situated because it is adjacent to the third ventricle and the median eminence, a structure that has an incomplete blood–brain barrier owing to its fenestrated capillaries. Food deprivation causes expansion of these fenestrated capillaries, allowing for circulating nutritional signals to easily reach and exert their effects on ARC neurons[52].

Act I: food procurement

ARC^{AgRP} neurons encode the properties of a starved state.

Agouti-related peptide (AgRP)-expressing neurons in the ARC (ARC^{AgRP}) are stimulated by ghrelin and inhibited by leptin[53-55]. In line with these hormonal effects, electrophysiology and fibre photometry recordings have revealed that ARC^{AgRP} neurons are most active when animals are fasted, or food-deprived, due in part to an increase in excitatory tone[56-61]. In rodents with ad libitum access to food, ARC^{AgRP} neuronal activity is intertwined with diurnal rhythm. ARC^{AgRP} neurons are mostly quiescent at the onset of the light cycle, during which rodents reduce energy expenditure after having consumed most of their daily caloric intake in the dark cycle. ARC^{AgRP} neuronal firing rate, however, slowly ramps up as the light cycle progresses, gearing up the animal for food seeking and consumption[59].

ARC^{AgRP} neurons release AgRP, neuropeptide Y (NPY), and γ-aminobutyric acid (GABA), all of which have been characterized as involved in food intake and metabolism[62-66]. Chemogenetic inhibition of ARC^{AgRP} neurons reduces food intake in hungry mice[67,68], and ARC^{AgRP} neuronal ablation in adult mice leads to a cessation of feeding[37]. Additionally, ARC^{AgRP} perturbations govern nutrient partitioning by favouring fat storage on consumption[69,70], lower energy expenditure and dissipation through inhibition of intrascapular brown adipose tissue (iBAT) thermogenesis triggered by decreased sympathetic nerve activity and a rapid re-programming of the iBAT gene expression profile[67,71,72], and potentiate the rewarding properties of food through the mesolimbic system[60,73,74]. Optogenetic or chemogenetic activation of ARC^{AgRP} neurons, however, is sufficient to drive voracious food seeking and consumption[67,75]. More recent work has shown that activation of ARC^{AgRP} neurons is sufficient to dampen other motivational systems—such as thirst, innate fear, nociception, aggression, courtship, parenting, sleep, and self-preservation—often in favour of feeding[76-82].

Role of ARC^{AgRP} neurons in food seeking.

While initially thought to drive food consumption specifically, several recent reports instead suggest that ARC^{AgRP} neurons are primarily involved in food seeking, or the appetitive phase, more so than the consummatory phase of feeding (Box 1). Following up on observations that artificial ARC^{AgRP} activation in the absence of food robustly increased locomotor activity often associated with foraging[67,81,83], three paradigm-shifting studies revealed the proactive and pre-emptive nature of these neurons. Using distinct neural-recording approaches, it was shown that ARC^{AgRP} neurons robustly exhibit a homogenous inhibitory response within seconds of food presentation, preceding the first bite of food[59,84,85] (Fig. 2a). This suppression of activity was specific to the sensory detection of

food including cues conditioned to predict food delivery, confirming a degree of learning at the neural level of this population[59,84-87]. This inhibition is at least in part emanating from an upstream glutamatergic LH–GABAergic DMH circuit with the capacity to shut down feeding behaviour[88,89]. The sustained silencing of ARC^{AgRP} neurons is dependent on future caloric consumption and scaled to the number of calories detected in the gut[84,86,90,91]. While the magnitude of ARC^{AgRP} inhibition is higher in hungry versus sated animals, palatable food substrates lead to greater suppression and are even detectable in well-fed animals[59,84].

This anticipatory physiological phenomenon was recapitulated by optogenetically stimulating ARC^{AgRP} neurons prior to, but not during, food availability[92,93]. Under this paradigm, mice still showed a robust increase in food intake, even with as little as 1 minute of pre-stimulation, or even if food presentation was delayed by minutes after priming had ended[93]. Food consumption that follows ARC^{AgRP} stimulation is likely due to the sustained activity of downstream targets as opposed to activity of ARC^{AgRP} neurons themselves. NPY is uniquely required for this long-lasting hunger signal[94,95], providing a molecular correlate linking ARC^{AgRP} neural dynamics with feeding behaviours. Collectively, these findings propose an updated role for ARC^{AgRP} neurons: their main responsibility is to guide the animal in caloric need to a food source. Supporting this notion, ARC^{AgRP} neurons are required for the elevated locomotion and exploration, presumably to discover food, near the onset of scheduled feeding[96].

Downstream targets of ARC^{AgRP} neurons.

To further understand how ARC^{AgRP} neurons orchestrate feeding, as well as the sensory detection and value of food, studies have dissected the contributions of multiple ARC^{AgRP} projections within and beyond the hypothalamus[80,87,97,98]. By expressing channelrhodopsin-2 in axons, it was shown that stimulating ARC^{AgRP} projections to the PVH, anterior bed nucleus of the stria terminalis (aBNST), or LH was sufficient to induce food intake at a comparable level to that following ARC^{AgRP} soma photostimulation (Fig. 1). Although photoactivation of projections to the paraventricular nucleus of the thalamus (PVT) promoted attraction to food odours[87] and led to a mild increase in food intake, projections to the central amygdala (CeA), periaqueductal grey (PAG), and parabrachrial nucleus (PBN) revealed no effect. Further studies uncovered that activation of ARC^{AgRP} terminal fields in the medial amygdala (MeA) and medial preoptic area (MPOA) are sufficient to support food intake[78,80]. Moreover, retrograde tracing established a one-to-one anatomical architecture whereby each ARC^{AgRP} projection field is a separate communication channel without collateralization[97]. Reinforcing this view, transcriptional profiling unveiled multiple ARC^{AgRP} subtypes and state-dependent changes in gene expression[99,100]. Thus, despite the observed homogenous activity response to food-related cues and ghrelin[97], there is a functional, molecular, and structural heterogeneity to ARC^{AgRP} signalling.

Effects of a high-fat diet on ARC^{AgRP} neurons.

Diet-induced obesity (DIO) in mice has been shown to cause a decrease in fasting-induced refeeding with standard chow or a high-fat diet (HFD)[101,102]. This reduction in food intake can be elevated by photostimulating ARC^{AgRP} neurons, indicating that fasting does not

fully activate ARC^{AgRP} neurons in DIO mice[103]. Longitudinal in vivo recordings reveal that long-term exposure to a HFD reduces the basal activity of ARC^{AgRP} neurons[60], although slice recordings show elevated intrinsic excitability of ARC^{AgRP} neurons following HFD exposure[104,105], demonstrating some discrepancy between in vivo and ex vivo studies.

ARC^{AgRP} neurons in fasted, HFD-challenged mice exhibit a diminished inhibitory response to standard chow, suggesting that less palatable food is not sufficient to completely attenuate the drive to seek food (Box 2). However, further suppression of ARC^{AgRP} activity can be achieved by HFD presentation[60,103]. Extended HFD exposure also disrupts the response of the mesolimbic reward system to food. Dopaminergic neurons in the ventral tegmental area (VTA) of HFD-challenged mice show a diminished response to standard chow while maintaining an increase in activity on HFD consumption[60]. Taken together, these studies demonstrate that exposure to a HFD rewires homeostatic and hedonic feeding systems to drive an animal to prefer and seek out more caloric foods, thereby promoting overeating and obesity.

ARC^{AgRP} neurons thus play a critical role in food procurement, the first phase of feeding that begins with hunger. ARC^{AgRP} projections demonstrate heterogeneity in their capacity to drive voracious food seeking. These findings suggest that ARC^{AgRP} neurons could be divided in multiple subpopulations, not just in terms of their projections but also their transcriptomic profiles. Though past studies typically looked at only total food intake when investigating the role of cell types and/or projections in feeding, further studies are needed to elucidate how different subpopulations of ARC^{AgRP} neurons orchestrate multiple aspects of feeding behaviour that may not necessarily affect total food intake, such as meal count, meal size, or motivation to obtain food. The functional heterogeneity of ARC^{AgRP} neurons could arise from other peptides, neurotransmitters, or receptors that they co-express. Future experiments can take advantage of newer genetic tools to manipulate ARC^{AgRP} neurons that overlap with the expression of other genes and dissect their role in feeding behaviour.

Interestingly, additional populations of inhibitory ARC neurons have been identified that have the capacity to drive food intake and body weight gain[106], including those marked by tyrosine hydroxylase[107], prepronociceptin[108] or somatostatin (SST)[100]. Although the orexigenic circuitry and neural dynamics of these subtypes remain unresolved, these populations have been shown to synapse on downstream targets similar to those of ARC^{AgRP} neurons[100,107,109].

Although ARC^{AgRP} neurons exhibit some functional and transcriptomic heterogeneity, they show a homogenous, rapid decrease in activity once hungry animals find food, suggesting that they are mainly necessary for food seeking and not consumption per se. The residual, low-rate spiking of ARC^{AgRP} neurons at the beginning of the meal, along with the sustained activity of downstream ARC^{AgRP} targets, may encode a persistent drive to eat and thus underlie the next phase of feeding: the consumption and ingestion of food.

Act II: food consumption

Control of feeding by the LH.

While the rhythmic actions of ingestion are moderated by hindbrain motor circuits[110], the command of consummatory properties, including meal size, duration, frequency, and rate, occurs in multiple brain nodes (Fig. 1). Cell types within these anatomical structures manifest divergent responses to food intake and have the capacity to bidirectionally modulate feeding behaviours (Fig. 2b). The LH and PVH sit directly downstream from ARC^{AgRP} neurons and thus are ideally situated to receive the metaphorical hand-off from food seeking to ingestion. In particular, the LH is a richly heterogeneous structure on the basis of gene expression, function, and structural organization[111-113]. In the LH of fasted rats, extracellular glutamate increases and returns to baseline on meal termination[114]. Optogenetic activation of LH vesicular glutamate transporter 2 (SLC17A6 or VGLUT2) neurons in mice evokes a decrease in food intake and is aversive[115]. Additionally, during an operant-conditioning paradigm in which mice were trained to discriminate fasted and sated periods, LH^{VGLUT2} activation attenuated the sensation of hunger in fasted mice[116]. Furthermore, LH^{VGLUT2} neurons receive inhibitory inputs from the BNST, and activation of this pathway triggers consumption in sated mice, whereas inhibition suppresses food intake in food-deprived mice[115].

Optogenetic or chemogenetic activation of vesicular GABA transporter (SLC32A1 or VGAT) LH neurons promotes food intake and positive valence in sated mice, whereas acute and/or chronic inhibition of these neurons decreases food intake and attenuates weight gain[117]. In vivo calcium imaging revealed that distinct, predominantly non-overlapping populations of LH^{VGAT} neurons become active during appetitive and consummatory feeding behaviours, although unlike ARC^{AgRP} neurons, these responses were heterogeneous[117]. Interestingly, when mice were trained to discriminate between fasted and sated states, activation of LH^{VGAT} neurons did not evoke a hunger sensation, suggesting that these neurons help sustain, rather than induce, hunger states[116]. Further partitioning of LH^{VGAT} cells found that a subset of these cells, namely the leptin-receptor-expressing neurons, project to the VTA[118], and activation of this pathway promotes motivation to obtain food[119] and mediates appetitive learning[120].

Non-GABAergic clusters[121] of LH neurons expressing pro-melanin concentrating hormone (PMCH) and hypocretin (HCRT) have long been implicated in appetite regulation[122-124]. Intracerebroventricular administration of either PMCH[122,125-129] or HCRT[123,130] increases food intake. Ablation of LH^{PMCH} neurons leads to a lean phenotype and obesity resistance[131], and ablation of LH^{HCRT} neurons decreases food consumption[132,133]. Paradoxically, ablation of LH^{HCRT} neurons induces an increase in body weight and obesity[132,133], possibly by regulation of energy expenditure. Chemogenetic activation of LH^{HCRT} neurons increases food intake[132,133], while inactivation leads to overeating and obesity[134]. However, optogenetic and chemogenetic activation of LH^{PMCH} neurons did not evoke food intake unless stimulation was temporarily paired with consumption. Moreover, activation of LH^{PMCH} neurons alone is rewarding[135]. A recent study suggested that the effect of LH^{PMCH} neurons on overeating is related to increased impulsivity rather than

to an increased motivation for food, and that the connections between these neurons with the ventral hippocampus (vHP) seem to play a role in driving increased impulsive responding[128].

Although it has been observed that some animals receiving electrical stimulation in the LH selectively consume food[136], others display selection of alternative actions depending on the presence of external variables to interact with, including drinking[137], predatory attack[138], gnawing[139], or sexual activity[140]. Artificial manipulation of LH^{VGAT} neurons not only regulates consumption of caloric foods but also of non-nutritional foods and inedible objects[116,141]. Moreover, specific photostimulation of the projection from the LH^{VGAT} to the VTA resulted in erratic licking and gnawing independent of caloric presentation[117,142]. Although LH-evoked goal-directed behaviour appears to lack specificity to food, newer techniques have reinforced previous observations that animals find activation of these consummatory neurons positively rewarding[117,142,143].

LH-VTA-NAc feeding loop.

The LH sends inhibitory and excitatory projection to the VTA, and LH^{VGAT} neurons drive feeding by inhibiting VTA neurons[142] (Fig. 1). Photoactivation of the LH^{VGAT}–VTA pathway increases food intake in sated mice and incites food seeking in aversive conditions. In a conditioned feeding task, electrical recordings in the LH uncovered activity of a subpopulation of neurons during the conditioned response of entering a food delivery area, but not during the consumption of food; another subpopulation reacted to food predictive cues via the VTA, suggesting a preparatory contribution to feeding in addition to a consummatory one[142]. The increase in LH^{VGAT} activity inhibits VTA GABAergic neurons, promoting dopamine (DA) release into the nucleus accumbens (NAc), whereas the activity of LH^{VGLUT2} neurons decreases DA release into the NAc[144]. The NAc comprises two major neuronal populations: medium spiny neurons (MSN) expressing dopamine D1 or D2 receptors. NAc^{D1} projections are an important source of inhibition of LH GABAergic neurons. NAc^{D1} MSN activity is lower during feeding, and activation of NAc^{D1} MSNs suppresses LH GABAergic neurons to stop feeding, whereas inhibition of the NAc^{D1}–LH pathway promotes food consumption[145].

Effects of diet-induced obesity on LH plasticity.

Studies using in vivo functional imaging have demonstrated that LH^{VGLUT2} neurons encode satiety states, and that their reward-encoding properties are modified during obesity[112] (Fig. 2b). In particular, LH^{VGLUT2} neurons from DIO mice become progressively less responsive to sucrose consumption and less active at rest[112], suggesting that these neurons lose their ability to limit feeding when mice consume a HFD. In a binge-eating model, only 3 days of exposure to a highly palatable food is capable of inducing long-term potentiation on inhibitory inputs from the NAc to both LH^{VGLUT2} and LH^{VGAT} neurons. Moreover, such potentiation is absent in mice fed with regular chow. Thus, increased inhibition onto LH^{VGLUT2} neurons triggered by exposure of highly palatable foods can induce overeating[146].

Control of feeding by the PVH.

Several lesion, pharmacological, and genetic knock-out studies have demonstrated the crucial role of the PVH in appetite control[4,7,30,147-149]. The majority of PVH neurons are marked by the transcription factor single-minded 1 (SIM1), which is required for proper development[150], and acute ablation of these cells or a subset of cells characterized by expression of melanocortin 4 receptor (MC4R) leads to obesity[151-153]. Further supporting the role of PVH neuronal subtypes in dictating consummatory behaviour, real-time silencing of numerous PVH neuronal subtypes increased food intake, while activation decreased food intake[68,152,154-157]. Activation of SIM1-, MC4R-, or oxytocin-expressing PVH neurons occluded photoactivated ARC^{AgRP}–PVH-evoked feeding[68,154]. Interestingly, while recordings of GLP1R or corticotropin-releasing hormone (CRH) population dynamics demonstrate a sharp and sustained increase or decrease in activity in response to food presentation, respectively[152,158], those marked by MC4R exhibited only a transient change in response to food, likely owing to their heterogeneity. Single-cell endomicro-scopic resolution of individual PVH^{MC4R} cells confirmed this neural diversity, as cells show varying responses to food introduction, subsequent consumption, and energy state[159]. Unbiased two-photon imaging from the PVH uncovered neurons enriched in *Crh* that co-express *Vglut2* and *Npy1r* that respond to caloric ingestion[160].

Control of feeding by the periLC.

Satiety-promoting PVH neurons send dense efferents to the brainstem, particularly the pons, where glutamatergic communication acts to signal fullness. Synaptic silencing of PVH^{SIM1} axons to the midbrain, near the ventral–lateral portion of the PAG and dorsal raphe, promptly and robustly stimulated feeding in sated animals[161]. Additional studies employing both gain- and loss-of-function experiments pinpointed a critical appetite-regulating projection from the PVH to the parabrachial complex, made up of the peri-locus coeruleus (periLC) and central lateral parabrachial nucleus (PBN)[152,154]. Although the molecular identity of these downstream neurons remains to be elucidated, a seminal study using hindbrain calcium imaging in freely moving mice found that $periLC^{VGLUT2}$ neurons are selectively tuned to ingestive behaviours and are scalably inhibited by palatability and the internal milieu[162]. Reducing $periLC^{VGLUT2}$ neural activity is rewarding and escalates consumption by augmenting palatability and prolonging ingestion duration[162]. A fundamental difference between PVH and periLC versus LH neural activation is that the former does not elicit fictive ingestive behaviours or alter lick frequency, but the latter often does. This finding suggests that, although LH circuits can control the motor actions of consumption through such pathways as the substantia nigra–superior colliculus–medullary reticular formation–motor nuclei circuits, PVH and periLC neurons have a more modulatory role during eating, whereby inhibition prolongs consumption[152,154,162-164].

Control of feeding by other brain sites.

A number of studies have pinpointed additional neuronal subtypes in discrete regions that regulate food intake. These include inhibitory SST neurons of the tuberal nucleus (TN), which are preferentially activated by palatable food and drive overconsumption through signalling to the PVH and BNST[108,165]. Another population of GABAergic cells in the

zona incerta (ZI) robustly stimulates food intake via projections to the PVT[166]. Additionally, impairment of cholinergic signalling in the basal forebrain promotes food intake through hypothalamic communication[167]. Temperature-sensitive neurons of the MPOA can also regulate food intake through synapses to ARC^{AgRP} or PVH neurons[166,168].

Overall, several lines of research suggest that ARC^{AgRP} downstream nodes act as a neural hub modulating the transition from food seeking to consumption. Among those targets, the activation of GABAergic neurons of the LH promotes food consumption, in part through communication with the midbrain dopamine system, and this is opposed by the actions of glutamatergic neurons, which act as a break on feeding. Despite the reliability of this system in modulating feeding, it is malleable and susceptible to maladaptation by exposure to less nutritional, highly caloric diets, which can contribute to the development of obesity. Another downstream target of ARC^{AgRP} neurons that regulate consumption is the PVH, a region that is marked by heterogeneity, particulary in PVH^{MC4R} neurons that display varying responses to food presentation and ingestion. The PVH and LH are intertwined, with a plethora of brain nuclei that act in concert to mediate consumption (Fig. 2). Neuronal activities that encode levels of hunger and satiation are then conveyed from hypothalamic nuclei to regions in the hindbrain to eventually signal the end of the meal.

Act III: meal termination

Multimodal signalling of satiation.

A merger of interoceptive signals arising from the periphery and exteroceptive processes from the environment leads to the end of a feeding bout. Meal termination is characterized by the cessation of interactions aimed at consumption, including reaching, holding, biting, chewing, and swallowing food. Ending a meal is influenced by several distinct but overlapping processes. First, gastrointestinal, blood-borne, and descending hypothalamic signals converge on the hindbrain and medulla when caloric need has been appropriately met. Satiation is associated with a range of peripherally derived hormone signals—such as cholecystokinin (CCK), GLP1, amylin, leptin, neurotensin, serotonin, insulin, and peptide YY—that communicate with neurons to wind down eating[169]. Second, mechanoreceptors in the digestive tract distend to accommodate food during a meal. As the volume of stomach content is increased, food intake decreases and information related to mechanical stretch and nutritional content is conveyed mainly via vagal afferents[170] to the nucleus of the solitary tract (NTS)[171-173], located in the caudal brainstem[172-175]. In the NTS, sensory peripheral information is integrated and processed to be relayed to the dorsal motor nucleus of the vagus, which provides parasympathetic motor input to the gastrointestinal tract to modulate gastric and intestinal motility, tone, secretion, and emptying to regulate meal termination and nutrient absorption[176]. Third, competing processes involved with the expression of rival motivated behaviours may shift an animal away from eating and towards a new goal, such as mating or territorial defence[77,78,177]. Last, aversive and nociceptive signals, such as anxiety, illness, malaise, pain, itch, and inflammation, are potent satiety stimuli capable of suppressing feeding despite caloric need[178-181].

Role of the PBN in halting food consumption.

Several lines of evidence have positioned the PBN, a part of the central gustatory and the visceral sensory system, as a neural hub for feeding suppression and taste memories[178,179,181-183] (Fig. 1). The majority of work has centred on a subpopulation of excitatory neurons in the outer external lateral PBN marked by the expression of calcitonin gene-related protein (CALCA or CGRP). These cells respond broadly to visceral stimuli, including nausea, itch, and pain, and are tuned to increasing intensities of aversive stimuli[178,180,184] (Fig. 3 and Box 3). Activation of PBN^{CGRP} neurons, including a subset projecting to the CeA, potently suppresses food intake regardless of internal need for calories while silencing mitigates the inhibition of feeding induced by pain, sickness, and exogenous administration of anorectic hormones[178,184]. These effects are probably mediated in part by inputs from ARC^{AgRP} (refs. [90,92]), area postrema[185], and NTS neurons[186-189] and outputs to the CeA[178,190] and parasubthalamic nucleus (PSTN)[191]. A subpopulation of GABAergic neurons marked by protein kinase C-δ (PKCδ) are responsive to and required for the influence of anorexigenic agents on food intake[192]. $CeA^{PKCδ}$ neuron stimulation abrogates food intake independent of anxiolytic effects[192]. It should be noted that an alternative projection from NTS neurons expressing calcitonin receptors (CALCR) to the PBN supports meal termination without producing aversion independent of PBN^{CGRP} signalling[189,193]. Further parsing of NTS^{CALCR} neurons uncovered a neuronal subset that expresses prolactin releasing hormone, which has the capacity to suppress food intake and reduce body weight without inducing conditioned taste aversion[194].

Although food deprivation lowered PBN^{CGRP} activity relative to the sated state, likely owing to a combination of increased inhibitory ARC^{AgRP} neuronal[68,92] and BNST input[195] and decreased excitatory input from anorexigenic neurons in the NTS[92,188,195], these neurons became more active as feeding progressed[180]. Further supporting their contribution to meal termination, silencing PBN^{CGRP} neurons increases meal duration without affecting the total amount of food consumed[92]. Reinforcing this notion, some PBN^{CCK} neurons respond to leptin, and leptin injections into the PBN dose-dependently reduce cumulative food intake and habitual meal size, but not meal number[186,196]. Interestingly, gastric bypass activates PBN^{CGRP} neurons[197], suggesting that these neurons may play a role in appetite loss and weight loss resulting from this surgery[198]. However, it should be noted that PBN^{CGRP} activation is aversive, emulating conditioned taste aversion, and results in avoidance of learnt cues paired with their elevated activity[179]. The strength of the conditioned taste aversion is modulated by the frequency and duration of PBN^{CGRP} stimulation[181]. Furthermore, PBN^{CGRP} neurons are required for the acquisition and expression of aversive taste memories[181].

Cerebellar control of meal termination.

In addition to the PBN, a recent report found that cerebellar activity acts as a ‘brake’ to reduce meal size and duration, but not frequency or rate[199] (Fig. 1). Neurons in the anterior deep cerebellar nuclei (aDCN) are engaged by feeding or direct nutrient infusion in the gut. Selective activation of aDCN neurons substantially decreased food intake, independent of caloric need. The underlying mechanism for this aDCN-induced meal termination is enacted via increasing striatal dopamine levels and attenuating the phasic dopamine response

to subsequent food consumption. These changes may diminish meal size by reducing the reward value of additional consumption similar to hindbrain satiation networks that modulate food motivation based on interoceptive state through dopamine signalling[23,200]. Supporting the translational relevance of these findings, individuals with the genetic disorder Prader–Willi syndrome (PWS), who are characterized by obesity and a lack of satiation[201], demonstrate dysregulated neural activity to food cues while fasted or after eating compared with healthy controls. This lack of cerebellar engagement in response to food cues may result in the extreme hyperphagia reported in individuals with PWS.

Therefore, several mechanisms interact to orchestrate the termination of a meal. Satiation hormones together with gastrointestinal mechanoreceptors signal for the fulfillment of caloric demand to the brainstem, enabling the suppression of food consumption. In addition, aversive and nociceptive stimuli are powerful feeding suppressors, inhibiting intake even in conditions of caloric deficiency. The PBN has a predominant role in mediating suppression of food consumption induced by fullness, aversion, illness, and pain.

A growing body of evidence is advancing towards the understanding of extrahypothalamic brain loci that modulate feeding behaviours. Dysregulation of these brain regions can contribute to eating disorders; however, the mechanisms by which diet and feeding habits could impact their function and the roles of phenotypically identifiable subpopulations of neurons are far from understood. The need for translational research is compelling and could shed light into how different neural feeding circuits modulate food consumption and become susceptible to maladaptive changes. The impact of diet nutrient composition and specific nutrients in neuronal activity is also something to be considered. Although past studies have characterized how ARC^{AgRP} neurons sense different macronutrients[86,90,202], this level of scrutiny has not yet been applied to other cell types or brain nodes.

Epiologue: managing obesity into the future

Recognizing obesity as a chronic disease helps to destigmatize the prevalent assumption that obesity is a product of inadequate self-discipline. Despite lifestyle and behavioural interventions, losing body weight is a daunting task in a world designed to make it so. Our understanding of the altered biological mechanisms and pathophysiology associated with excess fat accumulation helps us to understand why our best efforts often fall short of our goals for long-term weight loss. This growing barrier to improving general health has led to alternative obesity treatment strategies, including pharmacological mediation. While the quest for highly efficient anti-obesity medications has been challenging from both a technical and societal perspective, the work described above, outlining the molecular mechanisms and neural circuits overseeing appetite regulation, has served to navigate drug discovery and therapeutic interventions in attempts to abate overconsumption. Integrating the latest advances in our understanding of appetite homeostasis along with the continued identification of novel drug targets leads to an optimistic view of plausible treatments that could reduce body weight by more than 25%. To realize this objective, anti-obesity medications should be designed in a way to collectively impact the separate acts of feeding discussed in this Review. Having the means to simultaneously curb craving, hunger, and food-seeking behaviours, along with the rate and duration of food consumption, would

greatly benefit us in our struggle with obesity. This multi-branched targeting of these distinct processes could combat the profound amount of redundancy and regulation built into our systems designed to sustain our current body weight. Although monotherapy would be preferred for simplicity, a combination of pharmacological agents will have a higher probability of meeting the demands required to hit each of these phases and ultimately pare down caloric intake. Optimizing approaches on the basis of these and future findings to enhance and prolong efficacy of sustained weight loss is a unified goal of scientists and clinicians that is becoming more and more realistic with each passing day and discovery.

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Box 1 |

Motivational valence of ARC^{AgRP} neurons

How does ARC^{AgRP} neuronal firing prompt an animal to search for food? A simple explanation for this inquiry is to determine the valence associated with the activity of these cells. Mice fail to perform operant responses to shut off ARC^{AgRP} activity, which at first pass indicates that these neurons do not motivate behaviour by negative reinforcement. However, given the persistent effects of ARC^{AgRP} stimulation on feeding behaviour that endure even after they are silenced, mice may be unable to associate an action with acute inhibition of these neurons. In fact, sated mice can be trained to display an avoidance of ARC^{AgRP} neuron photostimulation in the absence of food, and fasted mice exhibit a conditioned preference for places paired with ARC^{AgRP} neuron inhibition85. Thus, ARC^{AgRP} neurons transmit a negative valence signal, which may motivate mice to procure food to mitigate or counteract this signal. However, mice engage in lever pressing to optically activate their ARC^{AgRP} neurons if food is present, demonstrating that stimulation can be positively reinforcing. Although not intrinsically rewarding, as is the case with midbrain dopamine neurons203, mice will self-stimulate their ARC^{AgRP} neurons to enhance the incentive value of food when it is directly in front of them and after a learnt positive association has been established93. This supports a model in which ARC^{AgRP} neuron activity results in an enduring potentiation of the rewarding properties of food, likely through enhanced mesolimbic dopamine activity and subsequent dopamine release in the nucleus accumbens of the striatum60,73. Therefore, the exact nature of the valence produced by ARC^{AgRP} neuronal activity is context-dependent. These findings support a model that in the absence of food, ARC^{AgRP} neuronal firing drives an aversive signal that mice attempt to mollify by seeking food, whose properties subsequently become more rewarding once it is found. This sustained positive valence of food during consumption is likely not driven by ARC^{AgRP} neurons themselves because their activity is already greatly reduced at the onset of the meal, but by downstream targets that prompt the consummatory phase of feeding.

Box 2 |

Feeding neurons conform to energy status and food palatability

A shared feature among neurons responding to food stimuli is the modulatory influence of both the internal energy state of the animal and hedonic palatability, often scaling with the length of caloric deprivation and the number of calories, respectively (Fig. 2). Cells react more strongly to food substrates when animals are in a caloric deficit, and this response is intensified with high energy composition, often of food with elevated fat content. For example, ARC^{AgRP} neurons exhibit little to no inhibitory response to chow when animals are sated but are rapidly and robustly reduced in the hungry state[59,84,85], when food holds incentive worth. Another explanation for this enhanced state-dependent response to food may lie in the diametric baseline activity under opposing energy conditions. ARC^{AgRP} neurons are active under caloric deprivation but are relatively quiescent following satiation[56,58-60]; thus, the inhibitory response to food is more pronounced in the fasted state when baseline activity is high. Comparable observations have been made in many feeding nodes where activity is contingent on energetic status[84,88,108,112,113,117,162,163,180,195].

Palatability is associated with food pleasantness, ranging from its enhanced sensory properties to post-digestive gut-to-brain feedback that prolongs bouts of consumption[204]. Palatable foods are often energy dense, engineered to heighten sensory perception and attraction, and from an evolutionary perspective, highly preferred. Just as hunger in humans increases the subjective reports of palatability[205], energy-rich food presentation to fasted animals augments neural activity responses compared to normal chow[60,84,88,103,108,112,113,117,162,163,195], and owing to the strong preference for these palatable foods, neural activity changes are evident even under conditions of energy surfeit. Although acute inhibition to these palatable foods is primarily driven by their enhanced sensory properties, the durable suppression often calibrates with the number of calories consumed either via active eating or through direct infusion into the gastrointestinal tract[84,86,90,91]. Moreover, recent studies have pinpointed neurons that are preferentially activated by palatable food[109,165]. Thus, palatability is a critical factor in controlling appetite[206].

Box 3 |

Feeling full, but not too full

It is well appreciated that sickness brought on by fever or infection suppresses appetite. This is presumably due to shared central sites that encode the sensation of unpleasantness with appetite control (Fig. 3). Nodes like PBN^{CGRP} neurons can be thought of as knobs for the satiety system, whereby a slight adjustment results in satiety but excessive turning leads to profound visceral malaise. While these cells respond to refeeding and satiation[92,180], they are also robustly activated by threats of diverse origin[178,180,181,184,207]. Moreover, activation of PBN^{CGRP} neurons soundly reduces food intake via meal termination but can also produce freezing and anxiety-like behaviour in conjunction with tachycardia or parasympathetic responses, depending on the stimulation frequency or how far the knob is twisted[92,178,184,208]. The aversive affective state transmitted by these neurons was reaffirmed using a real-time place preference assay, which demonstrated that mice choose to avoid a space paired with PBN^{CGRP} neuron activation. Thus, the spectrum between satiety and sickness is tunable to the length and intensity of stimulation, as acute activation of PBN^{CGRP} neurons reduces meal size but chronic activation leads to severe anorexia and starvation[92,178]. PBN^{CGRP} neurons are likely just one of many systems in the brain that impact both appetite and illness as these states are intrinsically intertwined. In fact, the most common side effect of efficacious anti-obesity medications is nausea and other associated gastrointestinal discomforts, including diarrhea, vomiting, and constipation[209-212]. Balancing this tightrope between feeling full but not too full to the point of sickness is a major obstacle in the development of modern-day therapeutics to blunt appetite.

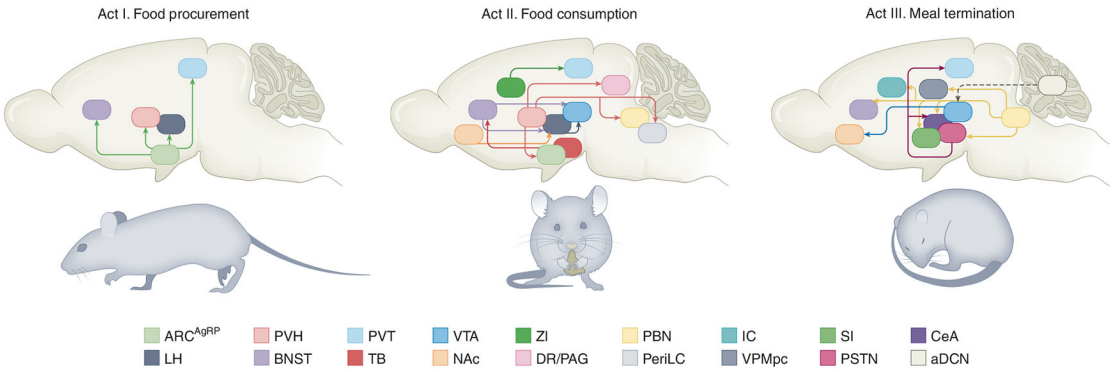

Fig. 1 |. Neural circuitry underlying the three acts of appetite.

Left, act I: food procurement. Inhibitory ARC^{AgRP} neuronal projections to the BNST, PVH, LH, and PVT promote food seeking and subsequent food intake. Middle, act II: food consumption. Activation of LH^{VGAT} and inhibition of LH^{VGLUT2} neurons increases food intake through direct projections to the VTA. Inhibitory circuits from the BNST and NAc^{D1R} neurons feed into this circuit to modulate consumption. GABAergic TB^{SST} neurons, via projections to the BNST and PVH, and ZI neurons, via projections to the PVT, potently drive ingestive behaviours. Excitatory PVH neurons regulate food intake through projections to the ARC, DR/PAG, PBN, and periLC. Right, act III: meal termination. Stimulation of excitatory PBN^{CGRP} suppresses food intake, generates learnt and defensive responses, and induces malaise via projections to the CeA, BNST, SI, PSTN, VPMpc, and IC. Activation of excitatory aDCN neurons reduces meal size by increasing striatal dopamine levels and attenuating the phasic dopamine response to subsequent food consumption. Solid arrows indicate direct connections. Dashed arrows indicate indirect connections. ARC, arcuate nucleus of the hypothalamus; AgRP, Agouti-related peptide; BNST, bed nucleus of the stria terminalis; PVH, paraventricular nucleus of the hypothalamus; LH, lateral hypothalamus; PVT, paraventricular nucleus of the thalamus; VGAT, vesicular gamma-aminobutyric acid transporter; VGLUT2, vesicular glutamate transporter 2; VTA, ventral tegmental area; D1R, dopamine 1 receptor; TB, tuberal nucleus; SST, somatostatin; ZI, zona incerta; DR, dorsal raphe nucleus; PAG, periaqueductal grey; PBN, parabrachial nucleus; periLC, peri-locus coeruleus; CeA, central amygdala; SI, substantia innominata, PSTN, parasubthalamic nucleus; VPMpc, parvicellular portion of the ventroposteromedial nucleus; IC, visceral insular cortex; aDCN, anterior deep cerebellar nuclei.

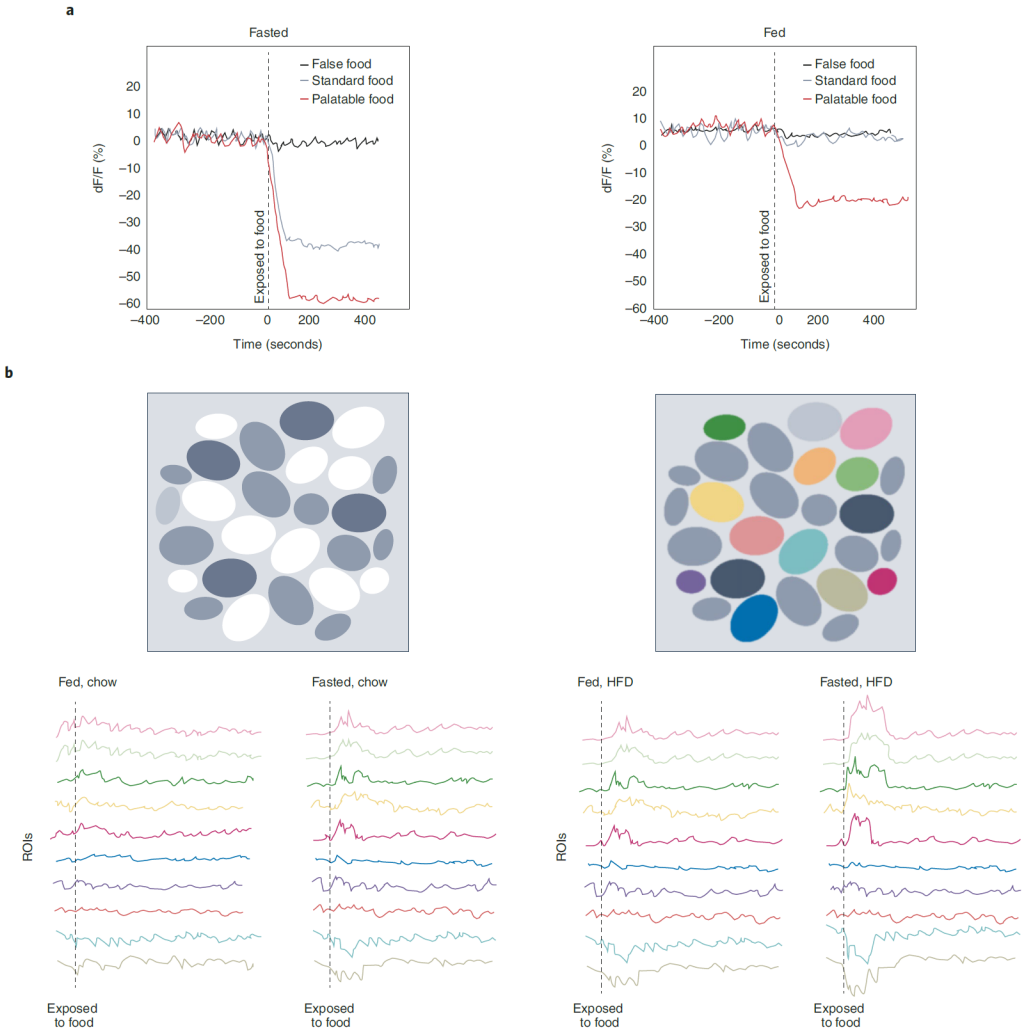

Fig. 2 |. Feeding neurons conform to energy status and food palatability.

Real-time recordings of neurons regulating appetite reveal stronger responses under periods of caloric deprivation and towards energy-dense food substrates. These changes can be determined directly by in vivo electrical-wire recordings and/or indirectly via the monitoring of calcium dynamics using genetically encoded calcium sensors (GECIs) that serve as a proxy of neural activity. These excitatory or inhibitory response properties can occur prior to, at the onset of, or after consumption. **a**, Example of optical-fibre photometry traces in fasted (left) or fed (right) mice expressing the GECI GCaMP (a synthetic fusion of green fluorescent protein, calmodulin and M13, a peptide sequence from myosin light-chain kinase) aligned to exposure of food (dotted vertical line). Although population dynamics are insensitive to false food (black traces), activity is rapidly and robustly suppressed to standard food, but in only energy-deficient mice (silver traces). Palatable-food presentation increases the magnitude of this inhibitory response and is even observed in calorically replete mice (red traces). dF/F in this case refers to the difference between initial fluorescence intensity at the resting state and after food exposure. Adapted from ref. [84] **b**, Example of single-photon microendoscopic or two-photon individual cellular activity (regions of interest, ROIs) in fasted or fed mice expressing GCaMP, aligned to exposure to food. In

vivo miniepifluorescence image of GCaMP expression (top left). Schematized cell map of an example animal's GCaMP-expressing neurons during a free-access feeding task (top right). The same neurons can be tracked between sessions (coloured cells). Calcium traces of individual neurons tracked in response to chow (left) or HFD (right) in fed versus fasted animals. Individual cells exhibit a variety of responses to food with activation (shifts upwards) or inhibition (shifts downwards) observed before, during, or after consumption. These responses are often exacerbated in hungry animals and towards energy-rich food, such as a HFD. Some neurons are non-responsive to food.

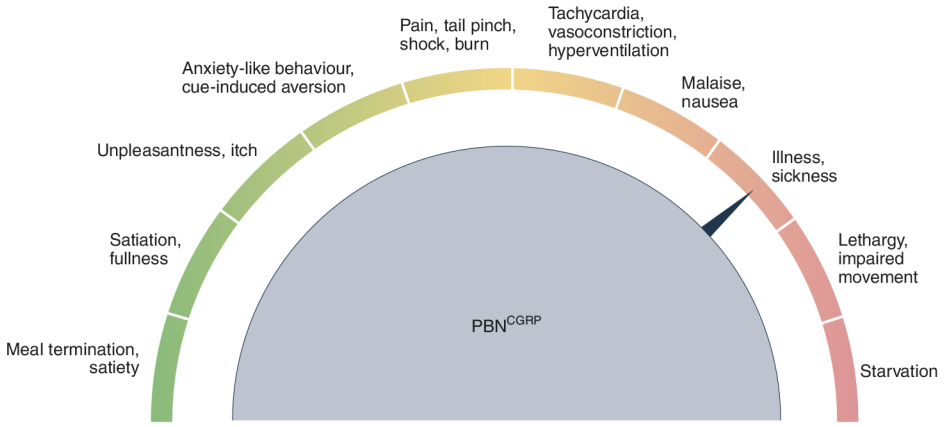

Fig. 3 |. Fine tuning of satiation circuits is required to avoid aversive outcomes.

The most common side effect of effective anti-obesity drugs is visceral malaise, including nausea, vomiting, and gastrointestinal issues. This likely stems from the overlapping features of cell types, such as PBN^{CGRP} neurons. Modest activation may signal meal termination or satiety, ultimately leading to the feeling of a full stomach. However, further stimulation could result in unpleasantness, including anxiety-like behaviour, pain, and malaise brought on by physiological changes, including tachycardia, vasoconstriction, and hyperventilation. Even stronger rousing of these circuits could ultimately culminate in severe sickness, impaired movement, and starvation. Therefore, understanding how this information is encoded at distinct brain nodes will aid in the careful crafting of therapeutics that curb overeating without negative consequences.