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Review

# Brain control of energy homeostasis: Implications for anti-obesity pharmacotherapy

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## SUMMARY

Despite the evolution of hardwired homeostatic mechanisms to balance food intake with energy needs, the obesity epidemic continues to escalate globally. However, recent breakthroughs in delineating the molecular signaling pathways by which neural circuits regulate consummatory behaviors, along with transformative advances in peptide-based pharmacotherapy, are fueling the development of a new generation of safe and effective treatments for obesity. Here, we outline our current understanding of how the central nervous system controls energy homeostasis and examine how emerging insights, including those related to neuroplasticity, offer new perspectives for restoring energy balance and achieving durable weight loss. Together, these advances provide promising avenues for treating obesity and managing cardiometabolic disease.

## INTRODUCTION

Across all kingdoms of life, the ability to sense and acquire nutrients has been essential for survival. This ancient fight among organisms to obtain sufficient fuel from the environment has driven a range of evolutionary adaptations, including the cross-communication between the brain and peripheral organs that makes mammals prefer nutrient-dense energy sources and efficiently store excess calories as lipids in fat depots.[1,2] Together with other advantageous traits,[3] the neuroendocrine signals that control energy homeostasis were likely vital for the successful migrations of humans out of Africa, a series of daunting journeys across other continents in which our ancestors inevitably faced periods of harsh weather, starvation, and recurrent episodes of anorexia caused by infectious diseases. However, what might have been an evolutionary advantage for millions of years has now turned into a major health challenge for modern humans. Since the 1980s, we have witnessed a dramatic increase in obesity rates,[4] with rural parts of the world being key areas of the accelerating obesity epidemic.[5] Around 1 billion individuals are now estimated to carry levels of body fat that pose substantial risks to health and longevity, with cardiovascular diseases being the major driver of obesity-associated deaths.[6]

The causal drivers underlying the obesity epidemic are likely complex and a topic of much debate.[7] Yet, decades of research in animal models, together with large and unbiased genetic studies of body mass index (BMI), point toward a key role of the central nervous system (CNS) in body weight regulation and the development of obesity.[8,9] This growing understanding of the neuronal mechanisms underlying energy homeostasis, coupled with advances in gut-brain axis physiology[10] as well as progress in medicinal chemistry,[11–16] has paved the way for effective weight loss therapies.[17] Emerging pharmacotherapies that mimic gut peptides, such as glucagon-like peptide-1 (GLP-1), have shown that targeting specific neurons in the brainstem and hypothalamus is an effective strategy for inducing weight loss and lowering the risk of obesity-associated comorbidities.[18]

In this review, we provide a comprehensive overview of the role of the CNS in body weight regulation, with a particular focus on the neuroendocrine signals and neuronal mechanisms that govern energy homeostasis. We explore and discuss recent advances in understanding the neural circuits and molecular pathways in the brain that regulate appetite, behavioral aspects of food intake, and energy metabolism. Lastly, we highlight how these insights can inform and inspire the development of next-generation brain-targeted therapeutics for obesity management.

## OBESITY: A COMPLEX AND CHRONIC CONDITION

For several decades, obesity has been defined narrowly by cut-off values for BMI. Yet, more nuanced ways to diagnose and stage obesity are emerging[19,20] together with an acceptance of obesity as an adiposity-based chronic and relapsing disease that is characterized by excessive, ectopic, and dysfunctional fat tissue that damages other organs.[21] The comorbidities

 

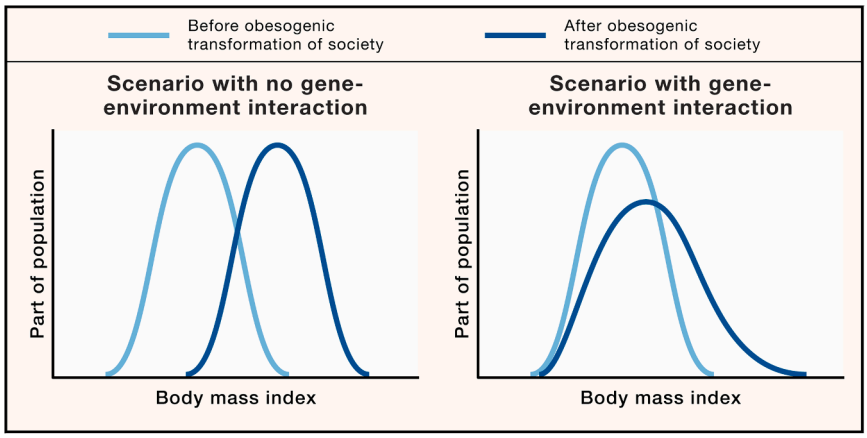


**Figure 1. Gene-environment interactions shape the obesity epidemic**

Left: Hypothetical scenario where the environment becomes more obesogenic and the entire population is equally affected by these environmental, obesogenic changes. In this scenario, the BMI distribution curve shifts to the right without changing shape, illustrating that the environment does not interact with genetic factors. Thus, the obesogenic changes to the environment affect all individuals to the same extent.

Right: Actual scenario observed in many countries, where the environment becomes more obesogenic, but individuals respond differently to the environmental, obesogenic changes. In this scenario, which illustrates what has happened globally over the last decades, the BMI distribution curve shifts to the right *and* changes shape, reflecting that the environment interacts differently with different genotypes, i.e., some individuals gain significantly more weight and adiposity than others. In both of these scenarios, it is assumed that the environmental changes have occured uniformly across the entire population.

associated with obesity involve both "mechanical" effects that promote sleep apnea and osteoarthritis and "metabolic" complications that drive cardiovascular diseases and cancers.[22]

Since the 20th century, we have witnessed major advances in the tools to study body composition, energy balance, and the neurobiology of energy homeostasis.[23] In the same period, the biomedical view of obesity has transformed from being regarded as a result of individual overeating to now being considered a complex public health challenge. Despite this, many people still believe that obesity is exclusively driven by eating too much and moving too little and that weight management is therefore simply a matter of willpower. Obesity, however, has a strong biological basis[24] and it seems highly unlikely that the obesity epidemic can be explained by a widespread drop in willpower happening in the late 1970s.[25] Decades of research paint a far more complicated picture[9,23] with many unanswered questions[7] and emerging data that challenge some of the widespread assumptions about what causes obesity.[26] While recent environmental changes are undoubtedly responsible for the global rise in obesity, inherited differences between people can largely explain why many are prone to becoming overweight, while others are protected from excessive weight gain.[27] In other words, obesity results from an interaction between environmental and (epi)genetic factors,[28] as illustratively captured by the quote, "Genes load the gun, but the environment pulls the trigger"[29] (Figure 1).

## Environmental drivers of the obesity epidemic

A prevailing explanation attributes the progression of obesity to the modern food environment with its global rise in easily available and cheap foods that are ultra-processed, energy-dense, highly palatable, and potently trigger reward pathways in the brain.[30,31] The emergence of this type of food, together with reduced physical activity, are the most often cited environmental drivers of the obesity epidemic and have therefore been termed "the Big Two[32]" (Figure 2).

The notion that physical inactivity has contributed to the obesity epidemic is often inferred from the observed decrease in occupational activity.[33] Yet, studies using doubly labeled water to assess free-living energy expenditure show not only that low energy expenditure from physical activity does not predict changes in body weight and adiposity later in life,[34,35] but also that energy expended by physical activity seems to have increased slightly since the 1980s.[26] These findings might be explained by an increase in leisure-time activity that has compensated for decreased occupational physical activity. Another explanation could be the elevated energetic costs of moving a heavier body, which could keep physical activity energy expenditure unchanged during obesity development, despite a decline in, e.g., number of daily steps.[36] Given this, it is worth considering that lower levels of physical activity could be a consequence rather than a cause of obesity.[37]

Evidence suggests that the rise in obesity is more complex than the introduction of Western fast-food culture and convenience lifestyles. Intriguingly, both basal metabolic rate and core body temperature have decreased slightly since the industrial revolution.[26,38] Other studies indicate that the obesity epidemic might have started many decades before the obesogenic transition of Western societies.[39,40] Given this, it is intriguing to speculate on the extent to which obesity is driven by other environmental factors, such as pollution, endocrine-disrupting chemicals, sleep disruption, microbiome changes, viral infections, social stress, and socioeconomic insecurity[29,32,41] (Figure 2).

## Adiposity: A heritable trait shaped by ancient genetic drift

It is often said that obesity development in current generations reflects that humans live in an abundance of calorie-dense foods and have inherited a "thrifty" ancestral physiology that aimed to promote fat accumulation in between periods of famine.[42] Yet, having too large fat depots can increase body weight to an extent that increases the risk of predation.[42] It therefore seems more likely that the biology of energy homeostasis evolved to maintain fat mass within a fairly narrow range, with physiological processes preventing adiposity from becoming both too low and too high.[43]

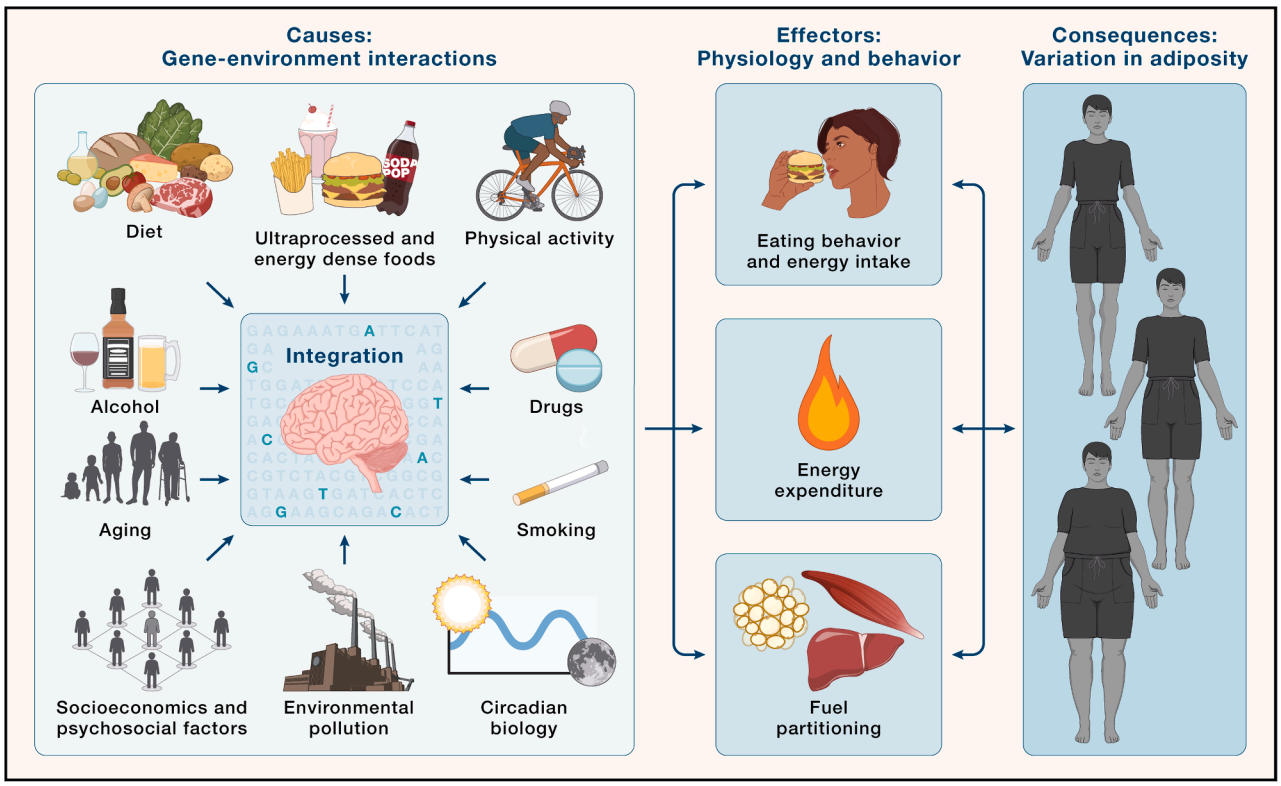


**Figure 2. Brain integration of environmental cues in the regulation of energy balance and adiposity**

Environmental factors (left) are integrated by the brain in the context of an individual's genetic makeup (illustrated by highlighted SNPs) and epigenetic profile. In response, the brain regulates behavioral and physiological outputs, such as energy intake, energy expenditure, and fuel partitioning (middle), which all influence energy balance, ultimately shaping interindividual variation in adiposity (right).

It is evolutionarily plausible that our early hominid ancestors tightly regulated their fat mass to mitigate the risks of starvation and predation.[44] Contemporary humans at the lower end of the BMI spectrum seem to display a similarly strong regulation, preventing them from developing overweight.[45,46] This fits both Kennedy's lipostatic theory from the 1950s[47] and the later set point model stating that adiposity is regulated tightly by physiological forces around a "set" body weight or level of adiposity.[43] However, these widely accepted concepts fail to explain why most modern humans experience large fluctuations in fat mass and, importantly, why hundreds of millions of people develop obesity.[48] Another line of thinking points out that humans have been at the top of the food chain for around 2 million years.[42] Because this minimizes the risk of predation, there has been no selection pressure to limit adiposity during this time, leaving the genes encoding the defense against obesity to be "eroded" by random mutations (genetic drift). This "drifty gene" hypothesis,[42] together with the dual intervention point model,[43] provides a more attractive explanation for why humans today differ in their propensity for weight gain. These concepts might also explain why there is no positive selection for several genetic variants associated with BMI[49] and why the genetic architecture of BMI is highly polygenic.[27,50]

Studies of families, twins, and adopted children support these evolutionary perspectives by providing solid evidence that genetic factors have a profound influence on BMI.[51] This can be illustrated by the striking similarity between the weight class of adoptees and the BMI of the biological parents but not the adoptive parents.[52] Moreover, studies of pairs of monozygotic twins who were either reared apart or together have estimated that the heritability of BMI is ~70%.[53,54] These findings are in line with subsequent analyses showing heritability estimates for BMI that range from ~40%–50% in family studies to ~60%–80% in twin studies.[55,56] That adiposity is a highly heritable trait also aligns with pioneering research by Bouchard and colleagues revealing that weight gain in monozygotic twins resulting from deliberate overeating was highly similar *within* twin pairs yet varied by at least 3-fold *between* twin pairs.[57] Like the variation in weight gain, studies of twin pairs have revealed a significant genetic contribution to variation in weight loss induced by exercise or calorie-restricted diets.[58,59] Together, these studies illustrate that some individuals, by nature, are markedly more prone not only to gaining weight but also to losing less weight when dieting. This notion is further supported by emerging genetic variants linked to lower BMI[60–63] and studies of "spendthrifty" individuals displaying metabolic traits that make them less susceptible to weight gain.[64–66]

The genetics of obesity can be divided into two main types: monogenic and polygenic obesity.[67] Monogenic forms of obesity are caused by single-gene mutations or chromosomal alterations and follow a Mendelian inheritance pattern. They

are usually very rare, start early in life, and rapidly progress to severe obesity.[27] A key physiological feature of monogenic obesity is increased appetite, illustrated by the profound hyperphagia seen in patients with loss-of-function mutations in genes encoding components of hypothalamic leptin-melanocortin signaling.[68] In addition to this, animal studies suggest that increased nutrient partitioning to adipocytes might also play a role in the pathogenesis of some forms of monogenic obesity.[9,69]

Polygenic obesity, on the other hand, is common, progresses slowly, and arises from the combined influence of thousands of genetic variants interacting with the environment, each with small effects on body weight.[27] Since 2007, genome-wide association studies (GWASs) have identified more than 500 genetic loci and around a thousand single-nucleotide polymorphisms that are associated with BMI.[50,70,71] *In silico* tools such as data-driven expression prioritized integration for complex traits (DEPICT)[72] have helped translate the numerous BMI-associated genetic signals into biological insights, showing that the most likely affected genes are preferentially expressed in the brain—particularly in regions like the hypothalamus that regulate food intake.[70] Additionally, it is evident that a subset of the common BMI-associated variants is found close to genes where loss-of-function mutations cause monogenic obesity, indicating that common forms of obesity might also be linked to an increased appetitive drive.[73] Other lines of research in humans also argue that genetic susceptibility to obesity is at least partly driven by appetite-related traits.[74,75] However, it is important to keep in mind that most common disease risk variants, including those associated with BMI, have unknown effects and are found in non-coding regions of the genome.[76] Moreover, higher expression of "obesity genes" has been observed outside of the hypothalamus in regions such as the hippocampus and the limbic system, suggesting that emotional and cognitive processes, including learning and memory, might also influence the variation in adiposity.[70,71] Pathway-based analyses highlight that genes linked to BMI-associated loci are enriched in pathways for neurogenesis, synaptic function, and neurotransmitter signaling (especially glutamatergic signaling but also signaling mediated by noradrenaline, serotonin, dopamine, and γ-aminobutyric acid [GABA]).[50,70,77] Furthermore, pathways related to, e.g., immune function, adipogenesis, glucose and lipid homeostasis, circadian rhythm, oxidative stress, and insulin biology have also been implicated in the genetics of BMI.[70,71,77–79] This indicates that the cellular and molecular processes underlying the variation in human body weight and adiposity extend beyond the CNS, a notion that is supported by the insights from genetic studies of body fat distribution[80,81] and exome-wide analyses of rare and low-frequency single-nucleotide variants associated with BMI.[60] Overall, this line of research illustrates that obesity has a strong basis in the brain and therefore can be considered a neurobiological disorder.[82] However, ongoing and future efforts to uncover the biological impact of BMI-associated variants could lead to a deeper and more nuanced understanding of obesity pathogenesis.

## Models of obesity pathogenesis

Weight gain, or more specifically, an increase in body energy content, requires a positive energy balance where energy input (calorie ingestion) exceeds energy output (energy expenditure and energy excretion via, e.g., gastrointestinal [GI] and urinary routes).[83,84] This is illustrated by the descriptive relationship between the change in body weight (stored energy) and energy balance:

$$\Delta\text{Body weight} = \text{Energy}_{\text{input}} - \text{Energy}_{\text{output}}$$

Yet, the fact that energy balance and body weight are linked to each other, as required by the law of energy conservation, provides no information on the causal relationship between the two and thus the drivers of weight gain and obesity development.[85] A positive energy balance can be envisioned to cause obesity, as is often done. This has also been referred to as the "push" principle, which argues that a high energy intake "pushes" excess calories into the fat depots, thus leading to weight gain.[9,86] However, it is also possible to envision a situation where the causal direction is reversed, with ongoing weight gain causing a positive energy balance. This scenario is considered similar to other types of growth, like puberty and pregnancy, where the positive energy balance is a permissive factor rather than a direct driver of weight gain. This is referred to as the "pull" concept, which argues that fat depots actively pull (take up) excessive calories from the circulation into adipocytes, thus increasing adiposity.[9,86] As a reaction to the decreased availability of circulating fuels for other organs, appetite increases, and energy expenditure might decrease.[86]

These two concepts have led to different models for understanding obesity pathogenesis.[87] According to the most widespread explanation, obesity is driven primarily by the high availability of hyperpalatable, energy-dense foods, coupled with abundant environmental food cues and low incentives for physical activity.[88] The energy balance model of obesity promotes this environmental "push" concept and highlights the appetitive traits and hedonic brain circuits that predispose many humans to eat in the absence of "homeostatic hunger," arguing that this leads to excess ingestion of calories and thus weight gain.[89] Other models are based on the "pull" concept, arguing that the development of obesity is driven by increased partitioning and trapping of fuels in fat depots.[69] According to these models, the global obesity epidemic is primarily driven by environmental factors that stimulate the sequestration of circulation substrates in adipocytes. Such changes to the milieu could be related to the diet[90] and/or involve societal transformations that promote psychosocial insecurity,[91] impair sleep, or increase exposure to pollution and endocrine-disrupting chemicals (Figure 2).

Given that push and pull forces might not be mutually exclusive, models that combine the two concepts have also been put forward.[86,92] For explaining the pathogenesis of obesity, these unifying "push-pull" models might provide the strongest explanatory power. Both appetite and fuel partitioning are largely controlled by the brain.[93,94] Thus, although the concepts of push and pull are fundamentally different in several ways,[87] they are both consistent with key GWAS findings that BMI-associated loci preferentially link to genes that are expressed in the CNS. Hence, the physiological differences between people encoded by these genetic variants could involve variations in both push and pull mechanisms. Exploring these pathophysiological

underpinnings of obesity is an important task for future research. A key part of this is to map the neuroendocrine signaling pathways and neuronal circuits that regulate energy homeostasis and coordinate substrate metabolism through cross-communication between the brain and peripheral organs.

## NEUROENDOCRINE REGULATION OF ENERGY HOMEOSTASIS

Brain circuits controlling energy balance must continuously integrate a diverse array of signals to maintain long-term stability of organismal fuel availability. These signals include information about adipose tissue mass, caloric intake, energy expenditure, and environmental or physiological changes that influence current and future energy needs.[10] While traditional neuroendocrine signaling pathways such as the hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-thyroid axis, and hypothalamic-pituitary-gonadal axis play important roles in energy regulation, endocrine signals from adipose tissue and the GI system, including accessory organs such as the pancreas and liver, are also recognized as key signaling mechanisms regulating adiposity and metabolic homeostasis[90,91,95] (Figure 3A).

More recently, signals from other peripheral organs, including skeletal muscle and bone, have emerged as potential contributors to homeostatic regulation of body weight and glucose metabolism.[96,97] Adding to this complexity, the major peripheral metabolic organs are densely connected to the CNS, which enables rapid and coordinated regulation of metabolic processes. Afferent signals provide continuous feedback to the brain, while efferent pathways allow the CNS to adjust organ function in real time.[98,99] Together with slower-acting endocrine pathways, this neuronal crosstalk ensures dynamic control over processes such as glucose metabolism, digestion, energy storage, and energy utilization/expenditure. In the following subsections, we briefly explore the key hormonal signals from adipose tissue, the gut, pancreas, and liver that influence energy balance and metabolic regulation.

### Adipose-brain crosstalk

Adipose tissue is a critical metabolic organ involved in energy storage and dissipation,[100] and its interactions with the brain play a central role in maintaining energy balance.[101] This notion dates back to 1953, when Kennedy hypothesized that fat depots secrete a factor that acts on the hypothalamus to regulate appetite.[47] The identification of leptin and its receptor in the 1990s confirmed this concept.[102,103] It later became clear that low levels of leptin in the blood act as a powerful starvation signal that stimulates food intake and decreases energy expenditure via the melanocortin axis to defend the organism against an excessive reduction in fat mass[104] (Figure 3B). Similar to this, overfeeding studies have revealed that physiological mechanisms also exist to protect against weight gain.[46,105] This involves a strong suppression of appetite and possibly also an adaptive increase in energy expenditure.[106,107] The signals mediating these responses are unidentified, but it is evident that the defense against overfeeding-induced weight can be engaged independently of the leptin-melanocortin pathway.[108,109] While a potential adipose-derived signal of overfeeding has yet to be discovered,[46,105] many secreted factors from the adipose tissue have been identified as regulators of metabolic homeostasis, including adiponectin, resistin, apelin, and several cytokines.[110]

### Gut-brain crosstalk

Each meal demands efficient energy management, illustrated by rapid restoration of euglycemia and stabilization of plasma lipid levels. In anticipation of meal-induced perturbations in energy homeostasis, a cephalic response is triggered even before ingestion begins. This preemptive physiological reaction is initiated by olfactory, visual, and internal cues related to memory and circadian rhythms, prompting responses such as saliva production, enzyme release, and hormone secretion (including insulin, ghrelin, GLP-1, and pancreatic polypeptide [PP])[95] (Figure 3). During ingestion, orosensory cues drive positive feedback related to food reward, while other signals inhibit hunger-promoting neurons in the dorsomedial hypothalamus (DMH) to regulate intake.[111] Following the cephalic phase, the GI tract communicates with the brain through subliminal hormonal and neural signals that contribute to the regulation of meal size and energy intake.[111]

The gut contains nutrient-absorbing enterocytes and specialized enteroendocrine cells, which, e.g., release humoral and paracrine factors that act either directly on neurons in the brain as endocrine signals or indirectly via sensory afferents, responding to apical nutrient availability and trans-epithelial energy flux. These factors include secretin, the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), the satiation factor cholecystokinin (CCK), peptide YY (PYY), and other hormones involved in metabolic regulation (Figure 3C). Together, these gut-derived hormones coordinate nutrient absorption, digestion, and food intake regulation, ensuring both GI and metabolic homeostasis. In contrast to the aforementioned hormones, ghrelin from the stomach acts as an orexigenic (food intake-promoting) hormone, which stimulates appetite by acting on its receptor on hypothalamic agouti-related peptide (AgRP) neurons[10,95] (Figure 3B).

Aside from gut-secreted hormones affecting energy balance, the GI tract is both extrinsically and intrinsically innervated, which contributes to sensing both the quantity and composition of ingested energy.[10] Apart from the extrinsic innervation of the GI tract, comprising both sensory afferents that inform the CNS about processes in the gut and efferent nerves impacting gut motor and secretory function, an intrinsic enteric nervous system communicates with the CNS and the gut microbiome.[112] The enteric nervous system allows the GI tract to intrinsically execute basic functions like mechanoception and contraction of the smooth muscle surrounding the gut.[113] The vagus nerve and its primary sensory neurons are part of the extrinsic innervation of the GI tract.[99] Neurons of the vagus nerve have their somata located in the nodose ganglia and are well-established as key regulators of feeding behavior. These neurons monitor inputs from the GI tract and control feeding indirectly through their interactions with neurons in the hindbrain and hypothalamus[114–117] (Figure 3). For example, the vagus nerve signals interoceptive mechanosensation from the GI tract to neurons in the hindbrain, which allows monitoring of ingestive

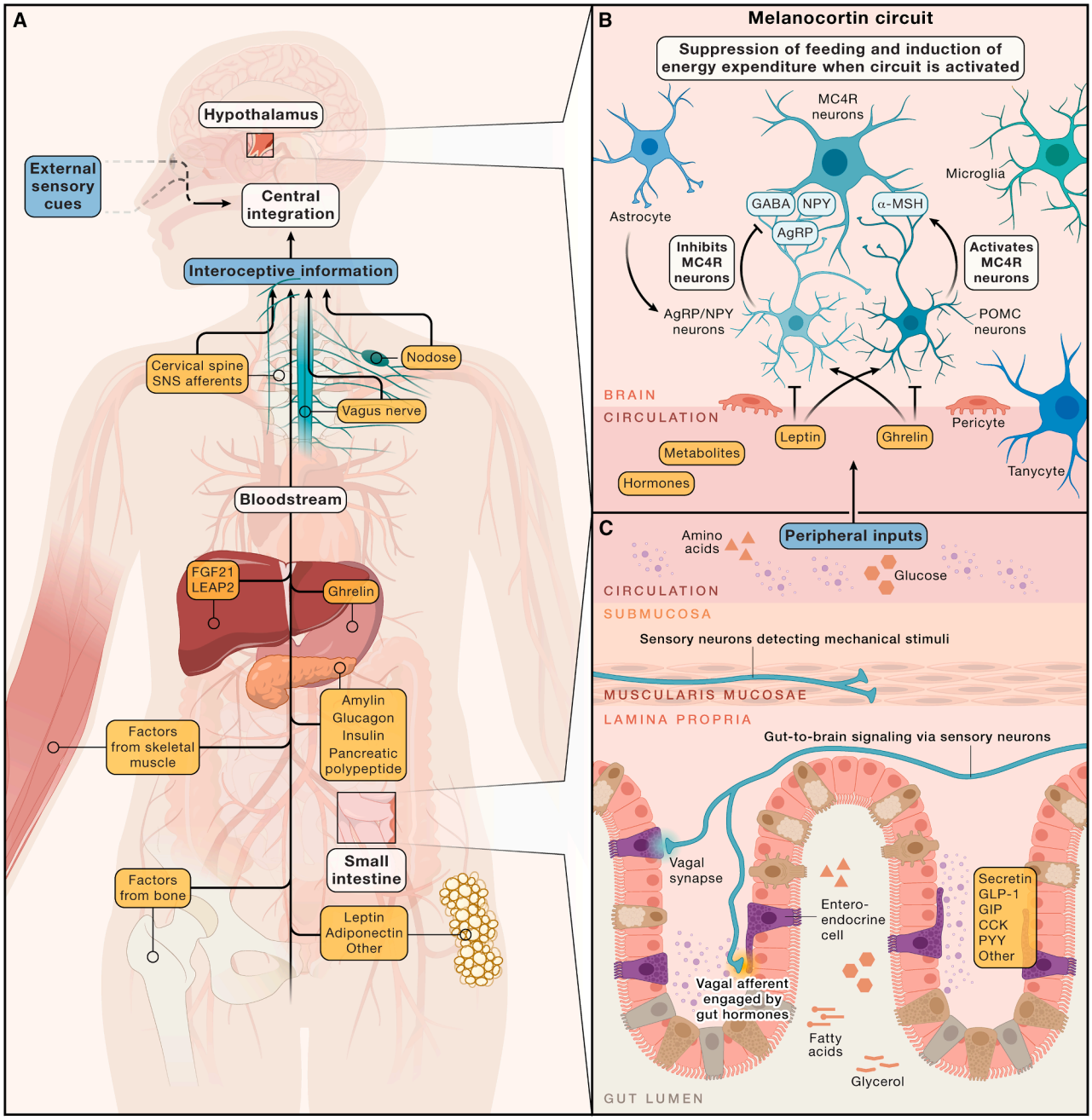


**Figure 3. Hormonal, metabolic, and neural inputs to brain circuits regulating energy homeostasis**

(A) Simplified overview of peripheral signals arising from multiple organ systems, along with sensory cues from the external environment. These signals are integrated by the central nervous system to regulate energy intake and expenditure, maintaining stable adiposity over time. This regulation involves both long-term energy storage signals, such as leptin, and short-term signals related to immediate intake of energy, like gastrointestinal hormones and nutrients.

(B) The arcuate nucleus of the hypothalamus harbors the melanocortin circuit, which is highly responsive to deviations in circulating hormones (e.g., those from the gastrointestinal tract) and the adipose tissue and metabolites. Central to this circuit are hunger-promoting AgRP neurons and satiety-promoting POMC neurons. These neuronal populations modulate energy balance via inhibitory and excitatory inputs to downstream MC4R-expressing neurons, respectively.

(C) Many peripheral inputs influencing brain circuits that regulate energy balance originate in the gut. Enteroendocrine cells release hormones, like secretin, GLP-1, GIP, CCK, and others, into the circulation in response to various stimuli, such as the presence of luminal nutrients. Additionally, vagal afferents relay mechanical and chemical information—such as gut distension and nutrient content—from the gastrointestinal tract to the brain.

behavior.[118] In addition, as the vagus nerve senses sucrose in the gut, it mediates activity of dopaminergic neurons in the brain, which supports food seeking in a postingestive state.[119] These and other findings have led to the concept that vagal communication from the gut may be implicated in food reward in the absence of taste receptor signaling. This notion is

supported by work showing that dopamine levels in the dorsal striatum are elevated upon fat and sugar sensing by gut-brain pathways.[120] In addition to vagal communication, afferent signaling pathways via spinal sensory neurons also relay information about macronutrient content in the intestines to hypothalamic food-intake-regulating neurons.[98,121,122] Finally, a special form of enteroendocrine cells, coined neuropods, forms glutamatergic excitatory synapses with vagal nodose afferents,[123] suggesting that synaptic signals from this type of GI cell inform the brain about energy availability already at the level of the gut.

### Pancreas-brain crosstalk

The pancreas is connected to the GI tract via the pyloric sphincter. In addition to its exocrine functions that assist digestion, the pancreas also regulates energy homeostasis through neural communication and secretion of hormones like insulin, glucagon, amylin, and PP[124] (Figure 3A). Both insulin and glucagon act on the brain to suppress food intake and promote energy expenditure, although the full extent of their central actions on energy homeostasis is poorly understood.[124] Amylin is co-secreted with insulin and serves as an important satiation signal, contributing to the regulation of food intake.[124,125] PP, depending on the route of administration, can exert both inhibitory and stimulatory effects on food intake.[126] Peripherally administered PP suppresses food intake and gastric emptying, whereas central administration of PP elicits feeding. The brain also modulates pancreatic function through descending neural signals, with parasympathetic activation promoting insulin secretion and sympathetic activation inhibiting it while stimulating glucagon release.[127,128] This bidirectional communication ensures proper responses to changes in energy balance, maintaining glucose homeostasis during periods of feeding, fasting, and stress.

### Liver-brain crosstalk

The liver is a central organ in metabolic regulation and is important for maintaining, e.g., glucose and lipid homeostasis. Key liver-derived hormones controlling energy metabolism include fibroblast growth factor 21 (FGF21) and insulin-like growth factor 1 (IGF-1), both of which modulate neural circuits that regulate energy expenditure and feeding behavior.[129] For example, FGF21 acts on the CNS to suppress sugar and alcohol intake while also regulating lipid oxidation.[130] The liver also produces other appetite-regulating hormones, including liver-expressed antimicrobial peptide 2 (LEAP2), a ghrelin receptor inverse agonist,[131] and growth differentiation factor 15 (GDF15)[132], which is not exclusively produced by the liver. In addition to classical peptide and protein hormones, the liver and several other organs also produce, metabolize, and secrete small molecule metabolites such as ketone bodies, lactate, and succinate, which are increasingly recognized as signaling molecules influencing metabolic regulation.[133] Bile acids have also emerged as important modulators of energy homeostasis and can reach the brain in the postprandial state.[134] Administration of bile acids reduces food intake in lean[134] and obese[135] mice. These various metabolites convey critical information about the organism's energy status to the brain, adding another layer of brain-periphery crosstalk in energy balance regulation.

## CNS CONTROL OF ENERGY HOMEOSTASIS

### Hypothalamic control of energy balance

The hypothalamus lies in the ventral diencephalon. This brain region contains several nuclei and regions that integrate peripheral signals of metabolic status, like hormones and nutrients, to regulate energy balance.[136] The arcuate nucleus (ARC) is at the core of this system. This small nucleus is located at the most ventromedial part of the hypothalamus, adjacent to the third ventricle and close to the median eminence, a circumventricular organ (CVO) with highly fenestrated capillaries and interspersed tanycytes. These features and cells allow some substances to be shuttled between peripheral blood and the brain.[137–141] Due to this anatomical and cellular organization, neurons of the ARC have privileged access to circulating signals, such as metabolites and peripheral hormones, whose blood level fluctuations reflect changes in substrate availability and energy status (Figure 4A). ARC neurons are strongly regulated by hormones, as reflected by the high expression level of the associated receptors, including those for leptin,[142] ghrelin,[143] and insulin.[144] Deletion of these hormone receptors, specifically from ARC neurons, causes significant alterations in food intake and body weight,[145–150] highlighting the importance of this ARC-based neuroendocrine axis in energy balance regulation.

In addition to circulating signals, ARC neurons are also modulated by neuronal inputs from numerous brain regions, including the nearby paraventricular hypothalamus (PVH),[151] ventromedial hypothalamus (VMH), and DMH,[152] as well as extrahypothalamic regions, such as the bed nucleus of the stria terminalis (BNST)[153] and the nucleus of the solitary tract (NTS)[154] (Figure 4A). These afferent synaptic inputs have been associated with transmission of, e.g., environmental signals that predict future food consumption, which rapidly reach the ARC even before nutrient uptake, as well as mechanical and chemical signals from the GI tract that arise within seconds to minutes following food ingestion.[114,150,155–159] Thus, ARC neurons receive multiple and widespread hormonal and neuronal signals communicating systemic energy status across different timescales. These inputs are integrated and then relayed through extensive projections to other hypothalamic and extrahypothalamic regions, where they coordinate the activity of downstream neural pathways. All this is achieved through complex afferent and efferent connectivity networks of fast-acting neurotransmitters and neuropeptides, enabling behavioral, neuroendocrine, and autonomic adaptations that align with the organism's energy state.

#### *AgRP neurons*

The most studied ARC-based pathway controlling energy balance is the melanocortin pathway with the AgRP and pro-opiomelanocortin (POMC) neurons, whose activation promotes positive and negative energy balance, respectively. These two types of ARC neurons modulate the second-order melanocortin 4 receptor (MC4R)-expressing neurons in the PVH, whose pharmacological antagonism or genetic deletion promotes feeding and obesity.[160–163] This is consistent with the activation of AgRP neurons and the inhibition of POMC neurons by energy deprivation[164–169] and low levels or absence of leptin, respectively.[148] POMC neurons produce and release the MC4R agonist α-melanocyte-stimulating hormone (α-MSH), which enhances satiety.

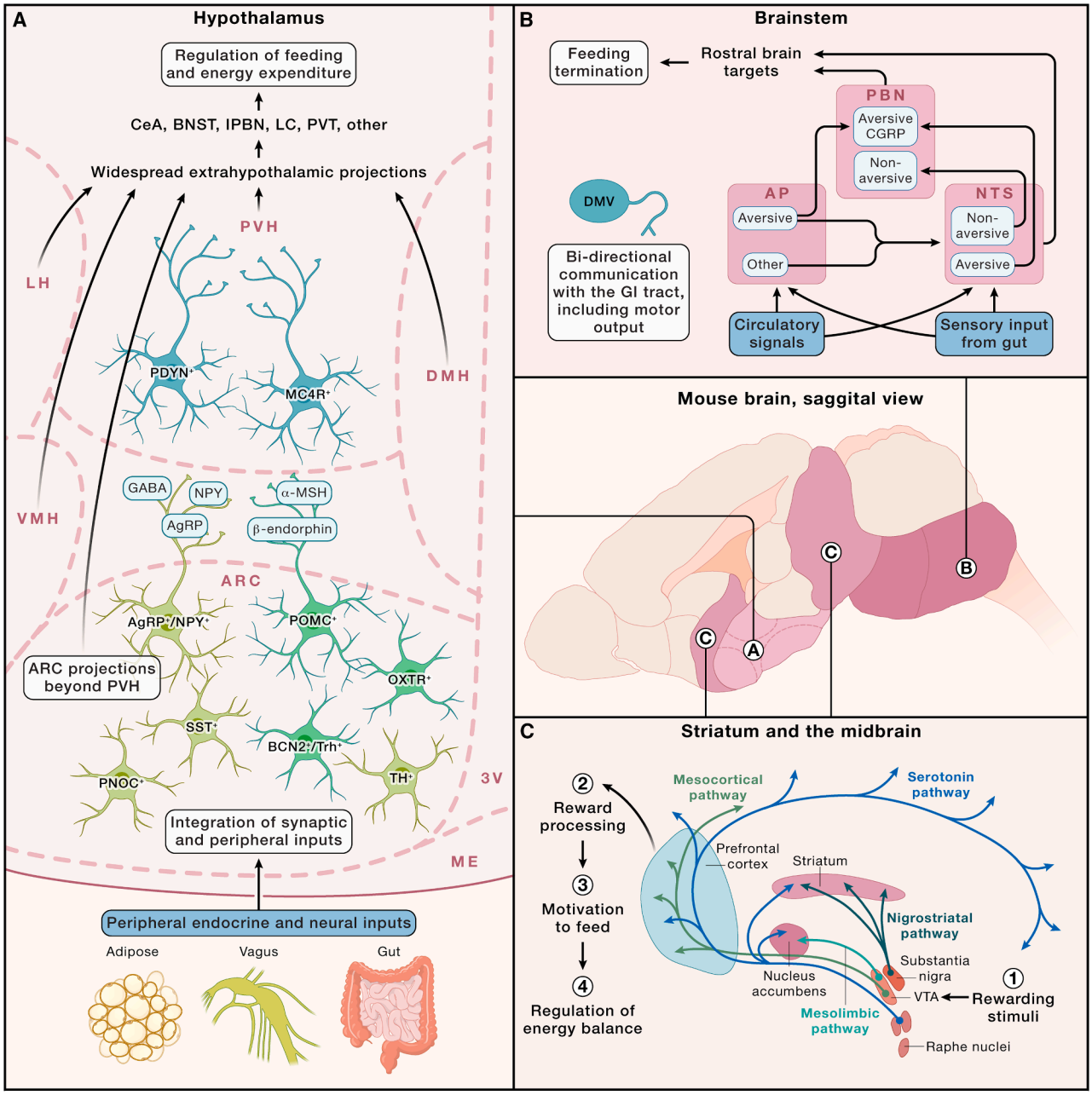


**Figure 4. Hypothalamic, brainstem, and reward circuitries governing energy balance**

(A) Endocrine and neural inputs from the periphery are integrated in the arcuate nucleus (ARC) of the hypothalamus (bottom). From here, both intrahypothalamic projections—connecting to other hypothalamic nuclei—and widespread extrahypothalamic projections to additional brain regions coordinate energy balance in accordance with peripheral metabolism (top).

(B) Circulatory and sensory signals reach brainstem nuclei, including nucleus of the solitary tract (NTS) and the area postrema (AP), to modulate energy intake and expenditure through local circuits and projections to more rostral brain regions. Notably, distinct brainstem neurocircuits can mediate aversive and non-aversive suppression of food intake.

(C) Reward-related neurocircuitries involved in motivated behavior contribute to the regulation of energy balance through distinct and overlapping pathways, including the mesocorticolimbic, nigrostriatal, and serotonergic pathways.

Conversely, AgRP neurons co-release GABA, neuropeptide Y (NPY), and AgRP, each acting on PVH neurons and promoting food intake with distinct temporal effects.[170] While AgRP's antagonistic action on MC4R triggers a prolonged feeding response, GABA and NPY induce more rapid feeding behavior.[162,163,171] In addition to PVH-MC4R neurons, extrahypothalamic cholinergic MC4R neurons also control energy balance by regulating energy expenditure.[172] Notably, the

melanocortin circuitry has been proposed to be biased toward homeostatic protection against a negative energy balance compared with a positive energy balance.[173]

AgRP neurons also communicate feeding-promoting information to neurons beyond those carrying MC4Rs in the PVH. Specifically, prodynorphin (PDYN)-expressing PVH neurons receive GABAergic synaptic input from AgRP neurons, and this circuit promotes food intake in a way that is distinct from that of PVH-MC4R neurons.[163] The PVH-MC4R and PVH-PDYN neurons, in turn, engage more caudally located neurons in the brainstem, through which they relay feeding signals to the forebrain.[160,161,163] In addition to the PVH, AgRP neurons send projections to other brain regions, such as the BNST, the lateral hypothalamus (LH), and the paraventricular thalamus, and stimulation of these inhibitory projections has been shown to induce feeding and additional behavioral effects associated with energy deprivation[174–176] (Figure 4A). As such, AgRP neurons and the neurocircuits within which they operate during states of energy deprivation can be viewed as the neural correlate of hunger. Consistent with the aversive nature of hunger, mice avoid the stimulation of AgRP neurons after conditioning, suggesting that the activity of AgRP neurons possesses negative valence.[177] Similarly, in behavioral experiments examining environment and flavor preferences, mice prefer the contexts that are associated with the inhibition of AgRP neurons.[177] However, during feeding, AgRP neurons have been shown to promote positive valence to reinforce feeding behavior,[178] suggesting that AgRP neurons transmit valence to optimize behavior in a context-dependent manner.

Ingestion of energy decreases AgRP neuron activity across different timescales. Exteroceptive stimuli, such as the smell of food, rapidly but transiently return AgRP neuron activity toward its baseline.[156,157,177] By contrast, the sensing of nutrients in the gut causes a slower decrease in AgRP neuron activity that persists for a longer duration.[113,158] Lastly, AgRP neuron activity decreases even slower, but enduringly, upon restoration of energy homeostasis.[113] Interestingly, it has been shown that the rapid decrease in AgRP neuron activity[177] by cues anticipating future food consumption[156,157,177] increases the incentive salience of food cues and facilitates learning.[179] Noteworthy, although AgRP neurons are often viewed as canonical hunger neurons, their activation also drives other metabolic aspects of the energy-deprived state, including activation of the HPA axis,[180] increased insulin sensitivity,[181] and activation of hepatic autophagy and ketogenesis.[182]

### POMC neurons

Research suggests that food intake is stimulated by an additive effect of AgRP neuron activation and POMC neuron inhibition.[171,183] Beyond the well-established role of POMC neurons in promoting satiety and energy expenditure upon activation in states of positive energy balance,[184,185] POMC neurons also fine-tune metabolic adaptations in peripheral tissues.[186] In the classical melanocortin pathway, activated POMC neurons release α-MSH, which binds and activates MC4R to suppress food intake and thus control energy homeostasis[187] (Figure 4A). This role of POMC neurons is supported by mouse[188–190] and human[191] genetic studies, where loss-of-function mutations of the POMC gene result in monogenic obesity. However, acute activation of POMC neurons has only minor effects on feeding,[166,187,192] indicating that other orexigenic neurons drive acute feeding behavior. In addition to releasing the excitatory neuropeptide α-MSH, POMC neurons also produce the inhibitory opioid neuropeptide β-endorphin, which has been found to acutely increase feeding.[193] The orexigenic action of β-endorphin from POMC neurons is consistent with the heterogeneity of POMC neurons and their functions beyond the melanocortin system.[194] In addition, this orexigenic effect of β-endorphin was shown to underlie the selective increase of sugar appetite after meals and in states of caloric surplus,[195] unfolding a mechanism that drives the overconsumption of sugar beyond energy needs.

### ARC neurons beyond AgRP and POMC in energy balance

While AgRP and POMC neurons are well-known neuronal populations regulating energy balance, more recent work, largely driven by the use of single-cell sequencing technology,[196–199] has revealed additional ARC neurons involved in the regulation of energy balance. Beyond AgRP neurons, other orexigenic ARC neurons also release inhibitory GABA onto PVH satiety neurons, thereby promoting feeding. These types of neurons include dopaminergic,[200] somatostatin (SST)-positive,[198] and prepronociceptin (PNOC)-expressing ARC neurons[201,202] (Figure 4A). ARC-PNOC neurons are rapidly activated by high-fat-diet (HFD) feeding[202] and were shown to increase their inhibitory tone onto POMC neurons when mice are shifted to a HFD, which is dependent on disinhibition from PNOC-expressing neurons of the BNST induced by the HFD.[159] These observations are interesting in light of carbohydrates being capable of selectively desensitizing AgRP neurons to intragastric nutrient infusion,[203] suggesting that macronutrient composition modulates neuronal excitability of feeding circuits, which may exacerbate obesity. Further, AgRP-negative NPY-positive ARC neurons have been implicated in promoting feeding in the context of HFD feeding.[204] While α-MSH released from POMC neurons regulates long-term energy balance, oxytocin receptor (OXTR)-expressing ARC neurons release glutamate onto anorexigenic PVH neurons,[187] including those expressing MC4R, to rapidly induce satiety. The glutamatergic synaptic connections between ARC-OXTR and PVH-MC4R neurons are strengthened by α-MSH from POMC neurons,[187] suggesting energy state-dependent synaptic adaptations in the melanocortin circuit.

In addition to satiety-inducing ARC-OXTR neurons, work from 2024 has identified basonuclin 2 (BNC2)-positive and thyrotropin-releasing hormone (TRH) neurons of the ARC, whose activation acutely suppresses feeding by inhibiting AgRP neurons through GABAergic synaptic connections.[150,205] The activity of these inhibitory neurons is regulated by sensory food cues, the energy state, GLP-1 receptors (GLP-1Rs), and, importantly, leptin, and thus fills an important gap in the temporal aspects of food intake regulation and the action of leptin and GLP-1R agonists.[150,205] Moreover, the high degree of neuronal subpopulations within the ARC adds to the complexity of the neural circuit that maintains energy balance. This is exemplified by subtypes of POMC neurons,[194] which exhibit distinct responses to hormonal fuel communicators[206,207] due to specific expression patterns of receptors and neurotransmitters.[196,197,207]

### Hypothalamic regulation of feeding beyond the ARC

In addition to the heterogeneous organization of the ARC, additional hypothalamic nuclei serve as important integrators of

hormonal and neuronal inputs that signal energy availability and regulate energy balance. For example, orexigenic SST neurons in the tuberal nucleus of the hypothalamus have been identified as feeding-promoting neurons that integrate metabolic and environmental cues.[208,209] An additional example is the LH, which is a well-established node of the neurocircuitry governing energy balance. Like the ARC, the LH is particularly heterogeneous,[196,210,211] though less neuroanatomically defined,[212] and integrates peripheral information, like circulating hormone levels, with inputs from other brain regions to orchestrate aspects of feeding and motivated behavior[212,213] (Figure 4A). Upon selective activation of GABAergic LH neurons, appetitive and consummatory behaviors are enhanced in mice[214] and non-human primates,[215] and activation of GABAergic projections from the LH to the ventral tegmental area (VTA) increases compulsive feeding behaviors.[216] These data suggest that the LH establishes a link between homeostatic feeding and food reward pathways, a notion that is consistent with other findings.[217,218] Conversely, ablating GABAergic LH neurons reduces energy intake and body weight in mice,[214,218] and genetic deletion of the vesicular GABA transporter, vesicular inhibitory amino acid transporter (Vgat), in GABAergic LH neurons causes leanness.[219] The LH also contains glutamatergic neurons, which reduce feeding when activated.[210,211] Therefore, it has been proposed that certain glutamatergic LH neurons deliver a "stop" message to terminate ongoing feeding,[210] which is consistent with the observations that these neurons are aversive, mediate avoidance,[220,221] and are highly active during feeding.[210,211] Finally, more than 30 distinct neuronal subpopulations in the LH have been characterized,[210] some of which are described to have important implications for energy balance, such as the orexin neurons involved in arousal and motivation[222] and ghrelin's orexigenic action,[223] melanin-concentrating hormone (MCH) neurons,[210,224] and leptin receptor and neurotensin neurons.[225–230]

Since the middle of the 20th century, the hypothalamus has been pivotal to research on the regulation of energy balance and body weight. However, as we shall explore in the following discussion, additional parts of the brain, such as the brainstem and mesocorticolimbic systems, also play critical roles in integrating homeostatic, hedonic, and environmental signals, influencing energy homeostasis and feeding behavior.

## Hindbrain control of energy balance

The hindbrain is composed of the brainstem and cerebellum and harbors key nuclei involved in regulating feeding. Specifically, the dorsal vagal complex (DVC) is located in the caudal part of the brainstem and supports the integration of neuronal inputs from the hypothalamus with peripheral cues traveling via the bloodstream or by afferent neuronal signals. Core hindbrain nuclei of the DVC include the NTS, area postrema (AP), and the dorsal motor nucleus of the vagus (DMV) (Figure 4B). Circulating signals, like hormones, enter via the AP, which is a CVO and thus localized outside the blood-brain barrier. This structural organization enables AP neurons to effectively sense and integrate blood-borne information. In addition, a subset of cues from the GI tract informing about gut distension and nutrient availability are rapidly relayed to the brain via vagal sensory neurons. These vagal afferents have their cell bodies located in the nodose ganglion situated just below the skull within the neck region, whereas their peripheral endings innervate the organs of the GI tract to detect mechanical and chemical signals and convey this information via synaptic connections onto AP and NTS neurons[231] (Figure 4B). For example, distension signals from vagal afferents originating in the stomach or small intestine coincide with extensive expression of the neuronal activity marker, Fos, within feeding-regulatory NTS and AP neurons.[114,232]

### *Nucleus of the solitary tract regulation of energy balance*

The NTS is a hub for neurons that mediate both satiation and illness responses, which can lead to similar behavioral outcomes—such as suppressing food intake and slowing gastric emptying—though these effects are thought to be driven by distinct circuits. In general, NTS neurons have been associated with suppressing consummatory behavior via projections to the parabrachial nucleus (PBN) of the hindbrain and more rostral brain regions, including the hypothalamus[233,234] (Figure 4B). Specifically, CCK-expressing NTS neurons were found to mediate the termination of feeding when activated by artificial stimulation[235–237] or by GLP-1R agonists.[238] Projections from NTS-CCK neurons to the lateral PBN (lPBN) have been suggested to mediate the pronounced aversion associated with suppressed food intake,[236] likely by activating calcitonin gene-related peptide (CGRP)-expressing lPBN neurons.[239–241] In addition, other lPBN neurons, such as those marked by PDYN expression, have been found to receive vagal input from the GI tract, likely via the NTS, to induce an aversion-associated appetite suppression.[118] In striking contrast, activation of projections from NTS-CCK neurons to the PVH, which also decreases food intake, has no aversive effects.[242] Further research is required to determine whether these distinct circuits underlie specific subpopulations of NTS-CCK neurons.

Of interest, other studies suggest that suppression of food intake by individual subpopulations of NTS neurons can manifest distinctly, with some not linked to aversion and others targeting hypothalamic neurons to affect feeding in the long term. Upon long-term chemogenetic activation, NTS neurons expressing the calcitonin receptor (CALCR) induce a non-aversive suppression of food intake via PBN neurons other than those expressing CGRP.[235] Thus, the PBN must harbor CGRP-negative neurons that are targeted by the NTS and promote appetite suppression without causing aversion. A subset of the NTS-CALCR neurons, which are marked by prolactin-releasing peptide (PRLH) expression, were found to control long-term energy balance by targeting AgRP neurons.[243] The suppression of AgRP-mediated food intake by these NTS-PRLH neurons is likely to occur via indirect, polysynaptic pathways, e.g., involving functional convergence of the projections from these neurons via areas like the PBN, BNST, and/or PVH.[243] These PRLH neurons also integrate orosensory inputs to control feeding bursts and restrain ingestion pace.[244] Interestingly, genetic data highlight a role of these non-aversive NTS-PRLH neurons in obesity development.[245] Other distinct subpopulations of NTS neurons have been shown to regulate food intake, including those expressing leptin and the GLP-1R.[246,247] Finally, some NTS neurons were also found to be

activated when animals were exposed to surgical implantation of capsules weighing 15% of the body weight,[248] indicating that the NTS may be involved in sensing body weight per se.

### *Area postrema regulation of energy balance*

Like the NTS, the AP exerts control over food intake, yet it has been primarily associated with promoting aversive reactions, including nausea[249] (Figure 4B). An example is the administration of exogenous GDF15 that both suppresses appetite and induces aversion through AP neurons expressing the GDF15 receptor, glial cell line-derived neurotrophic factor (GDNF) family receptor α like (GFRAL).[250,251] These AP-GFRAL neurons project to lPBN-CGRP neurons.[252] Transcriptomic analyses have defined additional molecularly distinct populations of AP neurons.[245,249] AP neurons that express the CALCR also suppress feeding when stimulated,[245] without collateral stimulation of aversive lPBN-CGRP neurons.[249] This observation supports the idea that amylin-based obesity pharmacotherapies, which act through the CALCR, may be associated with fewer aversive effects. In 2024, brain-region-specific manipulations uncovered that GLP-1R engagement in the AP drives aversion, while GLP-1 action in the NTS promotes satiety.[253] The group of glutamatergic AP neurons that is defined by the expression of the GLP-1R[245] can be further divided into distinct subpopulations, including one marked by GFRAL expression.[249,254] Whether this group of AP GLP-1R neurons represents a node mediating aversive responses remains to be elucidated. Importantly, lesioning experiments have shown that the AP is indispensable for the effect of a GLP-1R agonist on feeding.[255] GABAergic AP neurons are less studied, although transcriptionally described,[245,249,254] and may modulate the activity of glutamatergic neurons within the AP, given that these neurons show local projections in a manner largely restricted to the AP.[249] Because at least some GABAergic AP neurons are positive for the GIP receptor (GIPR),[249,256,257] it is tempting to speculate whether GIP agonism at GABAergic AP neurons results in increased inhibitory tone onto other glutamatergic AP neurons, thus mitigating some aversive and anorectic responses originating from the AP. This idea is supported by work showing that indeed GIP engages AP-GIPR neurons, which inhibit nausea-inducing neurons locally,[258] and that GIPR agonism alleviates aversive responses of GLP-1R agonism.[259] These findings are particularly interesting in the context of the greater weight loss achieved by dual engagement of GLP-1R and GIPR systems,[260] and that avoidance of adverse side effects may limit discontinuation of obesity treatment.

### *Crosstalk between the hypothalamus and brainstem in energy balance*

Emerging findings have expanded our understanding of the interactions between the hypothalamus and hindbrain. For example, an afferent pathway conveying inputs from nodose mechanoreceptors to AgRP neurons has been implicated in inhibiting feeding.[114] While it is still unknown how this information reaches the ARC, it may involve NTS neurons projecting there directly[237,242] or being relayed through the PBN.[114,236] Recently, a hindbrain-ARC circuit has been described to inhibit feeding when animals were subjected to heat,[261] in this case implicating the PBN in this circuitry.[261] Similarly, activation of catecholaminergic inhibitory projections from the NTS to PVH-MC4R neurons was reported to elicit strong motivational drives to feed, primarily through potentiating GABA release from AgRP neuron terminals.[262] AgRP neurons also send projections to the lPBN and can inhibit anorexigenic lPBN-CGRP neuron activity to increase feeding and overcome the appetite-suppressing effects of CCK and amylin but not inflammatory-related lipopolysaccharide treatment.[263] Further, GABAergic DVC neurons were found to project to the ARC and suppress appetite without causing aversion.[264] GABA release from these DVC neurons in the ARC resulted in the inhibition of orexigenic ARC neurons positive for NPY.[264] Some data also show that the LH receives ascending glutamatergic[265] and serotonergic[266] projections from the dorsal raphe nuclei (DRN) of the brainstem, and stimulation of both of these DRN neuronal populations suppresses feeding.[265,266] On the other hand, in some cases, hypothalamic and DVC neurons utilize distinct mechanisms to affect appetite, as demonstrated with central GIPR engagement.[267]

Together, the hindbrain is increasingly recognized not only for its role in meal termination, nausea, and illness but also for its crucial contribution to the long-term regulation of energy balance. However, important questions remain regarding the cellular organization of the DVC: how is neuronal communication between distinct DVC neuron types and downstream brain regions organized? How do peripheral inputs reach the specific subparts of the DVC, and how are the signals processed and integrated? Additionally, understanding how NTS neuronal subpopulations could drive non-aversive suppression of feeding may help guide drug discovery efforts toward generating non-aversive appetite-suppressing therapeutics. Finally, since vagal gut-to-brain communication has been identified as a crucial component of the brain's reward circuitry and motivational behavior,[268] future research may focus on investigating the molecular mechanisms by which hindbrain neurons affect reward-driven processes related to energy balance.

## Motivational and hedonic circuits in energy balance

The rewarding aspects of food are partly linked to its capacity to reinforce behavior, thereby enhancing its appetitive motivational value. Often described in contrast to "reward," "palatability" refers to the hedonic (pleasurable) value of food. The motivation to eat and the enjoyable properties of food strongly modulate the neurobiology that governs energy balance. The neuroscientific concept of separating "wanting" from "liking" is supported by the fact that motivational and hedonic elements of food reward can be independent of one another.[269,270] In some cases, both motivational and hedonic values of food are referred to as the "food reward" component in the regulation of ingestive behavior, likely because they often appear in conjunction.[270] However, they can be experimentally dissociated,[269] implying distinct underlying neurocircuitry. Regardless of the definition, reward neurocircuitry tunes the incentive salience associated with food and dictates its hedonic value while also consolidating food stimuli with palatability in neural learning and memory networks. This suggests an evolutionary wiring for hedonic eating.[271]

The mesocorticolimbic system, with dopamine as a core neurotransmitter, is crucial to reinforce motivated behavior. Here, rewarding stimuli, including food, get encoded in VTA neurons of the basal ganglia in the midbrain to release dopamine in the nucleus accumbens (NAc) of the ventral striatum

(mesolimbic/mesoaccumbal pathway) or the prefrontal cortex (mesocortical pathway)[272] (Figure 4C). Dopaminergic VTA neurons encode reward prediction error (discrepancy between actual and expected rewards), whereas GABAergic VTA neurons signal expected reward, allowing dopaminergic VTA neurons to estimate reward prediction error and facilitate reinforcement learning.[273–275] Together, the mesocorticolimbic projections modulate brain regions involved in motivation, learning and memory, valence, and executive and emotional control, which are dissociable[276] processes that guide feeding behavior.[272,277]

Dopamine from VTA neurons is classically viewed as a neuromodulator that conveys information about the salience, context, and value associated with a rewarding stimulus.[272] Glutamatergic basal forebrain neurons project to the VTA to decrease dopamine release in the NAc.[278] Functional connectivity between the NAc and prefrontal cortex associates with the degree of appetite in humans.[279] Interestingly, AgRP neurons have been reported to control the structure and function of parts of the prefrontal cortex.[280] A human study also found that responsive deep brain stimulation of the NAc in patients with loss-of-control eating and severe obesity improved their eating control, which was associated with weight loss.[281] Finally, in addition to the mesocorticolimbic pathways, dopaminergic nigrostriatal and serotonergic pathways regulate reward processing[282] (Figure 4C).

Studies in rodents have suggested that the dopamine system links addictive-like behavior and deficits in mesolimbic dopamine neurotransmission to diet-induced obesity.[283–285] In humans, neuroimaging studies have linked obesity and weight gain to blunted striatal dopamine responses in response to food.[277,286–289] Some observations have resulted in the idea that reward hyposensitivity, arising from deficits in reward processing, drives compensatory compulsive consumption of palatable foods.[283] Importantly, it remains unclear what the causal direction in this putative relationship is and whether compulsive consumption of highly palatable and energy-dense food can itself cause dysfunction of reward neurocircuitry and thereby drive diet-induced obesity. However, a growing body of evidence suggests that intake of high-fat foods induces neuroplastic changes in the NAc, increasing reward-induced impulsivity by altering striatal dopamine transmission independently of an obese phenotype in rodents.[290–294] This consumption of a high-fat diet in rodents appears to affect reward neurocircuitries in an input- and cell-type-dependent manner.[295] Moreover, it has been reported that an obesogenic diet promotes proinflammatory signatures in the NAc and increases food cravings.[296] Interestingly, selective inhibition of upstream components of the nuclear factor-κB pathway in the NAc blunted compulsive sucrose-seeking in these high-fat diet-fed mice.[296] Notably, devaluation of a standard chow diet following high-fat diet exposure was shown to alter AgRP and dopaminergic neuron responses, where standard chow after a high-fat diet could not completely suppress the negative affective state of hunger at the level of the ARC,[297] suggesting links between mesolimbic dopamine signaling and the hypothalamus in food devaluation and preference.

### *The hypothalamus and reward pathways*

The hypothalamus is extensively coupled with the mesocorticolimbic dopamine reward and motivation neurocircuitries. For example, modulation of either neurons in the hypothalamus or midbrain dopaminergic neurons affects changes in reward-induced activity in the other population.[122] As a specific example, POMC neurons have been shown to provide an inhibitory tone onto dopaminergic VTA neurons, regulating stress-induced hypophagia and anhedonia,[298] again exemplifying POMC functional and neuroanatomical diversity.[194] In addition to POMC neurons, an iterative neural processing sequence has been identified in which AgRP neurons, GABAergic LH neurons, and DRN neurons facilitate the preparation, initiation, and maintenance of segments in the feeding process, respectively. This is achieved by resolving motivational competition,[299] a general, yet remarkably complex, phenomenon observed during hunger and feeding processes.[300–303] These findings highlight how the hypothalamus and other brain regions interact with the dopamine system in a manner dependent on the ingestion phase. The different stages of the ingestion process might be represented at distinct times, possibly because midbrain dopamine systems track each stage separately.[304] In sum, the hypothalamus integrates oscillating networks of feeding and partakes in reward neurocircuitry, dynamically adjusting motivated behavior based on internal state and external environment to optimize survival and energy balance.[300–302,305]

At least two well-described LH cell populations, MCH- and orexin-expressing neurons, are involved in modulating classical reward neurocircuitry. Some glutamatergic LH neurons project to the VTA, whereas others project to the lateral habenula, which is another brain area integrating and processing emotional and sensory states.[211,306] LH-MCH neurons, driving both food-motivated appetitive and intake-promoting consummatory events,[224] also project to the NAc to regulate motivated behavior like feeding.[307] Further, LH-orexin neurons send projections to the VTA and NAc, and their activation is significantly associated with preferences for cues linked to food reward.[308] Additionally, activation of GABAergic LH neurons results in goal-directed behaviors and feeding motivation, particularly for palatable food, coinciding with LH-frontal functional connectivity.[215]

Importantly, while some peptide hormone signals may be transported across the blood-brain barrier to directly impact the connectivity of brain regions within the reward neurocircuitry, in most cases, these effects are likely mediated indirectly through polysynaptic circuits from CVOs to reward pathway areas.[311–314] There are many examples of peripheral GI and adipose hormones that engage the mesolimbic neurocircuitry to regulate food reward. These include ghrelin, CCK, GIP, GLP-1, PYY, and leptin. However, the evidence often relies on rodent studies using brain-region-specific infusion of gut peptides or genetic ablation of their cognate receptors in certain regions and rarely traces the actual arrival of endogenous or exogenous hormones to the studied neuronal populations. Since ghrelin, GLP-1, CCK, and PYY are also produced and secreted as neuropeptides by neurons within the CNS itself, it can be challenging to distinguish peripheral effects from central effects. As an example, there is evidence that hindbrain preproglucagon (PPG) neurons, which produce GLP-1, project to mesolimbic reward areas.[315]

### *The gut and reward pathways*

Extensive evidence points to the role of the gut in diet-induced regulation of dopamine neurocircuitry and food reinforcement.

For example, feeding mice a high-fat diet has been shown to diminish gut-stimulated dopamine release.[290] Similarly, exposing mice to a high-fat diet reduces the appreciation of other dietary sources.[297,316,317] The actual absorption of lipids from a high-fat diet appears critical in this devaluation of standard chow diet.[318] The vagal gut-brain axis is a critical component of reward neurocircuitry where the gut conveys valence signals in response to ingested macronutrients,[268] while spinal afferents also transmit gut signals to drive food-related learning.[117] Interestingly, distinct vagal afferents sense fat and sugar in the gut and facilitate nutrient-specific reinforcement, while the combination of fat and sugar increases nigrostriatal dopamine release and promotes overeating.[120,319] However, not all ingested components engaging reward neurocircuitry rely on vagal transmission like macronutrients do.[122] Importantly, adjusting decision-making by updating reward prediction errors helps adapt to uncertainty.[320] Thus, it remains possible that mismatches in the interoceptive state of the GI tract from nutrient signals and the predicted state by the organism contribute to diet-induced obesity. Compulsive overeating may therefore present itself when systems for correcting reward prediction errors and consolidating interoceptive memories are aggravated. The mechanisms that may underlie these processes remain unclear.

In sum, the regulation of energy homeostasis involves a network of CNS regions and peripheral signals that collectively regulate food intake, body weight, and energy expenditure, involving complex interplays between canonical feeding centers, like the hypothalamus and hindbrain, and neurocircuitry of reward and motivation. Together, these regions integrate homeostatic and hedonic signals, highlighting the interconnectedness of motivational, reward-driven, and executive control pathways. Other brain regions not covered in the present review contribute to the regulation of energy balance, including the preoptic area,[321] lateral septum,[322,323] parasubthalamic nucleus,[324] cerebellum,[325] central extended amygdala,[326,327] and hippocampus.[328,329] Lastly, brain regions like the paraventricular nucleus of the thalamus[309] or the xiphoid nucleus of the midline thalamus[310] participate in tracking motivational states to shape instrumental behavior, which is guided by internal drives, like hunger or cold, represented in distant brain areas. Notably, the overlap and interaction between homeostatic and hedonic regulation underscore the need to move beyond reductionistic models. The traditional dichotomy of ''homeostatic'' versus ''hedonic'' pathways oversimplifies their interwoven roles. The interconnectedness and adaptability of these systems during energy balance deviations remain pivotal areas of ongoing research, with implications for understanding and treating metabolic disorders.

## MOLECULAR AND NEUROSTRUCTURAL ADAPTATIONS IN NEUROCIRCUITS CONTROLLING ENERGY HOMEOSTASIS

Structural and molecular remodeling, along with dynamic changes in functional connectivity within brain regions and circuits involved in regulating energy balance, play an essential role in adjusting and optimizing complex behaviors like feeding. As such, synaptic adaptations are influenced by neuroendocrine feedback and the integration of hunger, satiety, and body fatness signals, as discussed above. Notably, these circuit adaptations are considered essential for maintaining energy homeostasis, whereas maladaptive adaptations may contribute to the pathogenesis of obesity (Figure 5A).

Some reports suggest that obesogenic diets can reorganize the synaptic architecture of hypothalamic neurons governing energy balance.[330,331] Interestingly, synaptic organization of the ARC has been found to predict the vulnerability of outbred rats to develop diet-induced obesity.[332] A mechanistic example by which this synaptic remodeling occurs is how diet-induced obesity uncouples the effect of leptin on the intrinsic excitability of AgRP neurons, which is needed to modulate the spontaneous activity and integration of synaptic input onto AgRP neurons[333] (Figure 5B). It has also been reported that sucrose consumption alters excitatory synaptic inputs to AgRP neurons.[334] Similarly, chronic high-fat diet exposure alters the firing frequency and postsynaptic currents of POMC neurons.[335] Synaptic plasticity outside of the ARC upon high-fat diet exposure has also been reported. For example, synaptic properties of the LH change dynamically and cell-type-dependently upon high-fat diet consumption.[336] Specifically, excitatory synaptic inputs to LH-orexin neurons increase transiently within the first week of a high-fat diet, while the density of excitatory synapses of LH-MCH neurons increases with a delay that still precedes significant weight gain.[336] These findings show that obesity-promoting diets can, in rodents, alter synaptic transmission in neurons that regulate energy balance. However, it is still unclear which specific circuits are affected, how these changes causally contribute to obesity, and what role they play in maintaining long-term diet-induced obesity.

Given the dynamic nature of organismal energy fluxes, it is not surprising that feeding neurocircuitries maintain properties of plasticity into adulthood, such as changes in synaptic connectivity, neurotransmitter dynamics, and postsynaptic actions (Figure 5A). For example, the density of excitatory synaptic inputs onto AgRP and POMC neurons are increased and decreased, respectively, in the fasted state in mice, and the opposite is observed in a fed state.[337–339] Specifically, fasting has been shown to elicit a reduction in the strength of excitatory inputs from the VMH to POMC neurons of the ARC.[338] This adaptive response was shown to be at least partially mediated by dynamic levels of the hormones ghrelin and leptin.[337] Adult mice deficient in leptin even present with increased synaptic densities of inhibitory and excitatory inputs onto POMC and NPY neurons in the ARC, respectively, compared with control mice.[337] This altered synaptic architecture is ameliorated upon a single leptin treatment.[337] By contrast, ghrelin administration in the fed state was found to increase excitatory inputs onto AgRP neurons.[340] Similarly, energy deficiency increases excitatory synaptic transmission between PVH and AgRP neurons,[341] a circuit whose activity is necessary and sufficient for driving hunger. The excitatory input to AgRP neurons is notable for its high degree of synaptic plasticity, which is energy state dependent[151] (Figure 5B) and is even observed following exercise.[342] Further, reorganization of the synaptic connections of LH-orexin neurons[343–345] and oxytocin-PVN neurons[346] is elicited contingent upon energy status. Synaptic

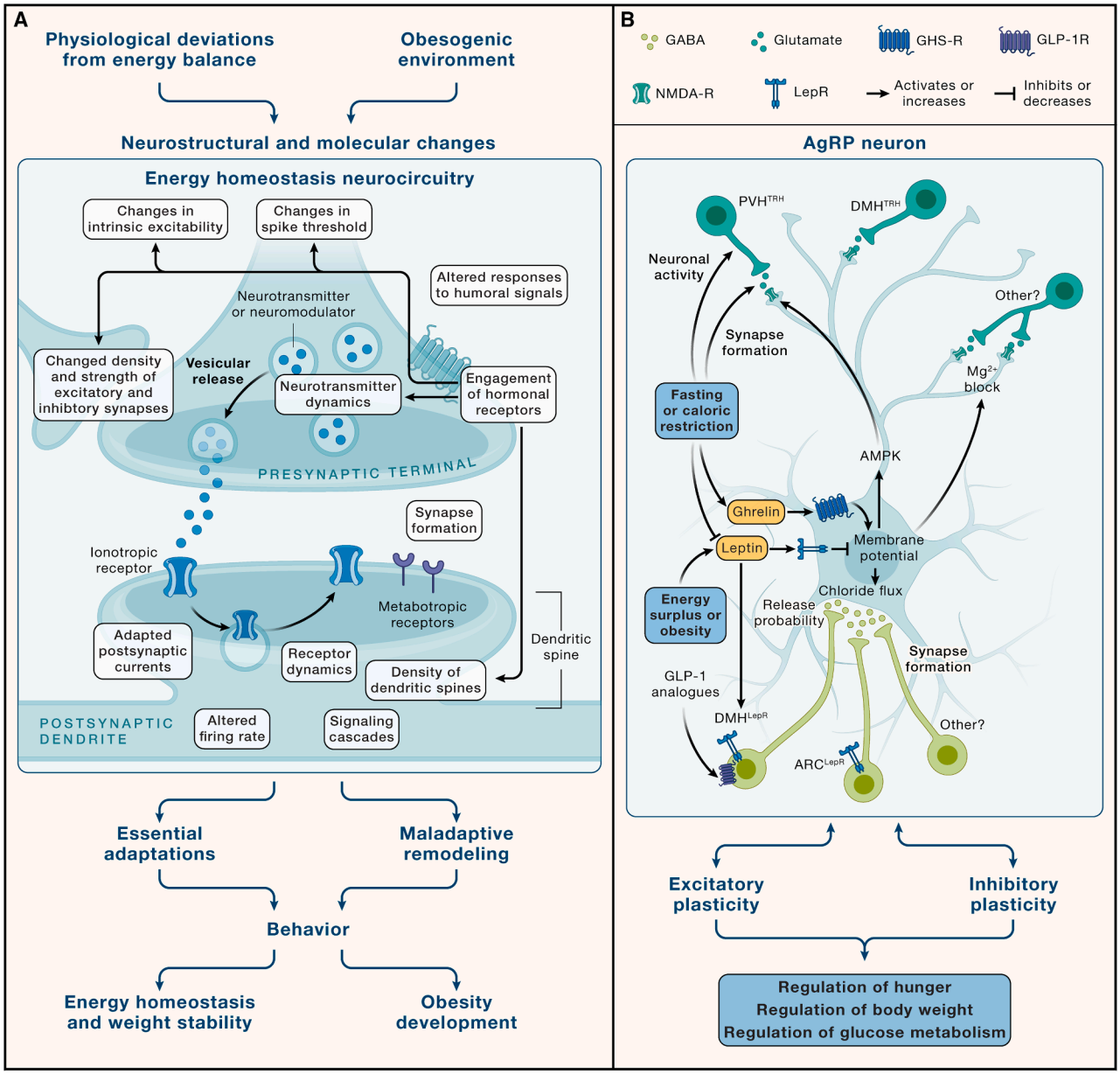


**Figure 5. Neuroplasticity and molecular remodeling in energy balance neurocircuitries**

(A) Simplified overview of neurostructural and molecular changes within energy balance neurocircuitries in response to either a pathologic obesogenic environment or physiological perturbations. Although exposure to an obesogenic environment can lead to maladaptive remodeling and contributes to obesity pathogenesis, certain neurostructural adaptations are essential for promoting behaviors that restore energy homeostasis.

(B) Simplified depiction of specific mechanisms driving molecular and structural plasticity in AgRP neurons, which influence hunger, body weight, and glucose metabolism.

plasticity was also shown to be a crucial mechanism for energy state-dependent tuning of behavioral responses like feeding in a manner dependent on AgRP neurons and NPY action.[176] Other factors, like those having neurotrophic effects, have been shown to affect plasticity of feeding neurocircuitries. As an example, vascular endothelial growth factor A (VEGFA) has also been shown to increase the spike threshold of an AgRP neuron subpopulation, which primes a net anorexigenic output.[261]

There are abundant examples of adaptations in presynaptic neurotransmitter release that are influenced by energy state. Seminal work includes how ghrelin was shown to increase the frequency of spontaneous synaptic GABA release from NPY neurons onto POMC neurons.[347] In addition, ghrelin was shown to potentiate glutamate release from excitatory synaptic terminals engaging AgRP neurons[340] (Figure 5B). Ghrelin also adapts the synaptic input of dopaminergic

neurons in the VTA to control appetite[348] and promotes synapse formation in the hippocampus.[349] Associated with synaptic changes in the VTA, ghrelin causes dopamine release in the NAc,[348] while it enhances learning and memory consolidation in the hippocampus by propagating long-term potentiation.[349] *In vitro* work suggests that ghrelin-mediated synaptic plasticity occurs via a calcium/calmodulin-dependent protein kinase kinase (CAMKK)-dependent adenosine monophosphate kinase (AMPK) activation.[340]

Postsynaptically mediated plasticity is well exemplified by research demonstrating how postsynaptic N-methyl-D-aspartate receptors (NMDARs) are essential for synaptic plasticity of AgRP neurons in an energy state-dependent manner.[164] AgRP-specific glutamatergic NMDAR ablation weakens fasting-dependent increases in excitatory drive, density of dendritic spines, synaptogenesis, and eventually activity of these hunger neurons[164] (Figure 5B). That glutamate receptors are key in facilitating the plasticity of feeding neurocircuitry is supported by the fact that fasting triggers translocation of the calcium-impermeable subunits into α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (AMPARs) on POMC neurons and reduces rectification of AMPAR-mediated excitatory postsynaptic currents.[350]

In addition to obesogenic diets, obesity-associated neuroinflammation may also result in maladaptive reorganization of neurocircuits orchestrating feeding behavior, implicating many cells beyond neurons, such as microglia, tanycytes, and astrocytes.[330,351] In context, gene expression of microglia-specific and astrocyte-specific markers is significantly upregulated in rats fed HFD for 4 weeks compared with chow-fed rats.[330] Although microglia activation is often associated with neuroinflammation, these glial cells may exert neuroprotective effects by producing and secreting neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), to support neuroprotection during obesity-associated neuroinflammation.[351] The absence of rigid blood-brain-barrier protection of some ARC neurons may even expose them to signals of obesity-associated systemic inflammation,[352] potentially impacting synaptic and hormonal integration by hunger and satiety neurons, thereby affecting energy balance.

Maladaptive plasticity has been firmly established as a concept in research on drugs of abuse, where these profoundly alter the mesocorticolimbic dopamine system, driving synaptic and circuit reorganization that underpins the development of addictive behaviors.[353,354] Notably, aspects related to feeding and motivated behaviors seem to converge on similar adaptive mechanisms. For example, food craving episodes are associated with remodeling of brain connectivity in the NAc,[355] and striatal plasticity has been suggested as a key feature in obesity.[356] This striatal plasticity may involve shifts in dopamine receptor subtypes and the reorganization of the interaction between dopaminergic and serotonergic neurons.[357] The adaptive response consequential to overconsumption of palatable food is proposed to have long-term effects on dopamine signaling, such as reducing dopamine receptors.[283,358] During conditioning, changes to synaptic plasticity are proposed to underpin the ability of palatable food to drive hedonic feeding.[209] Short-term consumption of highly palatable food has also been found to prime future foraging and feeding behavior, which is mediated by increased excitatory synaptic density onto VTA dopaminergic neurons.[359] Interestingly, deleting NMDARs in VTA neurons decreases lever pressing for postingestive sucrose reward.[119]

In summary, synaptic plasticity appears inherent to the neurocircuitry that controls energy balance. Structural and molecular adaptations in feeding neurocircuits facilitate energy homeostasis by mounting appropriate neuronal responses, which are integrated and translated into behavior (Figure 5A). Important fundamental questions remain to be addressed. For example, which synaptic connections are changed by alterations in energy balance, and how do such discrete circuit adaptations causally relate to energy balance control, particularly in the long term? What are the primary drivers underlying feeding and obesity-related changes in synaptic plasticity: deviations in peripheral hormones, changes in neuronal activity, or yet-to-be-identified molecular events? Do these inspire novel drug targets to rewire the brain? We predict that investigating the molecular alterations and cellular mechanisms underlying energy homeostasis in neurons, but also glial cells, is important for better understanding evolutionarily conserved adaptations in feeding behavior. Further, this may guide drug discovery in obesity and related disorders to minimize comorbidities by identifying viable molecular and cellular targets for cardiometabolic health. Whether specifically targeting synaptic plasticity holds potential for future anti-obesity medications remains to be tested.

## BRAIN-TARGETING WEIGHT LOSS PHARMACOTHERAPIES

Efforts to develop effective weight loss therapies have largely concentrated on targeting brain pathways to suppress appetite. Early drugs for obesity achieved this by influencing monoaminergic neurotransmitters, such as dopamine, norepinephrine, and serotonin. Some of these drugs are still used today, including the combination of phentermine (a norepinephrine transporter inhibitor) and topiramate (a glutamatergic modulator).[16] Another example is bupropion, a dual reuptake inhibitor of dopamine and norepinephrine, paired with the opioid receptor antagonist, naltrexone. These combinations of small molecules typically result in 8%–10% weight loss, but they are also linked to a broad range of adverse events, including hypertension, increased heart rate, insomnia, and GI issues, in addition to psychiatric side effects, including mood changes and depression. In the 21st century, however, the focus of anti-obesity drug discovery has shifted from targeting classical neurotransmitter systems to leveraging the metabolic benefits of gut hormones.[17,360]

### Clinical progression and success of incretin-based pharmacotherapies

The anorectic effects of GLP-1 were first observed in response to intracerebroventricular infusion of the hormone in rodents.[361] Intravenous infusions of GLP-1 subsequently demonstrated that this gut peptide also lowers food intake and enhances satiety in humans.[362] However, rapid enzymatic degradation and renal elimination of intestinally secreted incretins limit the exposure of native GLP-1, with ∼10% entering circulation and minimal amounts reaching the brain.[363] Hence, the therapeutic

utility of native GLP-1 is hampered by its short half-life in plasma. However, innovative biochemical solutions have been engineered to improve the pharmacokinetic profile of peptide therapeutics through fatty acid-mediated reversible binding to serum albumin.[11] This strategy enabled the development of liraglutide,[14] the first GLP-1-based drug amenable to daily dosing and to gaining regulatory approval for the treatment of obesity. In nondiabetic subjects with obesity, 56-week treatment with liraglutide resulted in a placebo-corrected average weight loss of 5.4%, with one-third of participants achieving >10% body weight reduction.[364] Using liraglutide as a starting point, chemical optimization of the peptide backbone along with additional half-life extension technologies enabled the creation of semaglutide, a once-weekly GLP-1 analog.[13] Semaglutide consistently provides superior improvements in glycemic control and body weight management relative to both placebo and other treatment options.[365] Notably, patients living with obesity and without type 2 diabetes (T2D) achieved an average 14.9% body weight reduction over 68 weeks of treatment with semaglutide.[366] For reasons that remain unclear, the weight loss efficacy of semaglutide is substantially reduced in patients with T2D, in addition to obesity, as this group of patients only achieves a 6.2% placebo-corrected average weight loss after 68 weeks of treatment.[367] Continued semaglutide treatment sustains the weight loss at its maximal level for up to 221 weeks, contingent on adherence to the drug regimen,[368,369] resulting in long-term improvements in cardiovascular health and reduced likelihood of developing T2D.[368,370,371]

## Dual GLP-1 and amylin receptor agonism for obesity treatment

Given the heterogeneity and complex pathogenesis of obesity, combination therapies that target distinct central mechanisms controlling energy balance may enhance weight loss efficacy.[15] Because amylin receptors (AMYRs) and GLP-1Rs exhibit distinct expression patterns in the brain, it was hypothesized that amylin could synergize with GLP-1-based drugs to enhance weight loss. Accordingly, cagrilintide, a long-acting amylin analog, was developed to create a suitable combination partner for semaglutide.[372,373] In a phase 3 clinical trial, co-treatment with a fixed dose of cagrilintide and semaglutide (CagriSema[374]) resulted in an average 20.4% body weight reduction relative to placebo after 68 weeks. However, the combination of two drugs complicates the regulatory pathway due to the risk of drug-drug interactions and potential differences in pharmacokinetic and pharmacodynamic properties. To address this, a head-to-tail fusion of the two analogs was achieved using a small peptide linker, successfully creating a single-molecule GLP-1R/AMYR co-agonist, known as amycretin. In a phase 1a/2b clinical trial, subcutaneous amycretin demonstrated significant efficacy, reducing body weight by an average of 24.0% over 36 weeks in otherwise healthy patients with obesity.[375,376]

## Incretin hormone-based unimolecular multi-receptor agonists

The insulinotropic effects of GIP suggest that combining it with GLP-1 could provide superior glycemic control in patients with T2D. The first generation of a GLP-1-R/GIPR co-agonist was reported in 2013.[377] This dual-incretin approach improves glycemic control and enhances weight loss in rodents and non-human primates. However, the compound only showed modest superiority to liraglutide in a phase 2b clinical trial,[378] and the program was shelved in favor of advancing the parallel clinical development of semaglutide.[379] Instead, another long-acting unimolecular GLP-1R/GIPR co-agonist, tirzepatide, was approved for obesity treatment in 2023. At the highest dose tested, tirzepatide elicits a placebo-corrected average weight loss of 17.8% in nondiabetic patients with obesity over 72 weeks.[380] Extended treatment with tirzepatide for up to 3 years sustained this weight loss and nearly eliminated the progression of T2D in individuals with prediabetes.[381] In patients with obesity and T2D, tirzepatide induced an average 11.6% placebo-corrected weight loss over 72 weeks, nearly double the weight loss observed with semaglutide in the same patient population.[382] In extension, evidence from an open-label phase 3b clinical trial highlights that tirzepatide outperforms semaglutide in terms of weight loss efficacy, seemingly without compromising safety and tolerability.[383] This superiority of tirzepatide may stem from multiple mechanisms, including engagement of GIPR-mediated satiety signaling, futile calcium cycling in white adipose tissue,[384] biased GLP-1R agonism,[385,386] reduced emetic response to GLP-1,[221] or a combination of these factors.

Although mounting clinical evidence supports the additive metabolic benefits of combining GIPR and GLP-1R agonism, similar clinical outcomes have been observed from pairing GIPR antagonism with GLP-1R agonism.[387] For instance, 1 year of once-monthly treatment with maritide, a bispecific GIPR antagonist antibody derivatized with two GLP-1 analogs, delivered a 17.3% average weight loss in subjects with obesity but without diabetes and a 15.6% average weight loss in subjects suffering from both obesity and T2D.[388] The paradoxical observation that both GIPR agonism and antagonism enhance the efficacy of GLP-1R agonists presents an intriguing avenue for future research in both academia and industry.[389]

The structural similarity of GLP-1 and GIP with glucagon has further motivated the engineering of chimeric peptide triple receptor agonists.[390,391] The rationale for targeting all three receptors is rooted in the complementary functions of GLP-1 and GIP in counteracting glucagon's hyperglycemic effects while simultaneously harnessing glucagon's lipolytic and thermogenic properties to achieve improved metabolic outcomes. Clinical trials with retatrutide, the most advanced GLP-1R/GIPR/glucagon receptor (GCGR) triple agonist, have demonstrated unprecedented weight loss efficacy in individuals with obesity but without T2D, with a safety profile similar to other incretin-based therapies. Findings from a phase 2 study revealed an average of 22.1% placebo-corrected weight loss over 48 weeks at the highest dose, with no plateau observed. Notably, 26% of participants in this group achieved a weight reduction exceeding 30%.[392]

## Neural pathways mediating weight loss by GLP-1 receptor agonists

Over the past decade, research has linked the effects of GLP-1R agonists on food intake, reward, and aversion to the activation of distinct GLP-1R populations across several brain regions. However, clinically available GLP-1R agonists are unlikely to directly

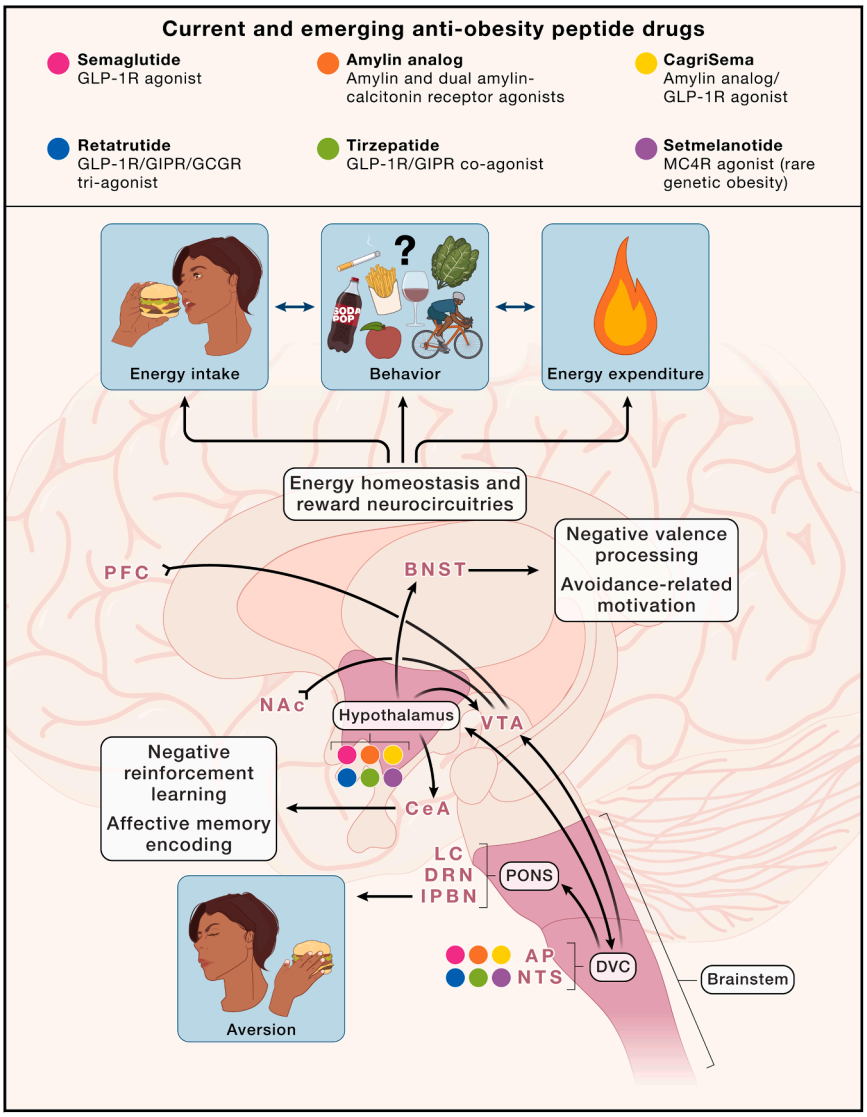


**Figure 6. Brain-targeting anti-obesity peptide drugs**

Schematic illustration of current and emerging peptide-based anti-obesity medications and their proposed central mechanisms of action. These drugs are thought to act via access to circumventricular organs and adjacent regions, such as the area postrema (AP) and arcuate nucleus (ARC), where they engage neurons that project broadly to brain regions regulating both energy homeostasis, aversion and reward processing, and complex behavior.

reach regions beyond the CVOs and neighboring areas, such as the ARC and NTS.[255,393,394] As a result, areas like the hippocampus, PFC, and VTA likely remain out of reach, meaning that the influence of GLP-1R agonists on motivational circuits, memory, and cognition are indirectly mediated through the CVOs and adjacent regions (Figure 6).

The weight-lowering benefits of GLP-1R agonists are primarily driven by a reduction in food intake (Figure 6). Early studies using loss-of-function mouse models suggested that the hypothalamus plays a key role in mediating the appetite-suppressing effects of GLP-1R agonists.[255,395] Recent research continues to support the involvement of the hypothalamus,[205,396–398] but the bulk of evidence points to GLP-1Rs on glutamatergic neurons in the DVC as one of the primary mediators of the appetite- and body weight-lowering effects of long-acting GLP-1R agonists[245,399] (Figure 6). While there is consensus that GLP-1Rs in the AP mediate the aversive effects of these drugs,[400] there is dissent about whether GLP-1Rs in the NTS are critical for their long-term weight-lowering benefits. Some studies suggest that selectively targeting NTS GLP-1Rs, as opposed to AP GLP-1Rs, could potentially improve drug tolerability without compromising efficacy.[253] However, other work emphasizes that AP GLP-1Rs drive both the satiating and aversive effects, making it difficult to separate the anorectic and aversive responses by targeting GLP-1Rs in distinct brainstem areas or cell types, at least with our current understanding.[400]

The potential of gut hormone mimetics in regulating motivation, reward, and addiction has gained increasing research interest. In preclinical models, GLP-1R agonists have been shown to influence macronutrient preference, reduce interest in palatable foods, and diminish the appeal of drugs of abuse.[393,401–403] These effects have been linked to the ability of GLP-1R agonists to suppress dopamine activity in the NAc, which is triggered by drugs or palatable foods.[404–406] The incretin-induced suppression of dopamine activity is likely indirect, as GLP-1R agonists are unlikely to access brain regions within the mesolimbic reward pathway following peripheral administration. Instead, GLP-1R activation in regions such as the NTS,[407] lateral septum,[322,403] and central amygdala[408,409] has been proposed as critical hubs through which these drug-induced actions are propagated to mesolimbic sites. Real-world data suggest that semaglutide and tirzepatide prescriptions are linked to a lower risk of opioid and alcohol use disorders,[402,410] supporting ongoing trials investigating GLP-1R agonists for treatment of addiction. For example, findings from a phase 2 trial showed that weekly injections with low-dose semaglutide reduce alcohol cravings and consumption, as well as the frequency of heavy drinking days in adults with alcohol use disorder symptoms.[411]

## Neural pathways mediating weight loss by GIP receptor targeting

Emerging evidence indicates that long-acting GIPR agonists reduce food intake and body weight by directly modulating

central GABAergic neurons.[257,412] Chemogenetic activation of GIPR-expressing cells in the hypothalamus or DVC reduces feeding. However, local genetic ablation of GIPRs in hypothalamic nuclei does not completely diminish the weight-lowering efficacy of incretin mimetics.[267,413] While both GLP-1R and GIPR agonism indirectly inhibit AgRP neuron activity, recent findings indicate that GIP, but not GLP-1, is essential for nutrient-mediated inhibition of AgRP neurons, suggesting distinct physiological mechanisms of action of these two gut hormones in the CNS.[414] Supporting this notion, single-cell RNA sequencing of hypothalami from both mice and humans has revealed that while GLP-1R-expressing cells in the hypothalamus are distributed between neurons and non-neuronal cells, a large part of GIPR-expressing cells are pericytes, oligodendrocytes, and vascular smooth muscle cells.[196,197,415,416] This distinct cellular expression pattern of the receptor, combined with the emerging evidence of diverging mechanisms of action in the brain, suggests that molecular synergy may drive the superior weight loss efficacy of GLP-1R and GIPR co-agonists. Interestingly, GIPR agonism has been shown to alleviate some of the aversion associated with GLP-1R agonism in mice[259] and humans.[417] This may be explained by the fact that GIPRs are expressed on GABAergic AP neurons, raising the possibility that GIPR agonism may enhance the inhibitory input onto glutamatergic AP GLP-1R neurons.[234] Notably, GIPR antagonism does not seem to worsen GI adverse events in clinical trials with maritide.[410]

Emerging evidence shows that GIPR antagonism potentiates GLP-1R agonist-induced weight loss through differential neuronal mechanisms than GIPR agonism.[418,419] While both whole-body and CNS deletion of GIPRs disrupts the body weight and food intake lowering effects of GIPR-blocking antibodies, deletion in the peripheral nervous system or specifically in GABAergic neurons does not impair its efficacy.[418,419] Furthermore, single-nucleus RNA sequencing of the DVC found that GIPR antagonism, but not agonism, induces transcriptional changes closely resembling GLP-1R agonism.[419] In line with this observation, the weight-lowering effects of GIPR-blocking antibodies vanish in both global GLP-1R and GIPR knockout mice, indicating that GIPR antagonism not only depends on functional GIPR signaling but also on functional GLP-1R signaling.[419] Supporting this idea, GIPR antagonists appear to primarily reduce food intake when used alongside GLP-1R therapy.[420,421]

## Neural pathways mediating weight loss by amylin receptor agonism

AMYR agonists suppress food intake by engaging AMYRs in the CNS. AMYRs are heterodimeric complexes formed by the CALCR combined with a RAMP1, RAMP2, or RAMP3 protein. Fluorescently tagged amylin accumulates in the AP and ARC of mice after systemic administration,[422] and administration of amylin directly into these brain regions lowers food intake in rats.[423,424] CALCR neurons in the AP are glutamatergic, and chemogenetic activation of these neurons robustly lowers food intake in rats,[234,245] pointing to an importance of the AP in mediating the anorectic effects of amylin.[125] As already introduced earlier, the AP is implicated in nausea-associated behaviors, including those elicited by GLP-1R agonists, yet chemogenetic activation of AP CALCR neurons fails to evoke conditioned taste aversion in mice.[249] However, in clinical trials, the amylin analog, cagrilintide, did not improve the tolerability of semaglutide but instead dose-dependently increased GI adverse effects.[397]

Amylin also plays a role in the ARC. For example, *in vivo* monitoring of calcium dynamics showed that high systemic doses of amylin inhibit AgRP neurons,[158] while the effects of amylin on POMC neuron excitability remain unconfirmed. Electrophysiological studies further showed that amylin directly suppresses the activity induced by ghrelin in the hypothalamus,[425] and optogenetic stimulation of AgRP neurons can override the anorectic effects of amylin.[263] Notably, amylin was one of the first hormones reported to restore leptin actions in obesity, supported by both preclinical and clinical data.[426] In extension, exogenous amylin is reported to exert neurotrophic effects on early postnatal brain development, promoting axonal outgrowth of POMC and AgRP neurons to the PVN.[427] The current literature on the actions of amylin in the brainstem and hypothalamus suggests that the weight loss effects of AMYR agonists may largely implicate satiation via AP neurons.

## Targeting neuroplasticity for sustained weight loss

The advancement of incretin-based therapies for weight loss has revolutionized the treatment of obesity. However, it has become increasingly evident that this drug class lacks durable effects on body weight after treatment cessation, underscoring the distinct challenges of achieving initial weight loss versus maintaining it. Addressing this gap and developing treatments to sustain long-term weight loss represents a growing unmet medical need.

In this context, ciliary neurotrophic factor (CNTF) serves as an early example of a molecule with sustained weight-lowering properties.[428] Interestingly, both rodents[429,430] and humans[431] were observed to maintain reduced body weight for weeks to months after treatment cessation. Follow-up studies revealed that rat CNTF acts in the hypothalamus to promote neurogenesis, a mitogenic effect essential for its long-term weight-reducing effect.[430] However, this mechanism remains uncertain, as another study observed only limited neurogenesis in the hypothalamus 3 weeks after 1 week of central administration of a human CNTF analog.[432] Instead, CNTF has been linked to hypothalamic microglial activation and astrogliosis in the ARC[433]—changes that may reflect neuroinflammatory processes but could also indicate neurostructural remodeling. Several studies have emphasized an overlap between CNTF and leptin signaling, yet the sustained weight-lowering effects of CNTF appear to operate independently of the leptin-melanocortin pathway.[428,429,434] While attempts to harness CNTF for obesity treatment were hindered by the development of neutralizing antibodies, investigating the mechanisms underlying CNTF's durable weight-lowering effects offers a promising avenue for gaining inspiration to develop new therapies for maintaining weight loss.

In addition to CNTF, several other neurotrophic factors have been linked to obesity, including BDNF, nerve growth factor (NGF), vascular endothelial growth factor (VEGF), IGF-1, and glial cell-derived neurotrophic factor (GDNF). Among these, BDNF is arguably the most extensively studied in the context of energy

homeostasis and obesity. However, in contrast to CNTF, which has primarily gained attention for its pharmacological potential, human genetic studies have found that mutations in *BDNF* and its receptor, tropomyosin receptor kinase B (*TRKB*), predispose to obesity,[435–437] attesting that this pathway may be crucial for the physiological regulation of energy homeostasis. Brain administration of recombinant BDNF suppresses appetite and increases energy expenditure to lower body weight in preclinical models of obesity and diabetes, emphasizing a therapeutic potential for BDNF mimetics. However, diverging pharmacological results have been observed in non-human primates, i.e., central administration leads to anorexia while peripheral administration stimulates food intake.[438] Nonetheless, as a neurotrophic factor recognized to promote hippocampal neuroplasticity, it is plausible that BDNF influences energy balance by modulating synaptic plasticity in feeding regions, such as the hypothalamus and brainstem.

Canonical metabolic hormones, such as ghrelin and leptin, are also known to influence synaptic activity and organization within hypothalamic neurocircuits that regulate feeding behavior.[358] For example, leptin replacement therapy in leptin-deficient mice normalizes synaptic density, highlighting synaptic plasticity as a potential regulatory mechanism through which hormones modulate energy homeostasis.[358] Incretin-based drugs have also been reported to influence synaptic plasticity, in association with changes in BDNF levels and synaptic markers, including postsynaptic density protein 95 (PSD-95).[439,440]

A key unresolved challenge is uncovering the mechanisms that enable sustained weight loss and appropriately counteract the neuroendocrine signaling and brain circuits that increase appetite or decrease energy expenditure to drive weight regain. CNTF presents one of the most promising frameworks for achieving this, underscoring the potential of further investigating hypothalamic neuroplasticity as a pathway for innovative and durable weight normalization strategies.

### NMDA receptor targeting for treatment of obesity

The rise of GWAS and advancements in human genetics have uncovered key insights into obesity biology and thus brought about anticipation for leveraging this to develop novel therapeutics.[441] Notably, several genes involved in glutamatergic signaling and NMDAR-mediated neuroplasticity have been linked to variations in BMI.[70] A functional role for NMDAR-mediated synaptic plasticity in hypothalamic feeding control has been demonstrated in rodent models, where inhibition of glutamatergic signaling in hunger-promoting AgRP neurons suppresses counter-regulatory hyperphagia in response to fasting.[164] Also, attempts to pharmacologically leverage NMDAR antagonism for obesity treatment have shown signs of promise, indicated by addressing binge eating and antipsychotic-induced weight gain in humans.[442,443] However, the ubiquitous expression of NMDARs in the CNS has made it difficult to achieve therapeutic efficacy that does not produce adverse effects.[444,445]

As an alternative, pharmacological modulation of NMDAR scaffolding proteins, such as PSD-95 and protein interacting with C kinase 1 (PICK1), provides a novel way to modify postsynaptic signaling beyond traditional receptor-targeting drugs. These proteins regulate glutamate receptor function, synaptic plasticity, and receptor trafficking within the postsynaptic density and are genetically linked to human obesity.[446] Peptide inhibitors targeting PSD-95 and PICK1 have demonstrated efficacy in preclinical models by reducing body weight and delaying weight regain compared with GLP-1R agonists or caloric restriction after treatment cessation.[446]

While the prolonged weight loss from NMDAR modulation is promising, its weight-lowering effects are far less prominent compared with incretin-based therapies. To overcome this, combining NMDAR antagonism with GLP-1R agonism in a peptide-drug conjugate has emerged as a promising strategy.[445] This approach seeks to enhance weight loss by targeting both neuroplasticity and appetite-regulating pathways, specifically in GLP-1R-positive cells, while minimizing the adverse effects associated with broad NMDAR antagonism across the entire CNS. GLP-1-directed delivery of the NMDAR antagonist dizocilpine (MK-801) to cells harboring the GLP-1R has been shown to effectively reverse obesity in preclinical models, with significant changes in the hypothalamic transcriptome and proteome, particularly in pathways linked to neuroplasticity and glutamatergic signaling. However, further research is required to better understand the interaction between NMDAR modulation and GLP-1R signaling, as well as to assess the long-term metabolic effects and safety. Finally, the implications of targeting modulators of synaptic plasticity to specific neuronal populations extend beyond obesity and could unveil new treatment avenues for a wide range of brain disorders.

## CONCLUSIONS AND FUTURE PERSPECTIVES

The brain is a master regulator of energy homeostasis, seamlessly integrating physiological and environmental signals to ensure optimal fuel availability for the body. Evolutionarily conserved neurocircuitry not only safeguard against starvation but also dynamically adapt to the ever-changing energy demands of growth, reproduction, and immune challenges. Furthermore, the inherently rewarding nature of food introduces a layer of complexity, intertwining homeostatic energy needs with motivational drives. Yet, despite significant advances in mapping neuroendocrine communication pathways and brain circuits that govern energy balance, the escalating global obesity epidemic—shaped by genetic predispositions and modern environmental factors—underscores the pressing need for continued research into the neurobiological control of energy homeostasis and the pathological hallmarks underlying obesity pathogenesis.

Recent advances in neurobiology, powered by transformative technologies such as functional circuit mapping, single-cell sequencing, and real-time imaging, have begun to unveil intricate networks spanning the hypothalamus, brainstem, and higher-order regions that orchestrate feeding behavior, energy expenditure, and fuel distribution. Together these findings have highlighted the brain's remarkable plasticity in adapting to metabolic demands, continuously reshaping the strength and efficacy of neurocircuits to regulate energy homeostasis. However, the precise temporal and spatial dynamics of these plastic changes remain only poorly understood. Future research should aim to further elucidate these dynamics, with an emphasis on

identifying the nodes and mechanisms most amenable to therapeutic intervention.

While we are still grappling to understand the pathogenesis of obesity, breakthroughs in medicinal chemistry have transformed the pharmacological treatment of obesity. The development of long-acting incretin-based drugs, notably GLP-1R agonists and next-generation combination therapies, has not only improved weight management but also demonstrated broader cardiometabolic benefits. Nonetheless, challenges persist in ensuring long-term efficacy and in overcoming adaptive, counter-regulatory mechanisms that may diminish treatment effects over time.

Moving forward, a synergistic approach that integrates mechanistic insights into the physiological regulation of body weight and neurobiology of feeding with innovative pharmacological strategies is essential. As we deepen our understanding of the neural circuits governing energy homeostasis—including their plasticity, spatial organization, and integration of peripheral signals—we move closer to identifying precise nodes for therapeutic intervention. Translating these discoveries into targeted therapies will be key to achieving more effective and durable weight loss strategies. However, given the complexity of obesity pathogenesis, no single sector is likely to address this challenge alone. Meaningful progress will require interdisciplinary collaboration between academia and the pharmaceutical industry to accelerate the translation of basic research discoveries into clinical solutions. The integration of neuroscience, biotechnology and drug development has the potential to deliver more targeted, durable, and individualized treatments for obesity and its cardiometabolic comorbidities.

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## AUTHOR CONTRIBUTIONS

V.B.I.J., J.O.P., J.L., H.F., and C.C. wrote and edited the manuscript draft. V.B.I.J. drafted the figures. V.B.I.J., J.O.P., J.L., H.F., C.V.M., and C.C. reviewed and edited the figures. V.B.I.J., J.O.P., C.V.M., and C.C. initiated the work. V.B.I.J., J.O.P., J.L., H.F., and C.C. further conceptualized the work. V.B.I.J., J.O.P., J.L., H.F., C.V.M., and C.C. reviewed and edited the work. V.B.I.J administered the project with supervision from J.O.P., J.L., H.F., and C.C.

## DECLARATION OF INTERESTS

C.C. and J.P. are co-founders of Ousia Pharma, a biotech company developing therapeutics for the treatment of obesity.

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