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## ► **To cite this version:**

Maya Faour, Nour Mesto, Claire Martin, Serge Luquet. Emerging role of AgRP neurons as integrators of metabolic, sensory and environmental cues in the control of energy homeostasis. *Reviews in Endocrine and Metabolic Disorders*, 2025, <10.1007/s11154-025-09990-5>. <hal-05355444>

**HAL Id: hal-05355444**

**<https://hal.science/hal-05355444v1>**

Submitted on 8 Nov 2025

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# Emerging role of AgRP neurons as integrators of metabolic, sensory and environmental cues in the control of energy homeostasis

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Accepted: 25 July 2025  
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## Abstract

The regulation of energy homeostasis is an essential function of every living organism. In mammals a complex interplay of neural networks has evolved to ensure proper adaptation to energy demands, availability, consumption, storage and utilization. While a large set of parallel and redundant brain networks are functionally intertwined in these processes, a specific subset of hypothalamic neurons producing the agonist and antagonist of the anorectic signaling pathway controlled by the melanocortin receptor have been extensively studied. The anorectic/catabolic pro-opiomelanocortin (POMC) producing neurons and the orexigenic/anabolic Agouti-related peptide (AgRP) producing neurons exert opposing functions of various aspects of foraging, ingestive and post-ingestive processes. Located close to circumventricular these two populations integrate circulating reflecting energy status but are dynamically controlled by food-predicting cues. This review will be focusing on recent advances in understanding the role of the hypothalamic AgRP neurons, as critical metabolic sensors and regulators. We explore the intricate mechanisms by which these neurons integrate diverse nutritional signals and coordinate autonomic and behavioral responses to maintain metabolic equilibrium.

**Keywords** AgRP · NPY · POMC · Feeding behavior · Metabolism · Obesity · Reward-dependent mechanisms

## Abbreviations

|               |                                   |       |                                                                  |
|---------------|-----------------------------------|-------|------------------------------------------------------------------|
| ME            | Median eminence                   | CRH   | Corticotrophin releasing hormone                                 |
| Arc           | Arcuate nucleus                   | AP    | Area postrema                                                    |
| AgRP          | Agouti related peptide            | SubP  | Subpostrema area                                                 |
| NPY           | Neuropeptide Y                    | cNTS  | Commissural nucleus tractus solitarii                            |
| GABA          | $\gamma$ -aminobutyric acid       | PBN   | Parabrachial nucleus                                             |
| BBB           | Blood–brain barrier               | CeA   | Amygdala                                                         |
| MCR           | Melanocortin receptors            | PAG   | The periaqueductal gray area                                     |
| PVN           | Paraventricular nucleus           | PVT   | Paraventricular thalamus                                         |
| POMC          | Pro-opiomelanocortin              | aBNST | The anterior division of the bed nucleus of the stria terminalis |
| $\alpha$ -MSH | Alpha-melanin stimulating hormone | LH    | Lateral hypothalamus                                             |
| ACTH          | Adrenocorticotrophic hormone      | DR    | Dorsal Raphe                                                     |
| CVO           | Circumventricular organ           | VMH   | Ventromedial hypothalamic nucleus                                |
| CSF           | Cerebrospinal fluid               | SCN   | Suprachiasmatic area                                             |
| TRH           | Thyrotropin-releasing hormone     | POA   | Preoptic area                                                    |
|               |                                   | CeA   | Central nuclei of the amygdala                                   |
|               |                                   | MeA   | Medial nuclei of the amygdala                                    |
|               |                                   | TRH   | Thyrotropin-releasing hormone                                    |
|               |                                   | Th    | Tyrosine hydroxylase                                             |
|               |                                   | PACAP | Pituitary adenylate cyclase-activating polypeptide               |
|               |                                   | iBAT  | Interscapular brown adipose tissue                               |
|               |                                   | PCOS  | Polycystic ovary syndrome                                        |

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|        |                                         |
|--------|-----------------------------------------|
| mTORC1 | Mammalian target of rapamycin complex 1 |
| Ucp2   | Uncoupling protein 2                    |
| GHRH   | Growth hormone releasing hormone        |
| GH     | Growth hormone                          |
| IGF-1  | Insulin-like growth factor-1            |
| ABA    | Activity-based anorexia                 |
| AR     | Androgen receptors                      |

## 1 Introduction

The regulation of energy homeostasis is essential for survival, relying on the complex interplay of brain networks and functions to anticipate energy intake in response to both internal and external cues. It is now clear that a large set of parallel and redundant brain networks are essential for driving feeding and regulating metabolic outcomes, integrating nutrient availability with metabolic needs and the cognitive aspects of feeding. Over the last 20 years, genetic research in both humans and mice has pinpointed several neural circuits that regulate appetite and metabolism. Chief among them is the hypothalamic leptin-melanocortin signaling pathway, which, when genetically disrupted, leads to most known cases of monogenic severe obesity.

This melanocortin pathway involves a complex hormonal network with three primary components. First is the prohormone proopiomelanocortin (POMC), which is enzymatically processed into active fragments such as  $\alpha$ -,  $\beta$ -, and  $\gamma$ -melanocyte-stimulating hormones (MSH), along with adrenocorticotropic hormone (ACTH) [1]. Second are the melanocortin receptors (MC1R through MC5R), a group of five G protein-coupled receptors that respond to these peptides [2]. Third, the system includes natural antagonists like agouti and agouti-related peptide (AgRP), which modulate receptor activity. This signaling network influences a wide range of biological functions, including pigmentation, adrenal development, reproductive behavior, and, most importantly in this context, the regulation of body weight and food consumption. POMC and AgRP neurons are located in the arcuate nucleus (Arc) of the hypothalamus. In both rodent and human, the hypothalamus shows a similar organization and contains several sub nuclei with convergent functions (Fig. 1). The Arc lies in close vicinity to the median eminence (ME), which is a specialized circumventricular organ (CVO), a structure of the blood–brain barrier (BBB) described as a fenestrated and densely irrigated endothelium that has evolved to allow selective exchange and passive diffusion of the blood-borne molecules through the cerebrospinal fluid (CSF) [3, 4].

This positioning grants Arc neurons unique access to circulating hormones and nutrients making them important sensors of metabolic activity. They integrate these circulating

signals reflecting energy status into synaptic signals that are then transmitted to downstream regions including the paraventricular nucleus (PVN) and brainstem. Although AgRP and POMC neurons located in the Arc represent a relatively small cell population they project to various hypothalamic and extra-hypothalamic areas [5, 6] and exert a central influence on the control of feeding behavior and energy balance.

AgRP neurons drive feeding in two distinct phases: an appetitive phase (food-seeking, motivation) and a consummatory phase (eating, chewing, swallowing, and satiety). While forebrain regions and reward circuits support appetitive behaviors, hindbrain circuits largely govern consummatory actions. Ablation of AgRP neurons disrupts both phases, regardless of melanocortin pathway involvement. These neurons are activated by caloric deficits and inhibited during feeding [7–9].

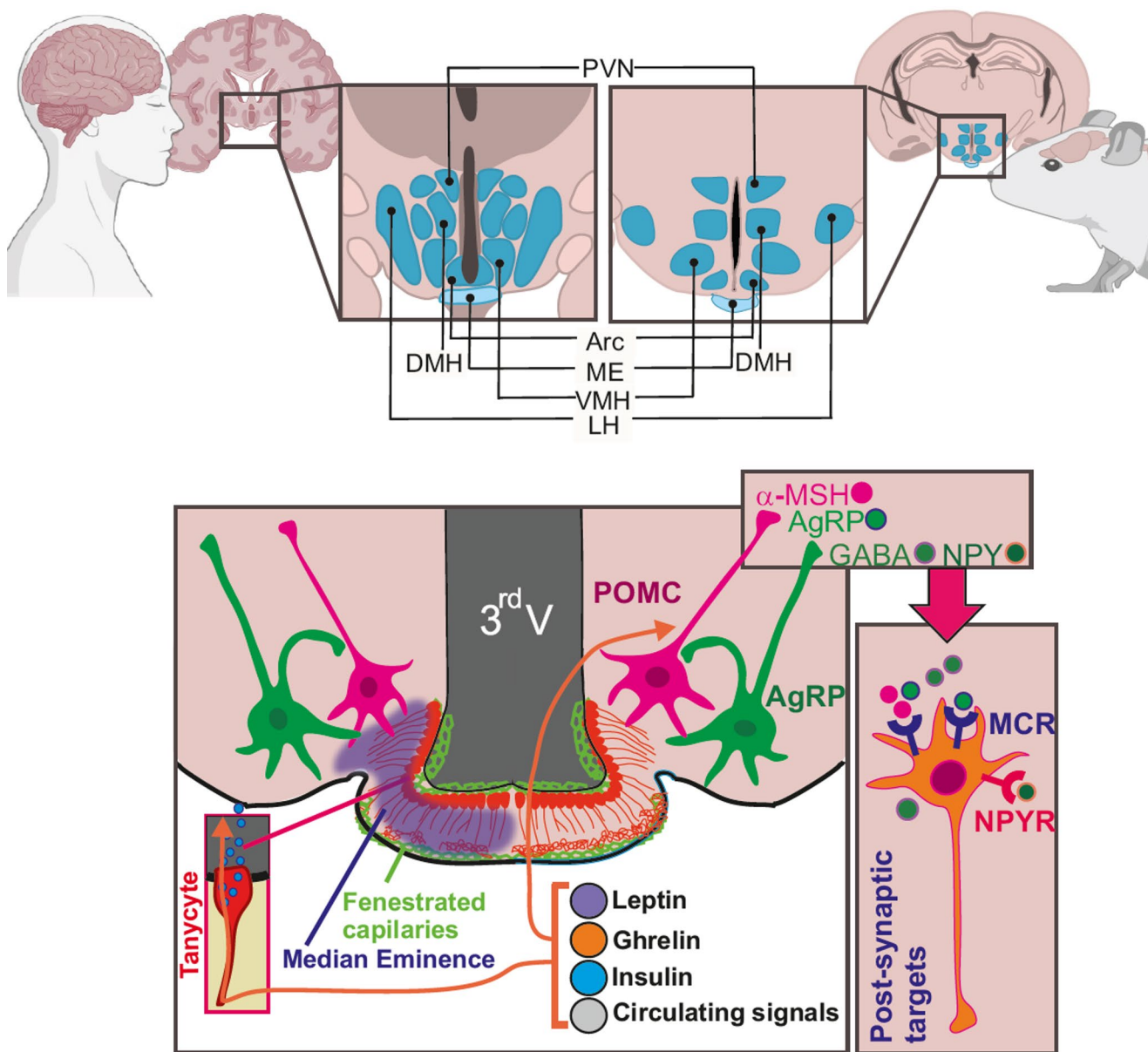
AgRP neurons also process environmental cues about food availability. They are rapidly suppressed—within seconds—by the sight, smell, or learned signals of food, well before ingestion begins. This fast inhibition, too quick to involve hormonal feedback, is attributed to sensory input from afferent circuits [7–9]. Notably, exposure to nutritive food strengthens these cue-based inhibitory responses, particularly for palatable meals [10, 11], suggesting that AgRP neurons encode learned associations between food cues and expected nutritional content.

This review explores recent advances in our understanding of the role of Arc AgRP neurons as key metabolic integrators. We examine how they integrate hormonal, sensory, and nutrient signals to regulate feeding, energy expenditure, and glucose homeostasis. We also consider emerging insights into their role in modulating the neural circuitry that governs the hedonic aspects of feeding behavior. Finally, we discuss how dysfunction of these neurons contributes to obesity and related disorders, and how targeting them may offer therapeutic potential.

## 2 AgRP neurons, a crucial component of the network that regulates feeding behavior

### 2.1 Melanocortin-dependent and independent mechanisms

POMC neurons form subpopulations that project to distinct brain areas. These neurons express receptors for leptin, insulin, and serotonin (Htr2c) and release either GABA or glutamate depending on their Arc location [12–15]. Some even express *Agouti related peptide (Agrp)* and *Neuropeptide Y (Npy)* transcripts, highlighting a functional overlap with orexigenic neurons [15]. Leptin, a hormone reflecting long-term energy stores, primarily activates POMC neurons,



**Fig. 1** Anatomical localization of the hypothalamic nuclei and AgRP neurons. **Upper panel:** Human (left) and rodent (right) coronal sections and localization of the hypothalamus and hypothalamic nuclei. Arc, arcuate nucleus; DMH, dorsomedial hypothalamic nucleus; LH, lateral hypothalamic area; PVN, periventricular nucleus; VMH, ventromedial hypothalamic nucleus; ME, median eminence. **Lower panel:** Rodent arcuate nucleus with pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons. Circulating energy-related

signals target arcuate neurons through fenestrated capillaries and via tanycytic-regulated transport. Integration of these signals by POMC and AgRP neurons leads to the release at post-synaptic targets of the melanocortin receptor (MCR) agonist alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) and antagonist AgRP by POMC and AgRP neurons, respectively. AgRP neurons also release neuropeptide Y (NPY) and  $\gamma$ -aminobutyric acid (GABA)

which release  $\alpha$ -MSH to stimulate melanocortin receptors on PVN neurons (PVN<sup>MC4R</sup>) and suppress appetite [16, 17]. These PVN neurons then release anorectic neuropeptides like TRH (thyrotropin-releasing hormone), CRH (corticotropin-releasing hormone), and oxytocin [18]. In contrast, AgRP neurons are activated by energy-deficit signals like ghrelin and promote feeding [19]. AgRP neurons enhance appetite through the release two neuropeptides AgRP and

NPY, and the fast acting neurotransmitter  $\gamma$ -aminobutyric acid (GABA) [20–23]. AgRP peptide, unique to these neurons, antagonizes  $\alpha$ -MSH at MC4R in the PVN to promote feeding [24]. NPY a very potent orexigenic molecule, co-expressed in 90% of Arc AgRP neurons, promotes feeding via Y1 and Y5 receptors, particularly in PVN oxytocin neurons [25] but also in other hypothalamic nuclei [26, 27]. GABA directly inhibits POMC neurons, reinforcing

the orexigenic drive of AgRP neurons [21, 28]. However, this classical vision of a Yin and Yang control of feeding through the opposite regulation of POMC and AgRP neurons has recently been challenged. A study by De Solis et al. showed that the promotion of food intake is actually the result of a simultaneous activation and inhibition of AgRP and POMC neurons respectively. Both inputs coordinately and cooperatively leads to the activation of NPY receptor-1 expressing neurons in the PVH (PVN <sup>Npy1R</sup>) which in turn project to Tyrosine hydroxylase (Th<sup>+</sup>) positive neuron in the NTS (NTS<sup>Th+</sup>) [29].

## 2.2 Initiating feeding and preventing starvation

Functional studies using cell-specific ablation based on restricted expression of the diphtheria toxin receptor (DTR) confirmed the critical role of AgRP neurons in feeding: removal of these neurons in adult mice led to anorexia [30, 31]. Additional models of either progressive postnatal cell death [32, 33] or incomplete ablation (less than 50%) of AgRP neurons [32] consolidate previous findings, showing that post-embryonic ablation of AgRP neurons leads to a lean, hypophagic phenotype with reduced adiposity. A recent study has challenged the notion that the integrity of AgRP neurons located in the Arc are critical for survival. Using intra-arcuate toxin injection to achieve targeted ablation of Arc AgRP neurons selectively and sparing to other *Agrp* expressing cells in the rest of brain and body, the authors found no changes in daily *ad libitum* feeding, while refeeding after a 24-hour fast was impaired [34]. This result suggests that Arc AgRP neurons are not indispensable for normal feeding in adult mice.

One possible explanation is the existence of other *Agrp*-expressing cells identified in the hindbrain notably, at the level of the area postrema (AP), the adjacent subpostrema area (SubP), and the commissural nucleus tractus solitarii (cNTS). These cells are collectively referred to as AgRP<sup>Hind</sup> neurons. It has been shown that food deprivation stimulates AgRP<sup>Hind</sup> expression. Moreover, chemogenetic activation of AgRP<sup>Hind</sup> neurons results in hyperphagia and weight gain in adult mice with or without hypothalamic AgRP neurons, suggesting that AgRP<sup>Hind</sup> neurons drive feeding independently of hypothalamic AgRP neurons [35]. Other recent studies have demonstrated the existence of peripheral AgRP-expressing cells, in the pituitary [36] and adrenal glands [37], that are also involved in food intake regulation. Chemogenetic inhibition of *Agrp*-expressing cells of the pituitary gland causes weight loss [36]. Meanwhile, short-term fasting leads to an increase in adrenal *Agrp* expression [37]. Despite these discoveries, the specific mechanisms by which these peripheral AgRP cells influence energy balance and homeostasis remain largely unknown. Hence, the

absolute necessity for Arc AgRP neurons (referred to as AgRP<sup>Arc</sup> neurons) to prevent starvation is disputed, prompting a more refined vision of their role as key regulator/modulator of behavior and metabolic control. In that line, the fact that AgRP<sup>Arc</sup> neurons are sufficient to drive feeding sequence has been clearly established using approaches aiming at transiently manipulating Arc AgRP neurons in behaving animals. Optogenetic and/or chemogenetic activation of AgRP<sup>Arc</sup> neuron induces feeding, even in the presence of food while AgRP inhibition reduces food intake [25, 38–40]. Moreover, chronic activation of these neurons leads to hyperphagia and obesity [41].

Furthermore, since the initial studies charting the widespread projections of AgRP neurons to both hypothalamic and non-hypothalamic regions, the use of tracing techniques—alongside targeted stimulation of AgRP axon subsets at their downstream sites—has helped to reveal overlapping and parallel neural pathways by which AgRP<sup>Arc</sup> neurons influence feeding behavior, metabolic regulation, and cognition. These methods have enabled to functional separation of the specific circuits that either drive or sustain feeding behavior i.e. prevents starvation after AgRP<sup>Arc</sup> neuron ablation. Direct manipulation of Arc AgRP neurons projections at their post-synaptic targets demonstrated coordinated and timely controlled release of NPY and GABA which mediate immediate feeding responses, while the release of AgRP ensured the continuation of feeding [22, 39]. It also arises from these approaches that feeding control by AgRP<sup>Arc</sup> neurons also involved melanocortin-independent mechanisms. AgRP neurons ablation leads to the parabrachial nucleus (PBN) hyperactivity, anorexia, and weight loss, reversible by GABA agonist infusion [31, 42, 43]. Blocking MC4R in the PVN fails to prevent starvation caused by AgRP<sup>Arc</sup> ablation neurons [38, 44], but on the other hand, AgRP-ablated mice are protected from anorexia by restoring GABAergic signaling in a structure that receive important projections from the AgRP<sup>Arc</sup>, the PBN. However, no feeding response resulted from the acute stimulation of AgRP<sup>Arc</sup> fibers projecting to the PBN, the periaqueductal gray area (PAG) or the central nucleus of the amygdala (CeA), while similar activation of Arc AgRP fibers in the paraventricular thalamus (PVT), the anterior division of the bed nucleus of the stria terminalis (aBNST) or lateral hypothalamus (LH) triggered feeding [39].

A recent study capitalized on feeding sequence analysis assisted by machine-learning combined with *in vivo* manipulation and imaging of subtle neural substrates, revealed that AgRP<sup>Arc</sup> neurons and GABAergic neurons in the LH and Dorsal Raphe (DR) proceed by iteration to balance the urge to consume food with the motivation to explore unfamiliar and potentially hazardous environment [45]. Altogether, these results exemplify the rare complexity by which

discreet, sequential release and signaling initiated at individual post-synaptic targets is instrumental in the orchestration of feeding by AgRP<sup>Arc</sup> neurons, while undergoing fine tuning as a consequence of both metabolic need and environmental cues.

### 3 Diversity in arcuate AgRP neurons nature, inputs and outputs

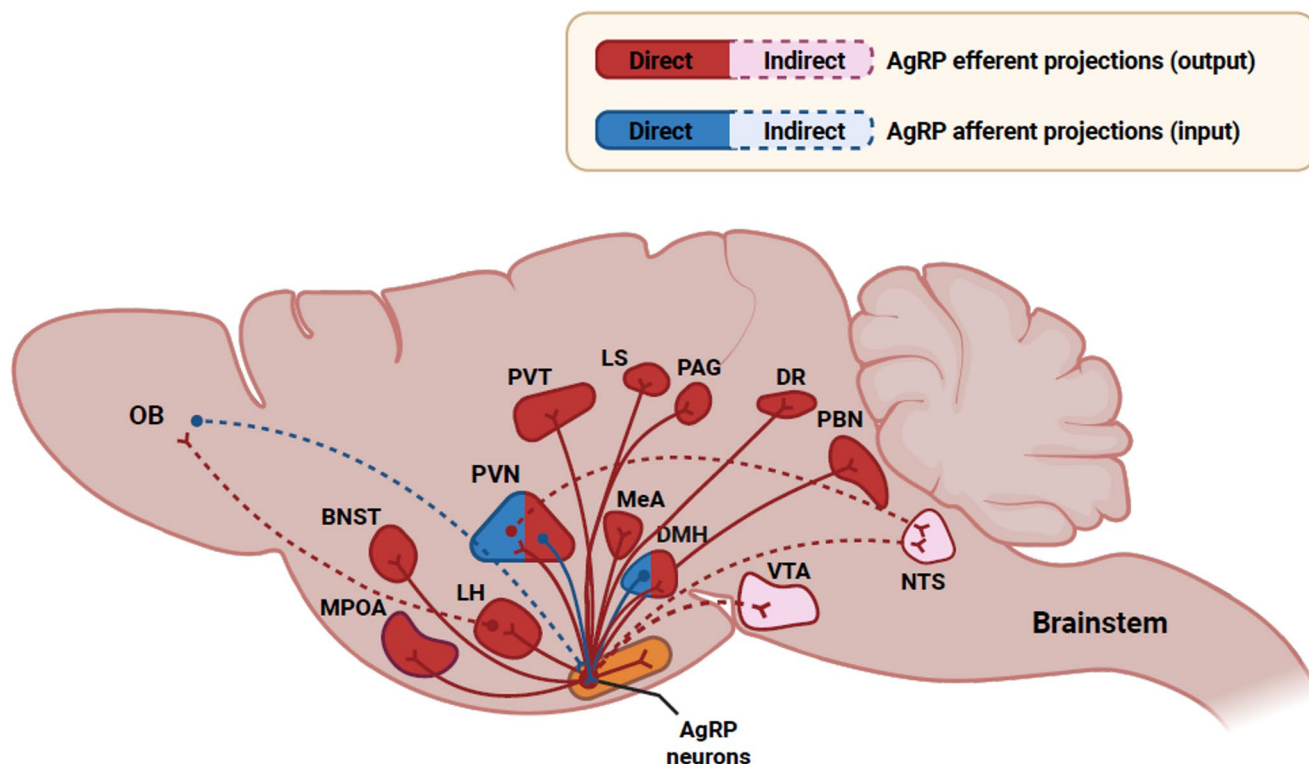
Both POMC<sup>Arc</sup> and AgRP<sup>Arc</sup> neurons contact many brain regions within the hypothalamus. Among these, the PVN receives the densest AgRP innervation (~30%) [39, 46]. Activation of AgRP→PVN projections powerfully stimulates feeding via melanocortin pathway inhibition [25, 39]. As a major hypothalamic output hub, the PVN regulates autonomic outflow to liver, adipose tissue, and other metabolic organs [47].

Other intrahypothalamic AgRP neuron projections include the lateral, ventromedial, and dorsomedial, hypothalamic areas (LH, VMH, and DMH, respectively), the supra-chiasmatic area (SCN) and the preoptic area (POA). AgRP projections also extend beyond the hypothalamic borders,

innervating the central and medial nuclei of the amygdala (CeA and MeA, respectively), the aBNST, the PVT, the PBN, the lateral septum (LS), and the PAG [46, 48] (Fig. 2).

Single-cell transcriptomic analysis combined with functional tracing and manipulation methods have revealed the heterogeneity in different POMC and AgRP subpopulations, defined by their selective receptor equipment, post-synaptic targets and function ranging from feeding behaviors to cognitive and metabolic control [15, 39, 49, 50]. This modular organization enables specific circuits to mediate distinct aspects of hunger and food-seeking behavior using segregated and parallel output. Optogenetic stimulation of fiber terminals in specific brain regions has revealed that AgRP projections to the LH, aBNST, PVT, mPOA, or MeA are sufficient to induce feeding [25, 39, 51, 52].

AgRP projections to the LH stimulate food intake and induce insulin resistance, partly by suppressing interscapular brown adipose tissue (iBAT) metabolism [53]. AgRP→aBNST activation also stimulates feeding and reprograms iBAT gene expression, increasing muscle-related genes and altering glucose uptake. Fasting strengthens AgRP→BNST connectivity while weakening CeA→BNST circuits, favoring orexigenic tone [54].



**Fig. 2** Efferent and afferent projections of AgRP neurons. Direct (dark blue and red) and indirect (light blue and red, dashed) projections of AgRP neurons are presented. AgRP neurons directly project to the anterior bed nucleus of the stria terminalis (BNST), medial preoptic area (MPOA), lateral hypothalamus (LH), amygdala (medial and central, MeA, CeA), dorsomedial hypothalamus (DMH), dorsal raphe (DR),

parabrachial nucleus (PBN), paraventricular thalamus (PVT), lateral septum (LS) and Periaqueductal gray (PAG). AgRP neuron indirectly exert a control on the nucleus tractus solitarius (NTS), ventral tegmental area (VTA), and olfactory bulb (OB). They receive direct afferent projections from the DMH and PVH and are indirectly controlled by OB input. Created in BioRender

Other projections have more nuanced roles. Stimulating AgRP→CeA, →PAG, or →PBN terminals alone does not trigger feeding [39]. PBN CGRP neurons mediate satiety; AgRP projections inhibit them, delaying meal termination [55]. AgRP neurons targeting the MeA suppress defensive behaviors, allowing feeding to override fear and aggression responses [52]. Collectively, these pathways demonstrate how AgRP neurons coordinate diverse metabolic, behavioral, and autonomic responses.

Compared to their outputs, AgRP afferents remain less well defined. These neurons receive dense synaptic input, enabling fast modulation. Tracing and electrophysiology studies have identified major inputs from PVH and DMH, along with local Arc inputs, including POMC neurons [46, 56, 57]. Fasting enhances excitatory PVH input to AgRP neurons [58, 59]. A subset of PVH neurons expressing thyrotropin-releasing hormone (TRH) and pituitary adenylate cyclase-activating polypeptide (PACAP) provide strong glutamatergic input. Their activation increases AgRP activity and feeding in sated mice, while silencing suppresses hunger-driven intake, highlighting a PVH<sup>PACAP</sup>→AgRP pathway crucial for hunger signaling [57]. The DMH supplies inhibitory GABAergic input via LepR/dynorphin-expressing neurons. Stimulating DMH<sup>GABA</sup>→AgRP circuits reduces AgRP activity at mealtime, especially after fasting [56]. Additional inputs from LH, PBN, BNST, CeA, and MeA form reciprocal loops that integrate environmental and emotional cues [60].

Together, these afferent and efferent pathways place AgRP neurons at the center of a distributed circuit that controls feeding behavior, integrating sensory and metabolic signals to shape adaptive behavior.

#### 4 AgRP neurons: control of nutrient partitioning and peripheral function

Beyond promoting feeding, AgRP<sup>Arc</sup> neurons shape how the body utilizes and stores nutrients. Early studies showed that the intracerebroventricular administration of AgRP fragments reduced energy expenditure (EE), increased adiposity, and induced weight gain—without necessarily increasing food intake—suggesting direct effects on substrate use [61]. In addition, chemogenetic activation of AgRP neurons demonstrated their implication in substrate storage and utilization (nutrient partitioning): stimulation rapidly raises the respiratory exchange ratio (RER), indicating a shift towards carbohydrate use and reduced fat oxidation [22, 40, 62, 64]. Mice lacking AgRP neurons from early life show altered metabolism despite normal food intake—developing late-onset obesity, hyperinsulinemia, and a shift towards lipid

use, alongside hepatic triglyceride synthesis from carbohydrates [63].

Interestingly, this altered nutrient partitioning provides some protection from glucose intolerance and fat accumulation during high-fat feeding. In adult mice receiving controlled enteral nutrition, AgRP neuron ablation reduced fat mass compared to controls on identical diets [62, 63].

Conversely, activating AgRP neurons promotes glucose utilization and suppresses lipid oxidation, encouraging lipogenesis and fat gain. This also blunts the browning of white adipose tissue (WAT) and reduces thermogenic activity in iBAT [65]. AgRP neurons act as a metabolic brake, using mTORC1 signaling to regulate iBAT thermogenesis based on internal and external cues [66].

AgRP neurons also impact glucose metabolism. Their activation causes insulin resistance by impairing glucose uptake in iBAT—a process dependent on NPY. NPY-deficient mice do not develop insulin resistance after AgRP stimulation, but selective *Npy* re-expression in AgRP neurons restores this effect [67]. This regulation is melanocortin-independent; activating POMC neurons does not affect insulin sensitivity [53]. Interestingly, a recent study by De Solis et al. reveals that, while coordinated activation and inhibition of AgRP and POMC neurons cooperatively control feeding, these neurons exert a control on liver glucose production through segregated autonomic branch and liver signaling pathway [29].

AgRP dysfunction contributes to obesity-related glucose dysregulation and to diabetic hyperglycemia. High-fat and high-sugar diets raise *Agrp* expression [68, 69] and hyperactivate these neurons, independent of caloric content [70]. Obesogenic diets also impair AgRP responsiveness to food cues—blunting the typical rapid inhibition during chow presentation [71, 72] while weight loss partially restores AgRP sensitivity to sensory cues but does not fully recover hormonal responsiveness (e.g., ghrelin, leptin, cholecystokinin (CCK)) or nutrient-driven inhibition [70, 71, 73]. This persistent dysfunction suggests a potential for diet composition to induce neural remodeling. AgRP neurons activity is elevated in multiple diabetic models, including leptin-deficient ob/ob mice, Zucker diabetic fatty rats, and streptozotocin (STZ)-induced diabetes [74–76]. Inhibiting AgRP neurons in STZ models reduces both hyperphagia and hyperglycemia [77]. Central leptin administration lowers *Agrp* expression and improves glycemia. Additionally, CRISPR-mediated deletion of leptin receptors in AgRP neurons induces diabetes—highlighting their role in leptin's antidiabetic effects [77–79].

Together, these findings position AgRP neurons not just as drivers of feeding, but as key regulators of systemic nutrient handling—modulating glucose metabolism, insulin

sensitivity, fat storage, and energy partitioning (for review see [80]).

The indirect control exerted by AgRP neurons on the autonomic nervous system also allows them to coordinate energy availability with bone remodeling and reproductive function, in coordination with metabolic demands [81, 82]. Mice lacking uncoupling protein 2 (Ucp2) in AgRP neurons develop osteopenia, while restoring Ucp2 rescues bone density. Deleting AgRP itself increases bone mass despite leanness, particularly in males. Mechanistically, AgRP neurons influence bone formation via the PDK1-FoxO1 pathway, which modulates the GHRH (growth hormone releasing hormone)-GH (Growth hormone)-IGF-1 (insulin-like growth factor-1) axis AgRP-specific 3-phosphoinositide-dependent protein kinase-1 (PDK1) knockout mice show impaired bone formation and GH release, linked to enhanced FoxO1 activity [83].

Notably, this pathway appears to be independent of leptin signaling. In leptin-deficient *ob/ob* females, AgRP and NPY mRNA levels are elevated. Deleting AgRP neurons in this model restores both reproductive and metabolic functions [84]. Although AgRP neurons express androgen receptors (AR), excess androgens (as in polycystic ovary syndrome: PCOS) do not disrupt their function, suggesting that ARs in these neurons are not major contributors to PCOS phenotypes [85].

During food scarcity or AgRP activation, reproductive behaviors decline. Interest in mates drops, likely via AgRP-mediated inhibition of kisspeptin neurons in the reproductive axis [86]. The VMH may serve as a key postsynaptic target, given its role in regulating mating and aggression [87]. Food deprivation also reduces parental behaviors, reflecting an adaptive shift towards energy conservation [88].

## 5 AgRP neurons: cognitive integration and behavioral regulation

AgRP neurons also process environmental cues about food availability. They are rapidly suppressed—within seconds—by the sight, smell, or learned signals of food, well before ingestion begins. This fast inhibition, too quick to involve hormonal feedback, is attributed to sensory input from afferent circuits [7–9]. Notably, exposure to nutritive food strengthens these cue-based inhibitory responses, particularly for palatable meals [10, 11], suggesting that AgRP<sup>Arc</sup> neurons encode learned associations between food cues and the expected nutritional content. AgRP<sup>Arc</sup> neurons are dynamically regulated by interoceptive (ingested nutrients, hormones...) or exteroceptive (encountered food-related

sensory cues) signals which have different regulatory effects on AgRP neuronal activity.

Hence, beyond hunger AgRP<sup>Arc</sup> neurons shape sensory perception, motivation, mood, and adaptive behavior [89–91]. Amongst extra hypothalamic areas targeted by these neurons are regions of the limbic reward systems, notably the dopaminergic circuits of the nucleus accumbens (NAcc) and striatum, which mediate the reinforcing effects of high-fat, high-sugar foods [92–94]. In physiological and pathophysiological conditions, these circuits can override homeostatic regulation, resulting in continued eating despite the absence of energy requirements.

### 5.1 AgRP neurons modulation of dopamine signaling and reward-associated behaviors

Several reports emphasize the relationship between AgRP neurons and the limbic system. While the stimulation of AgRP neurons in the presence of food increases food consumption, manipulating these neurons in the absence of food triggers compulsive and stereotypic behaviors that recapitulate the behavioral adaptations observed during starvation. This behavior is associated with reduced anxiety, as assessed using an open field or elevated plus maze test [90]. It also modulates the territorial aggression behavior observed in conditions of starvation. Interestingly the specific activation of AgRP→MeA but not AgRP→PVN circuits reduces territorial aggression [52], while inhibition of AgRP neurons reverses this anxiolysis [95].

Furthermore, elevated activity of AgRP neurons induced by optogenetics has been associated with a negative valence—a motivational drive to escape hunger—that influences learning and behavior: in the context of flavor choice or place preference, animals will avoid the stimulus paired with AgRP stimulation. This aversive state can be reversed by food cues, which highlights the sensory-based regulation of AgRP activity [7, 52].

Early during development, AgRP neurons play a role in establishing reward system function. Indeed, early postnatal AgRP ablation impairs the ventral tegmental area (VTA) dopaminergic plasticity, leading to a long-term imbalance between homeostatic and reward-driven feeding [89, 96]. Disruption of metabolic signaling in AgRP neurons reduces dopamine (DA) release in the NAcc and blunts caloric reward responses [97]. These effects depend on ghrelin signaling, which gates sensory control over AgRP neurons [98].

AgRP neurons indirectly influence DA-dependent behaviors. Although they are unlikely to exert direct monosynaptic input onto the VTA, they shape reward circuitry through developmental programming and circuit interactions. AgRP ablation leads to long-term adaptations in motivational

systems, shifting behavior towards reward-driven rather than energy-driven feeding [89].

Chemogenetic inhibition of AgRP neurons during puberty disrupts medial prefrontal cortex (mPFC) activity and produces long-lasting cognitive and behavioral deficits, partially mediated by VTA and medial thalamic inputs [99].

On the other hand, the role of DA signaling in AgRP neurons has only recently been documented. Using tracing techniques, Zhang et al. showed that DA in the Arc originates primarily from dopaminergic neurons located in hypothalamic regions and the zona incerta [100]. Presentation of food is immediately followed by DA release in the Arc in fasted mice. DA release is modulated both by food palatability (standard vs. high fat diet) and the metabolic state of the animal. In addition, genetic ablation of DA receptor D1 (*Drd1*) expressed in AgRP neurons reduces refeeding of high fat diet.

## 5.2 AgRP neurons and sensory detection of food

Smell and taste are highly relevant sensory cues predicting food palatability, food danger and are likely to play a key role in food choice and food consumption. Even before ingestion, and well before nutrients and hormones reach the Arc, the smell and sight of food are sufficient to transiently inhibit AgRP neuronal activity [7, 9, 101]. Interestingly, this modulation is learning-dependent, as it is only observed for familiar foods and varies according to their palatability and the animal's metabolic status. As the neuronal pathway linking olfactory detection with AgRP modulation remains unknown, these data suggest that in the presence of food, AgRP neurons play a role in the anticipatory modulation of metabolism triggered by sensory cues. This inhibition would help drive satiation as suggested by a recent study. In mice licking a bottle containing liquid diet, each bout of ingestion was precisely locked to phasic dips in AgRP neuron activity, confirming the impact of orosensory sensory signals driving AgRP neurons. Interestingly, preventing these transient dips via closed-loop stimulation delays satiety and increases food intake [102]. Furthermore, this rapid inhibition may serve adaptive functions. Indeed, as suggested by Berrios et al., the rapid inhibition of negative value promoted by AgRP activation could optimize food cue-based learning. This aspect seems to be a pivotal function of AgRP neurons as they can learn the nutritive value of foods in a single trial [11].

In addition, this regulation is bidirectional, since AgRP activity can also modify sensory perception. According to tracing studies, the effects of AgRP neurons on taste and smell are likely to be indirect. The paraventricular thalamus has been identified as a possible relay. In the context of an odorant preference test between food and social cues, fasted

but not fed animals have a longer exploration of food odors. However, optogenetic activation of AgRP→PVT terminals in fed mice increases attraction to food odors, this was not observed when activating other projection sites of AgRP neurons. This effect is mediated by AgRP-neuron-derived NPY binding on the NPY-Y5 receptor [103].

In addition to modulating the perception of food odors, AgRP neurons also play a role in modulating taste perception. AgRP→LHGlut projections enhance sweet taste sensitivity while reducing aversive responses to taste [104]. AgRP activity also influences the insular cortex (InsCx), where hunger shifts sensory processing of food cues. A specific pathway via the PVT and the basolateral amygdala (BLA) has been shown to connect AgRP neurons to the InsCx and to be involved in the hunger-dependent enhancement of food cue responses in mice. AgRP activation during satiety can restore hunger-like neuronal responsiveness in the InsCx [105]. AgRP→PVT projections are critical for cue-driven food seeking; their ablation impairs spatial and contextual learning related to food availability [60].

## 5.3 AgRP neurons and social behaviors

AgRP neurons also influence social behaviors. A subset projecting to MeA→pBNST circuits suppresses territorial aggression and fear in favor of food-seeking behaviors [52]. However, hunger does not always suppress social drive. In fasted or AgRP-activated males, the competition between food seeking and social dominance remains context-dependent [88]. Finally, AgRP neurons can also be indirectly modulated by the peripheral detection of food composition. Alcohol and other non-nutritive drugs inhibit the activity of hypothalamic AgRP neurons, in a vagus-independent manner, whereas fats and other satiety signals depend on vagal input. Simultaneously, nutrients, alcohol, and drugs enhance midbrain DA signaling, demonstrating a bidirectional interaction between hypothalamic and DA circuits [106]. Notably, alcohol's effects on AgRP neurons suggest it is not perceived as calories by the brain, consistent with its minimal impact on long-term feeding behavior and body weight regulation. These findings highlight that non-nutritive, rewarding substances can regulate homeostatic feeding systems, and that natural and drug rewards are processed through interdependent modulation of hypothalamic and reward circuits, providing new insights into the neural mechanisms underlying feeding behavior and addiction [106].

Together, these findings position AgRP neurons as key integrators of homeostatic requirements and environmental input. They dynamically modulate sensory processing, reward, cognition, and emotional behavior to promote survival.

## 6 AgRP neurons and the integration of environmental cues

### 6.1 Integration of circadian rhythms

Since sleep and feeding are both critical for energy homeostasis it is not surprising that AgRP neurons also regulate sleep–wake states. Fasting or chemogenetic activation of AgRP neurons promotes wakefulness and disrupts sleep, while their inhibition increases non-rapid eye movement (NREM) sleep and reduces fragmentation during fasting [107]. Sleep deprivation, in turn, suppresses AgRP-driven feeding, suggesting a trade-off between sleep and food-seeking.

Furthermore, AgRP neuron activity follows circadian patterns entrained by fluctuations in circulating hormones as well as by an intrinsic clock. Levels of leptin, ghrelin, and insulin oscillate in line with light/dark cycles and feeding rhythms [108], and AgRP neurons gradually ramp up firing across the light period, peaking to promote feeding during the active phase [9].

In addition, AgRP neurons regulate time-of-day-specific gene expression related to metabolism and synaptic plasticity, aligning feeding with energy demand. Their clock also mediates leptin's transcriptional actions [109]. Moreover, AgRP neuron activity primarily follows the circadian rest-activity cycle and integrate time-of-day information from past feeding experiences with current metabolic needs to predict circadian feeding times [110]. Novel feeding patterns or periodic stimulation of AgRP-neurons can resynchronize the daily rhythm of AgRP-neuron activity. This resynchronization drives anticipatory-like behavior through a process involving prodynorphin neurons in the DMH (DMH<sup>PDYN</sup>) neurons [110]. In addition, a recent study using long-term calcium imaging reveals that AgRP neurons display intrinsic circadian rhythm that is independent of the feeding rhythm imposed by excitatory inputs from *Trh* expressing neurons in the DMH through a SCN→DMY<sup>Trh</sup>→AgRP This circuits activates AgRP neurons in a feed-forward manner to prevent energy deficit [111].

Altogether, these findings highlight the intricate relationship between circadian rhythms and feeding behavior, demonstrating how AgRP neurons participate in the brain circuits that integrates multiple signals to regulate energy homeostasis, anticipate mealtimes and prevent energy deficits.

### 6.2 Thermal sensing and feeding

Cold exposure increases energy expenditure in order to maintain core temperature, which requires a higher food intake to preserve energy balance [112, 113]. However, this response is

not driven by energy deficit signals—AgRP activation occurs too quickly for this to be the case. Instead, it is a feedforward signal that anticipates energy needs. Silencing AgRP neurons blocks cold-induced hyperphagia but not thermogenesis [114]. Conversely, heat suppresses appetite: during exercise, in warm environments, or during fever, food intake drops. This suppression is driven by TRPV1-expressing POMC neurons that are heat-activated, leading to appetite inhibition [115].

## 7 AgRP neurons and anorexia nervosa

Feeding is a fundamental survival behavior that is tightly regulated in response to varying environmental conditions [116, 117]. In anorexia nervosa (AN), however, this regulation breaks down, resulting in severe malnutrition. Despite its complexity and high mortality rate, effective treatments remain limited, emphasizing the need to understand the neural mechanisms underlying pathological feeding behaviors [118].

Genetic studies have identified variants of the *Agrp* gene as potential risk factors for AN [119, 120]. Elevated plasma AgRP levels have been observed in patients with AN and replicated in rodent models of activity-based anorexia (ABA), which combines food restriction with voluntary exercise. In these models, *Agrp* expression increases at both the mRNA and protein levels [121–124].

Chronic central infusion of AgRP alleviates ABA symptoms, increasing food intake while reducing hyperactivity [124–126]. Further studies have shown that AgRP neurons are essential for survival under conditions of food restriction and high exercise. In vivo calcium imaging shows that AgRP neuron activity drops sharply after voluntary cessation of running. Paradoxically, daily activation of AgRP neurons increases running but improves survival in food-restricted animals. In contrast, AgRP ablation in such conditions leads to death within 72 h due to compulsive running [127]. Similarly, neonatal ablation of AgRP/NPY neurons results in high mortality under restricted feeding, with surviving mice showing delayed recovery and absence of anticipatory food-seeking behavior [128]. These outcomes reflect not just a failure of intake, but a broader failure in fuel mobilization under stress.

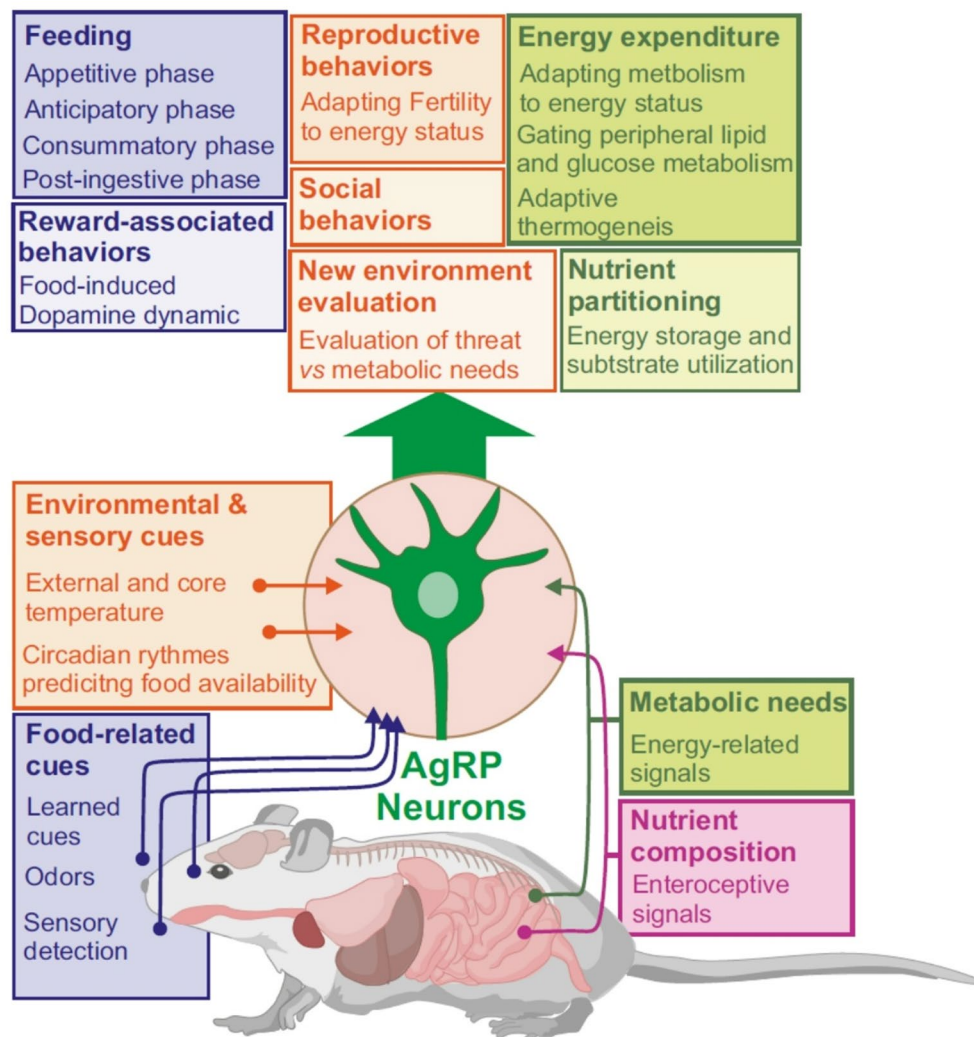
Providing a high-fat diet to AgRP-deficient, food-restricted mice prevents mortality and long-term behavioral disruption, underscoring AgRP neurons' role in coordinating energy needs with behavioral output [127]. ABA mice also exhibit reduced meal frequency and longer delays between pellet retrievals [129]. AgRP neurons in these mice show abnormally prolonged inhibition in response to food, contributing to sustained hypophagia. Activating AgRP neurons during feeding restores normal intake patterns and reduces hyperactivity, thereby preventing the development of ABA [129].

Taken together, these findings suggest that AgRP neurons act as critical survival nodes, integrating caloric needs with behavioral drives. In AN and its models, dysfunction of these neurons contributes to reduced intake and maladaptive behaviours such as compulsive exercise. Targeting this circuitry could offer new therapeutic strategies for treating AN.

## 8 Concluding remarks

As a whole, recent technological advances have allowed to depict a far more complex picture of the function of AgRP neurons in the ecosystem of behavior regulation. While

initially focused on acute feeding regulation, the ability to manipulate and image the dynamic responses of AgRP neurons and their post-synaptic responses in various conditions has drastically broadened our understanding of their function and how AgRP neurons act as critical hubs for various signals that are directly or indirectly connected to metabolic demands. AgRP neurons are diverse in nature, and projection and exploit the full range of target-specific neurotransmission, coordinated synaptic shaping and cell specific response to energy-related signals. They integrate environmental, exteroceptive and interoceptive food-predicting cues and exerting control not only over feeding, but also over the fate of ingested calories, sleep, reproduction, bone health, and adaptive behavior (Fig. 3). Given their pivotal



**Fig. 3** Integrative inputs and outputs of AgRP neurons. AgRP neurons integrate metabolic needs (encoded by circulating signals of hunger and satiety) and nutrient composition (encoded by gut to brain nervous inputs) with both environmental and food-related cues. In turn AgRP neurons exert a control on various components of feeding (appetitive, anticipatory, consummatory and post-ingestive phases), they exert an indirect control on dopamine-encoded reward value. In addition,

they couple metabolic needs assessment with reproductive and social, and exploratory behaviors (balancing hunger with new environment threats). At metabolic level AgRP neuron are paramount in regulating adaptive thermogenesis and energy expenditure while exerting control through the autonomic nervous system on peripheral substrate storage and utilization (nutrient partitioning)

role as master metabolic coordinators, AgRP neurons represent an ideal target to leverage anti-obesity strategies. However, much work remains to be done to apprehend their role in a pathophysiological context whether it is two opposite ends of body weight regulation i.e. obesity and anorexia but also in other food-related diseases such as compulsive and addictive behaviors.

**Author contributions** SL and CM.: Conceptualization, funding acquisition, Writing and editing. MF & NM– original draft, figures preparation and writing and editing.

**Funding** This work was funded by the Université Paris Cité & the Centre National de la Recherche Scientifique (CNRS). NM was supported by MSD-Avenir grant “EndoMetabo”. MF was supported by the UChicago– CNRS Research Collaboration Program 2020 and the IdEx Université Paris Cité (ANR-18-IDEX-0001).

**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

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## References

- Bertagna X. Proopiomelanocortin-derived peptides. *Endocrinol Metab Clin North Am.* 1994;23:467–85. 1994/09/01.
- Cone RD. Studies on the physiological functions of the melanocortin system. *Endocr Rev.* 2006/11/02 ed. 2006;27:736–49.
- Langlet F, Levin BE, Luquet S, Mazzone M, Messina A, Dunn-Meynell AA et al. Tancytic VEGF-A boosts blood-hypothalamus barrier plasticity and access of metabolic signals to the arcuate nucleus in response to fasting. *Cell Metab.* 2013/04/09 ed. 2013;17:607–17.
- Norsted E, Gomuc B, Meister B. Protein components of the blood-brain barrier (BBB) in the mediobasal hypothalamus. *J Chem Neuroanat.* 2008;36:107–21.
- Broberger C. Brain regulation of food intake and appetite: molecules and networks. *J Intern Med.* 2005;258:301–27.
- Toda C, Santoro A, Kim JD, Diano S. POMC neurons: from birth to death. *Annu Rev Physiol.* 2017;79:209–36.
- Betley JN, Xu S, Cao ZF, Gong R, Magnus CJ, Yu Y, et al. Neurons for hunger and thirst transmit a negative-valence teaching signal. *Nature.* 2015;521:180–5.
- Chen Y, Lin YC, Kuo TW, Knight ZA. Sensory detection of food rapidly modulates arcuate feeding circuits. *Cell.* 2015;160:829–41.
- Mandelblat-Cerf Y, Ramesh RN, Burgess CR, Patella P, Yang Z, Lowell BB et al. Arcuate hypothalamic AgRP and putative POMC neurons show opposite changes in spiking across multiple timescales. *Elife [Internet].* 2015;4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26159614>
- Nyema NT, McKnight AD, Vargas-Elvira AG, Schneps HM, Gold EG, Myers KP, et al. AgRP neuron activity promotes associations between sensory and nutritive signals to guide flavor preference. *Mol Metabolism.* 2023;78:101833.
- Su Z, Alhadeff AL, Betley JN. Nutritive, Post-ingestive signals are the primary regulators of AgRP neuron activity. *Cell Rep.* 2017;21:2724–36.
- Campbell JN, Macosko EZ, Fenselau H, Pers TH, Lyubetskaya A, Tenen D, et al. A molecular census of arcuate hypothalamus and median eminence cell types. *Nat Neurosci.* 2017;20:484–96.
- Dicken MS, Tooker RE, Hentges ST. Regulation of GABA and glutamate release from Proopiomelanocortin neuron terminals in intact hypothalamic networks. *J Neurosci.* 2012;32:4042–8.
- Hentges ST, Otero-Corchon V, Pennock RL, King CM, Low MJ. Proopiomelanocortin expression in both GABA and glutamate neurons. *J Neurosci.* 2009/10/30 ed. 2009;29:13684–90.
- Lam BYH, Cimino I, Poley-Wolf J, Nicole Kohnke S, Rimmington D, Iyemere V, et al. Heterogeneity of hypothalamic pro-opiomelanocortin-expressing neurons revealed by single-cell RNA sequencing. *Mol Metab.* 2017;6:383–92.
- Cone RD. Anatomy and regulation of the central melanocortin system. *Nat Neurosci.* 2005;8:571–8.
- Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the Agouti obesity syndrome. *Nature.* 1997;385:165–8.
- Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Central nervous system control of food intake. *Nature.* 2000;404:661–71.
- Cowley MA. Hypothalamic melanocortin neurons integrate signals of energy state. *Eur J Pharmacol.* 2003;480:3–11.
- Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of *Agrp* and *NPY* in fasting-activated hypothalamic neurons. *Nat Neurosci.* 1998;1:271–2.
- Horvath TL, Bechmann I, Naftolin F, Kalra SP, Leranth C. Heterogeneity in the neuropeptide Y-containing neurons of the rat arcuate nucleus: GABAergic and non-GABAergic subpopulations. *Brain Res.* 1997/05/09 ed. 1997;756:283–6.
- Krashes MJ, Shah BP, Koda S, Lowell BB. Rapid versus delayed stimulation of feeding by the endogenously released AgRP neuron mediators GABA, NPY, and AgRP. *Cell Metabol.* 2013;18:588–95.
- Tong Q, Ye C-P, Jones JE, Elmquist JK, Lowell BB. Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. *Nat Neurosci.* 2008;11:998–1000.
- Ollmann MM, Wilson BD, Yang YK, Kerns JA, Chen Y, Gantz I et al. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science.* 1997/10/06 ed. 1997;278:135–8.
- Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. *Nature.* 2012/07/18 ed. 2012;488:172–7.
- Beck B. Neuropeptide Y in normal eating and in genetic and dietary-induced obesity. *Philos Trans R Soc Lond B Biol Sci.* 2006/08/01 ed. 2006;361:1159–85.
- Pedrazzini T, Seydoux J, Kunstner P, Aubert JF, Grouzmann E, Beermann F et al. Cardiovascular response, feeding behavior

- and locomotor activity in mice lacking the NPY Y1 receptor. *Nat Med*. 1998/06/12 ed. 1998;4:722–6.
28. Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature*. 2001;411:480–4.
  29. De Solis AJ, Del Río-Martín A, Radermacher J, Chen W, Steuernagel L, Bauder CA, et al. Reciprocal activity of AgRP and POMC neurons governs coordinated control of feeding and metabolism. *Nat Metab*. 2024;6:473–93.
  30. Gropp E, Shanabrough M, Borok E, Xu AW, Janoschek R, Buch T, et al. Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat Neurosci*. 2005;8:1289–91.
  31. Luquet S, Perez FA, Hnasko TS, Palmiter RD. NPY/AgRP neurons are essential for feeding in adult mice but can be ablated in neonates. *Science*. 2005;310:683–5.
  32. Bewick GA, Gardiner JV, Dhillon WS, Kent AS, White NE, Webster Z, et al. Postembryonic ablation of AgRP neurons in mice leads to a lean, hypophagic phenotype. *FASEB J*. 2005;19:1680–2.
  33. Xu AW, Kaelin CB, Morton GJ, Ogimoto K, Stanhope K, Graham J, et al. Effects of hypothalamic neurodegeneration on energy balance. *PLoS Biol*. 2005;3:e415.
  34. Cai J, Chen J, Ortiz-Guzman J, Huang J, Arenkiel BR, Wang Y et al. AgRP neurons are not indispensable for body weight maintenance in adult mice. *Cell Reports* [Internet]. 2023 [cited 2023 Jul 10];42. Available from: [https://www.cell.com/cell-reports/abstract/S2211-1247\(23\)00800-8](https://www.cell.com/cell-reports/abstract/S2211-1247(23)00800-8)
  35. Bachor TP, Hwang E, Yulyaningsih E, Attal K, Mifsud F, Pham V, et al. Identification of AgRP cells in the murine hindbrain that drive feeding. *Mol Metabolism*. 2024;80:101886.
  36. Liu S-M, Ifebi B, Johnson F, Xu A, Ho J, Yang Y, et al. The gut signals to AGRP-expressing cells of the pituitary to control glucose homeostasis. *J Clin Invest*. 2023;133:e164185.
  37. Gupta R, Ma Y, Wang M, Whim MD. AgRP-Expressing adrenal chromaffin cells are involved in the sympathetic response to fasting. *Endocrinology*. 2017;158:2572–84.
  38. Aponte Y, Atasoy D, Sternson SM. AGRP neurons are sufficient to orchestrate feeding behavior rapidly and without training. *Nat Neurosci*. 2011;14:351–5.
  39. Betley JN, Cao ZFH, Ritola KD, Sternson SM, Paralle. Redundant circuit organization for homeostatic control of feeding behavior. *Cell*. 2013;155:1337–50.
  40. Krashes MJ, Koda S, Ye C, Rogan SC, Adams AC, Cusher DS, et al. Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. *J Clin Invest*. 2011;121:1424–8.
  41. Zhu C, Jiang Z, Xu Y, Cai Z-L, Jiang Q, Xu Y, et al. Profound and redundant functions of arcuate neurons in obesity development. *Nat Metab*. 2020;2:763–74.
  42. Carter ME, Soden ME, Zweifel LS, Palmiter RD. Genetic identification of a neural circuit that suppresses appetite. *Nature*. 2013;503:111–4. 2013/10/15 ed.
  43. Wu Q, Howell MP, Palmiter RD. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. *Cell*. 2009;137:1225–34.
  44. Wu Q, Howell MP, Cowley MA, Palmiter RD. Starvation after AgRP neuron ablation is independent of melanocortin signaling. *Proceedings of the National Academy of Sciences*. 2008;105:2687–92.
  45. Liu Q, Yang X, Luo M, Su J, Zhong J, Li X et al. An iterative neural processing sequence orchestrates feeding. *Neuron* [Internet]. 2023 [cited 2023 Mar 16];0. Available from: [https://www.cell.com/neuron/abstract/S0896-6273\(23\)00129-0](https://www.cell.com/neuron/abstract/S0896-6273(23)00129-0)
  46. Wang D, He X, Zhao Z, Feng Q, Lin R, Sun Y et al. Whole-brain mapping of the direct inputs and axonal projections of POMC and AgRP neurons. *Frontiers in Neuroanatomy* [Internet]. 2015 [cited 2022 Aug 19];9. Available from: <https://www.frontiersin.org/articles/https://doi.org/10.3389/fnana.2015.00040>
  47. Kalsbeek A, Buijs RM. Organization of the neuroendocrine and autonomic hypothalamic paraventricular nucleus. *Handb Clin Neurol*. 2021;180:45–63.
  48. Broberger C, Johansen J, Johansson C, Schalling M, Hokfelt T. The neuropeptide y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc Natl Acad Sci USA*. 1998;95:15043–8.
  49. Henry FE, Sugino K, Tozer A, Branco T, Sternson SM. Cell type-specific transcriptomics of hypothalamic energy-sensing neuron responses to weight-loss. *Elife* [Internet]. 2015/09/04 ed. 2015;4. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26329458>
  50. Steuernagel L, Lam BYH, Klemm P, Dowsett GKC, Bauder CA, Tadross JA, et al. HypoMap—a unified single-cell gene expression atlas of the murine hypothalamus. *Nat Metab*. 2022;4:1402–19.
  51. Li MM, Madara JC, Steger JS, Krashes MJ, Balthasar N, Campbell JN et al. The Paraventricular Hypothalamus Regulates Satiety and Prevents Obesity via Two Genetically Distinct Circuits. *Neuron* [Internet]. 2019 [cited 2019 Apr 8]; Available from: <http://www.sciencedirect.com/science/article/pii/S0896627319301631>
  52. Padilla SL, Qiu J, Soden ME, Sanz E, Nestor CC, Barker FD, et al. Agouti-related peptide neural circuits mediate adaptive behaviors in the starved state. *Nat Neurosci*. 2016;19:734–41.
  53. Steculorum SM, Ruud J, Karakasilioti I, Backes H, Engstrom Ruud L, Timper K, et al. AgRP neurons control systemic insulin sensitivity via myostatin expression in brown adipose tissue. *Cell*. 2016;165:125–38.
  54. Dodt S, Widdershooven NV, Dreisow M-L, Weiher L, Steuernagel L, Wunderlich FT, et al. NPY-mediated synaptic plasticity in the extended amygdala prioritizes feeding during starvation. *Nat Commun*. 2024;15:5439.
  55. Campos CA, Bowen AJ, Schwartz MW, Palmiter RD. Parabrachial CGRP neurons control meal termination. *Cell Metab*. 2016;23:811–20. 2016/05/12.
  56. Garfield AS, Shah BP, Burgess CR, Li MM, Li C, Steger JS, et al. Dynamic GABAergic afferent modulation of AgRP neurons. *Nat Neurosci*. 2016;19:1628–35.
  57. Krashes MJ, Shah BP, Madara JC, Olson DP, Strohlic DE, Garfield AS, et al. A novel excitatory paraventricular nucleus to AgRP neuron circuit that drives hunger. *Nature*. 2014;507:238–42.
  58. Liu T, Kong D, Shah BP, Ye C, Koda S, Saunders A, et al. Fasting activation of AgRP neurons requires NMDA receptors and involves spinogenesis and increased excitatory tone. *Neuron*. 2012;73:511–22.
  59. Yang Y, Atasoy D, Su HH, Sternson SM. Hunger States switch a flip-flop memory circuit via a synaptic AMPK-dependent positive feedback loop. *Cell*. 2011;146:992–1003.
  60. Wang C, Zhou W, He Y, Yang T, Xu P, Yang Y, et al. AgRP neurons trigger long-term potentiation and facilitate food seeking. *Transl Psychiatry*. 2021;11:11.
  61. Goto K, Inui A, Takimoto Y, Yuzuriha H, Asakawa A, Kawamura Y, et al. Acute intracerebroventricular administration of either carboxyl-terminal or amino-terminal fragments of agouti-related peptide produces a long-term decrease in energy expenditure in rats. *Int J Mol Med*. 2003;12:379–83.
  62. Cavalcanti-de-Albuquerque JP, Bober J, Zimmer MR, Dietrich MO. Regulation of substrate utilization and adiposity by AgRP neurons. *Nat Commun*. 2019;10:311.
  63. Joly-Amado A, Denis RGP, Castel J, Lacombe A, Cansell C, Rouch C, et al. Hypothalamic AgRP-neurons control peripheral substrate utilization and nutrient partitioning. *EMBO J*. 2012;31:4276–88.

64. Zhang J, Li S, Luo X, Zhang C. Emerging role of hypothalamus in the metabolic regulation in the offspring of maternal obesity. *Front Nutr.* 2023;10:1094616.
65. Ruan HB, Dietrich MO, Liu ZW, Zimmer MR, Li MD, Singh JP, et al. O-GlcNAc transferase enables AgRP neurons to suppress Browning of white fat. *Cell.* 2014;159:306–17.
66. Burke LK, Darwish T, Cavanaugh AR, Virtue S, Roth E, Morro J, et al. mTORC1 in AGRP neurons integrates exteroceptive and interoceptive food-related cues in the modulation of adaptive energy expenditure in mice. *Elife.* 2017;6:e22848.
67. Engström Ruud L, Pereira MMA, de Solis AJ, Fenselau H, Brüning JC. NPY mediates the rapid feeding and glucose metabolism regulatory functions of AgRP neurons. *Nat Commun.* 2020;11:442.
68. Harrold JA, Williams G, Widdowson PS. Changes in hypothalamic agouti-related protein (AGRP), but not alpha-MSH or pro-opiomelanocortin concentrations in dietary-obese and food-restricted rats. *Biochem Biophys Res Commun.* 1999;258:574–7.
69. Lin S, Storlien LH, Huang XF. Leptin receptor, NPY, POMC mRNA expression in the diet-induced obese mouse brain. *Brain Res.* 2000;875:89–95.
70. Wei W, Pham K, Gammons JW, Sutherland D, Liu Y, Smith A, et al. Diet composition, not calorie intake, rapidly alters intrinsic excitability of hypothalamic agrp/npv neurons in mice. *Sci Rep.* 2015;5:16810.
71. Beutler LR, Corpuz TV, Ahn JS, Kosar S, Song W, Chen Y, et al. Obesity causes selective and long-lasting desensitization of AgRP neurons to dietary fat. *eLife.* 2020;9:e55909.
72. Lorch CM, Hayes NW, Xia JL, Fleps SW, McMorro HE, Province HS et al. Sucrose overconsumption impairs AgRP neuron dynamics and promotes palatable food intake. *Cell Reports [Internet].* 2024 [cited 2024 Sep 27];43. Available from: [https://www.cell.com/cell-reports/abstract/S2211-1247\(24\)00003-2](https://www.cell.com/cell-reports/abstract/S2211-1247(24)00003-2)
73. Mazzone CM, Liang-Guallpa J, Li C, Wolcott NS, Boone MH, Southern M, et al. High-fat food biases hypothalamic and mesolimbic expression of consummatory drives. *Nat Neurosci.* 2020;23:1253–66.
74. Havel PJ, Hahn TM, Sindelar DK, Baskin DG, Dallman MF, Weigle DS, et al. Effects of streptozotocin-induced diabetes and insulin treatment on the hypothalamic melanocortin system and muscle uncoupling protein 3 expression in rats. *Diabetes.* 2000;49:244–52.
75. Park ES, Seong JK, Yi SJ, Kim JS, Lee HS, Lee IS, et al. Changes in orexin-A and neuropeptide y expression in the hypothalamus of obese and lean Zucker diabetic fatty rats. *J Vet Med Sci.* 2005;67:639–46.
76. Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte D Jr. Cerebrospinal fluid leptin levels: relationship to plasma levels and to adiposity in humans. *Nat Med.* 1996;2:589–93.
77. Xu J, Bartolome CL, Low CS, Yi X, Chien C-H, Wang P, et al. Genetic identification of leptin neural circuits in energy and glucose homeostases. *Nature.* 2018;556:505–9.
78. Bentsen MA, Rausch DM, Mirzadeh Z, Muta K, Scarlett JM, Brown JM, et al. Transcriptomic analysis links diverse hypothalamic cell types to fibroblast growth factor 1-induced sustained diabetes remission. *Nat Commun.* 2020;11:4458.
79. Hwang E, Scarlett JM, Baquero AF, Bennett CM, Dong Y, Chau D, et al. Sustained Inhibition of npv/agrp neuronal activity by FGF1. *JCI Insight.* 2022;7:e160891.
80. Manceau R, Majeur D, Alquier T. Neuronal control of peripheral nutrient partitioning. *Diabetologia.* 2020;63:673–82.
81. Enriquez RF, Lee NJ, Herzog H. AgRP signalling negatively regulates bone mass. *J Neuroendocrinol.* 2021;33:e12978.
82. Kim JG, Sun B-H, Dietrich MO, Koch M, Yao G-Q, Diano S, et al. AgRP Neurons Regulate Bone Mass *Cell Rep.* 2015;13:8–14.
83. Sasanuma H, Nakata M, Parmila K, Nakae J, Yada T. PDK1-FoxO1 pathway in AgRP neurons of arcuate nucleus promotes bone formation via GHRH-GH-IGF1 axis. *Mol Metab.* 2017;6:428–39.
84. Wu Q, Whiddon BB, Palmiter RD. Ablation of neurons expressing agouti-related protein, but not melanin concentrating hormone, in leptin-deficient mice restores metabolic functions and fertility. *Proc Natl Acad Sci U S A.* 2012;109:3155–60.
85. Kerbus RI, Decourt C, Inglis MA, Campbell RE, Anderson GM. Androgen receptor actions on AgRP neurons are not a major cause of reproductive and metabolic impairments in peripubertally androgenized mice. *J Neuroendocrinol.* 2024;36:e13370.
86. Padilla SL, Qiu J, Nestor CC, Zhang C, Smith AW, Whiddon BB, et al. AgRP to Kiss1 neuron signaling links nutritional state and fertility. *Proc Natl Acad Sci U S A.* 2017;114:2413–8.
87. Lo L, Yao S, Kim D-W, Cetin A, Harris J, Zeng H, et al. Connectional architecture of a mouse hypothalamic circuit node controlling social behavior. *Proc Natl Acad Sci U S A.* 2019;116:7503–12.
88. Burnett CJ, Funderburk SC, Navarrete J, Sabol A, Liang-Guallpa J, Desrochers TM et al. Need-based prioritization of behavior. Elmqvist JK, Dulac C, Stuber GD, editors. *eLife.* 2019;8:e44527.
89. Denis RGP, Joly-Amado A, Webber E, Langlet F, Schaeffer M, Padilla SL, et al. Palatability can drive feeding independent of AgRP neurons. *Cell Metabol.* 2015;22:646–57.
90. Dietrich MO, Zimmer MR, Bober J, Horvath TL. Hypothalamic AgRP neurons drive stereotypic behaviors beyond feeding. *Cell.* 2015;160:1222–32.
91. Sternson SM, Nicholas Betley J, Cao ZFH. Neural circuits and motivational processes for hunger. *Curr Opin Neurobiol.* 2013;23:353–60.
92. Dallman MF, Pecoraro NC, la Fleur SE. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun.* 2005;19:275–80.
93. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci U S A.* 1988;85:5274–8.
94. Narayanan NS, Guarnieri DJ, DiLeone RJ. Metabolic hormones, dopamine circuits, and feeding. *Front Neuroendocrinol.* 2010;31:104–12.
95. Li C, Hou Y, Zhang J, Sui G, Du X, Licinio J, et al. AGRP neurons modulate fasting-induced anxiolytic effects. *Transl Psychiatry.* 2019;9:111.
96. Dietrich MO, Bober J, Ferreira JG, Tellez LA, Mineur YS, Souza DO, et al. AgRP neurons regulate development of dopamine neuronal plasticity and nonfood-associated behaviors. *Nat Neurosci.* 2012;15:1108–10.
97. Reichenbach A, Dempsey H, Andrews ZB. Metabolic sensing in AgRP regulates sucrose preference and dopamine release in the nucleus accumbens. *J Neuroendocrinol.* 2024;36:e13389.
98. So WL, Hu J, Jeffs L, Dempsey H, Lockie SH, Zigman JM, et al. Ghrelin signalling in AgRP neurons links metabolic state to the sensory regulation of AgRP neural activity. *Mol Metabolism.* 2023;78:101826.
99. Stutz B, Waterson MJ, Šestan-Peša M, Dietrich MO, Škarica M, Sestan N, et al. AgRP neurons control structure and function of the medial prefrontal cortex. *Mol Psychiatry.* 2022;27:3951–60.
100. Zhang Q, Tang Q, Purohit NM, Davenport JB, Brennan C, Patel RK et al. Food-induced dopamine signaling in AgRP neurons promotes feeding. *Cell Reports [Internet].* 2022 [cited 2024 Oct 15];41. Available from: [https://www.cell.com/cell-reports/abstract/S2211-1247\(22\)01596-0](https://www.cell.com/cell-reports/abstract/S2211-1247(22)01596-0)
101. Chen Y, Knight ZA. Making sense of the sensory regulation of hunger neurons. *BioEssays.* 2016;38:316–24.

102. Aitken TJ, Liu Z, Ly T, Shehata S, Sivakumar N, Medina NLS, et al. Negative feedback control of hypothalamic feeding circuits by the taste of food. *Neuron*. 2024;112:3354–e33705.
103. Horio N, Liberles SD. Hunger enhances food-odour attraction through a neuropeptide Y spotlight. *Nature*. 2021;1–5.
104. Fu O, Iwai Y, Narukawa M, Ishikawa AW, Ishii KK, Murata K, et al. Hypothalamic neuronal circuits regulating hunger-induced taste modification. *Nat Commun*. 2019;10:4560.
105. Livneh Y, Ramesh Rn, Burgess R, Levandowski KM, Madara J et al. c., Fenselau henning,. Homeostatic circuits selectively gate food cue responses in insular cortex. *Nature*. 2017;546:611–6.
106. Alhadeff AL, Goldstein N, Park O, Klima ML, Vargas A, Betley JN. Natural and drug rewards engage distinct pathways that converge on coordinated hypothalamic and reward circuits. *Neuron*. 2019;103:891–e9086.
107. Goldstein N, Levine BJ, Loy KA, Duke WL, Meyerson OS, Jamnik AA, et al. Hypothalamic neurons that regulate feeding can influence sleep/wake States based on homeostatic need. *Curr Biol*. 2018;28:3736–e37473.
108. Oster H, Damerow S, Kiessling S, Jakubcakova V, Abraham D, Tian J, et al. The circadian rhythm of glucocorticoids is regulated by a gating mechanism residing in the adrenal cortical clock. *Cell Metab*. 2006;4:163–73.
109. Cedernaes J, Huang W, Ramsey KM, Waldeck N, Cheng L, Marcheva B, et al. Transcriptional basis for rhythmic control of hunger and metabolism within the AgRP neuron. *Cell Metab*. 2019;29:1078–e10915.
110. Sayar-Atasoy N, Aklan I, Yavuz Y, Laule C, Kim H, Rysted J, et al. AgRP neurons encode circadian feeding time. *Nat Neurosci*. 2024;27:102–15.
111. Douglass AM, Kucukdereli H, Madara JC, Wang D, Wu C, Lowenstein ED, et al. Acute and circadian feedforward regulation of agouti-related peptide hunger neurons. *Cell Metabol*. 2025;37:708–e7225.
112. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev*. 2004;84:277–359.
113. Rintamäki H. Human responses to cold. *Alaska Med*. 2007;49:29–31.
114. Deem JD, Faber CL, Pedersen C, Phan BA, Larsen SA, Ogimoto K, et al. Cold-induced hyperphagia requires AgRP neuron activation in mice. *Elife*. 2020;9:e58764.
115. Vicent MA, Mook CL, Carter ME. POMC neurons in heat: A link between warm temperatures and appetite suppression. *PLoS Biol*. 2018;16:e2006188.
116. Alcantara IC, Tapia APM, Aponte Y, Krashes MJ. Acts of appetite: neural circuits governing the appetitive, consummatory, and terminating phases of feeding. *Nat Metab*. 2022;4:836–47.
117. Sternson SM, Eiselt A-K. Three pillars for the neural control of appetite. *Annu Rev Physiol*. 2017;79:401–23.
118. Treasure J, Duarte TA, Schmidt U. Eating disorders. *Lancet*. 2020;395:899–911.
119. Dardennes RM, Zizzari P, Tolle V, Foulon C, Kipman A, Romo L, et al. Family trios analysis of common polymorphisms in the obestatin/ghrelin, BDNF and AGRP genes in patients with anorexia nervosa: association with subtype, body-mass index, severity and age of onset. *Psychoneuroendocrinology*. 2007;32:106–13.
120. Vink T, Hinney A, van Elburg AA, van Goozen SH, Sandkuijl LA, Sinke RJ, et al. Association between an agouti-related protein gene polymorphism and anorexia nervosa. *Mol Psychiatry*. 2001;6:325–8.
121. de Rijke CE, Hillebrand JGG, Verhagen La, Roeling W, Adan TaP. a. H. Hypothalamic neuropeptide expression following chronic food restriction in sedentary and wheel-running rats. *J Mol Endocrinol*. 2005;35:381–90.
122. Merle JV, Haas V, Burghardt R, Döhler N, Schneider N, Lehmkuhl U, et al. Agouti-related protein in patients with acute and weight-restored anorexia nervosa. *Psychol Med*. 2011;41:2183–92.
123. Moriya J, Takimoto Y, Yoshiuchi K, Shimosawa T, Akabayashi A. Plasma agouti-related protein levels in women with anorexia nervosa. *Psychoneuroendocrinology*. 2006;31:1057–61.
124. Rokot NT, Ataka K, Iwai H, Suzuki H, Tachibe H, Kairupan TS, et al. Antagonism for NPY signaling reverses cognitive behavior defects induced by activity-based anorexia in mice. *Psychoneuroendocrinology*. 2021;126:105133.
125. Hillebrand JGG, Kas MJH, Scheurink AJW, van Dijk G, Adan RAH. AgRP(83–132) and SHU9119 differently affect activity-based anorexia. *Eur Neuropsychopharmacol*. 2006;16:403–12.
126. Kas MJH, van Dijk G, Scheurink AJW, Adan R. a. H. Agouti-related protein prevents self-starvation. *Mol Psychiatry*. 2003;8:235–40.
127. Miletta MC, Iyilikci O, Shanabrough M, Šestan-Peša M, Cammisa A, Zeiss CJ, et al. AgRP neurons control compulsive exercise and survival in an activity-based anorexia model. *Nat Metab*. 2020;2:1204–11.
128. Tan K, Knight ZA, Friedman JM. Ablation of AgRP neurons impairs adaption to restricted feeding. *Mol Metabolism*. 2014;3:694–704.
129. Sutton Hickey AK, Becker J, Karolczak EO, Lutas A, Krashes MJ. Dietary fat content and absorption shape standard diet devaluation through hunger circuits. *Mol Metab*. 2024;89:102021.

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