



# Neuroendocrine regulation of appetite and energy balance in metabolic disorders

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## ABSTRACT

The physiological control mechanisms that govern appetite and energy balance function through neuroendocrine systems that link central nervous system functions to peripheral organ activities and hormonal distribution pathways. The hypothalamus operates as the main control center, which processes metabolic information from hormones like leptin, insulin, ghrelin, and gut-derived peptides to govern both eating and energy use. People consume food through homeostatic processes, which control appetite together with non-homeostatic processes, which include reward pathways and circadian rhythms. The body develops metabolic disorders like obesity, type 2 diabetes, and cachexia because these systems experience dysregulation. Central-peripheral communication breakdowns occur because of chronic energy surplus and inflammation, together with hormonal resistance. People establish their feeding behavior patterns through reward-related dopaminergic signaling, circadian misalignment, and sex hormone fluctuations. Researchers have discovered that neuroinflammation, genetic, epigenetic factors, and newly identified neuropeptides all contribute to the metabolic diseases that they study. Therapeutic strategies that target neuroendocrine pathways, which include GLP-1 receptor agonists, melano-cortin receptor agonists, and bariatric surgery, demonstrate potential to restore appetite control and enhance metabolic health. This study explains how neuroendocrine systems control appetite and how metabolic disorders disrupt these regulatory processes while identifying new therapeutic possibilities and future research needs in metabolic neuroscience.

## 1. Introduction

Energy homeostasis occurs when individuals maintain their body weight through stable energy balance, which results from their energy consumption from food and their energy output through base metabolic functions, physical movements, and body heat production (Roh et al., 2016; Tran et al., 2022). The system operates under strict control because multiple brain regions, especially the hypothalamus, interact with peripheral organs like the liver, pancreas, adipose tissue, and muscle to process hormonal signals, which the nervous system uses to detect and react to changes in nutrient supply as well as energy consumption (Jais and Brüning, 2022). Mitochondria potentially become central operatives in the energy trade situation at the cellular level to accommodate the metabolic needs (Yu and Pekkurnaz, 2018). The liver

controls body energy balance through its glucose and lipid metabolic functions, which it uses to send out hepatokines to communicate with all other body tissues (Jensen-Cody and Potthoff, 2021). The disruption of energy homeostasis leads to the development of metabolic diseases, which include obesity, type 2 diabetes, and fatty liver disease (Chapelot and Charlot, 2019). The brain uses nutritional signals, hormonal signals, and energy storage information to decide when to eat, how much food to consume, and how much energy to burn, while the body clock and interorgan communication pathways work together to create precise control of these processes (Roh et al., 2016). Maintaining energy homeostasis is therefore essential for health, as its failure underlies many chronic metabolic disorders (Furlan and Petrus, 2023).

The brain, endocrine system, and peripheral organs use their communication system to control neuroendocrine and peripheral body

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systems to maintain body balance. The hypothalamus functions as a neuroendocrine control center that produces hormones that target the pituitary gland and enter the bloodstream to control body organs while managing stress response, metabolic function, and body fluid regulation (Makrygianni and Chrousos, 2023; Astiz et al., 2019). The brain uses both neural pathways through the autonomic nervous system together with hormonal signals to control immune responses, glucose metabolism, and other essential body functions in the liver, adipose tissue, and intestinal tract (Chan et al., 2023; Lin et al., 2021). Peripheral organs send feedback through hormonal and cytokine pathways to the central nervous system, which uses this information to adapt to changes in body status (Zhang et al., 2020). The hypothalamo-neurohypophyseal system functions as a specialized neuroendocrine circuit, which simultaneously regulates central behaviors and peripheral physiological processes through its dual functional ability (Valstad et al., 2017). Circadian rhythms illustrate the coordination, whereby central clocks in the brain integrate peripheral clocks in organs to sustain the daily physiological cycles (Selcho et al., 2017). Extracellular vesicles and neuropeptides enable cell communication through their ability to cross the blood-brain barrier while delivering stress and metabolic signals. The health impact of neuroendocrine and peripheral network disruptions manifests through their role in developing metabolic disorders, immune system disorders, and psychiatric disorders (Palamiuc et al., 2017).

The metabolic disorders like obesity, type 2 diabetes T2D and cachexia result from severe energy balance disturbances and breakdowns in inter-organ communication. The excessive energy intake in obesity and T2D leads to adipose tissue dysfunction, low-grade systemic inflammation, and insulin resistance, which results in hyperglycemia and dyslipidemia and additional metabolic disorders (Rodén and Shulman, 2019; Varra et al., 2024). The normal signaling system between the brain, liver, muscle, and pancreas is disrupted because dysfunctional fat tissue produces altered adipokines and inflammatory cytokines, which impair central-peripheral coordination (Divella et al., 2022). The insulin resistance and metabolic inflexibility of these conditions develop through two processes, which involve mitochondrial dysfunction and epigenetic alterations that change mitochondrial DNA methylation patterns (Rautenberg et al., 2022). Cachexia develops in cancer and chronic disease patients because their bodies waste energy while they lose both muscle and fat despite getting enough food, which occurs because of whole-body inflammation, elevated catabolic signals, and disturbed body clock functions (Ma et al., 2021). Both obesity/T2D and cachexia share features of metabolic dysregulation, but obesity and T2D show energy storage together with insulin resistance, whereas cachexia manifests through continuous tissue loss and augmented energy use (Porporato, 2016). The neuroendocrine and peripheral interaction mechanisms that cause these disorders must be understood because it enables researchers to create specific treatments that will help restore metabolic balance and enhance patient health.

The neuroendocrine mechanisms that control appetite and energy balance, and their alterations during metabolic diseases like obesity, type 2 diabetes, and cachexia, will be presented as the main content of our review. This review demonstrates how feeding behavior regulation depends on homeostatic and non-homeostatic mechanisms through current scientific understanding of hypothalamic pathways, peripheral hormonal signals, the gut-brain axis, reward systems, and circadian rhythms. The study presents a detailed analysis of essential molecular and physiological pathways that control appetite, the effects of neuroendocrine dysfunction on metabolic health, and new therapeutic methods that target these systems. The review presents current knowledge about neuroinflammation, genetic, and epigenetic control mechanisms, and newly discovered neuropeptides, which help guide future studies in metabolic neuroscience research.

## 2. Overview of energy homeostasis

Energy homeostasis defines a biological system that controls energy consumption and energy output, which operates as the fundamental mechanism for body weight management and metabolic function preservation. The hypothalamus serves as the central control system for this balance because it processes hormonal signals from peripheral body systems, which include leptin and insulin together with glucose, fatty acids, and nutrient information (Huang and Xiao, 2018). Dietary reports are used to assess energy intake, but they show low reliability, especially with obese people, while energy expenditure measurement can be done accurately through indirect calorimetry methods (Perseghin, 2001). Energy balance requires assessment of both caloric intake and caloric expenditure while considering physiological and environmental factors that affect these energy balance systems. The brain needs a lot of energy because it processes information through aerobic pathways, which shows how energy balance must be maintained for proper brain and behavioral functioning (Vergara et al., 2019). This helps us address the disorders of obesity and its metabolic implications.

The central nervous system (CNS) and peripheral organs, which include adipose tissue, the pancreas, and the gut, operate through continuous double-sided communication to maintain energy balance. The hypothalamus functions as the central point for the brain to receive hormonal and nutritional signals, which the body uses to determine its energy levels, to regulate food intake, energy burning, and metabolic processes (Puentes-Ruiz and Jais, 2022).

Fig. 1 diagrammatic illustration of the hypothalamus's two-way communication with peripheral metabolic organs, such as the pancreas, liver, gut, skeletal muscle, and adipose tissue. Leptin, insulin, ghrelin, and GLP-1 are examples of hormones that communicate metabolic state to the brain, which controls food intake and energy expenditure. Adipose tissue functions as an endocrine gland that produces hormones and cytokines to transmit energy storage information to the brain. The central nervous system controls fat storage and release through its neural pathways which include the autonomic nervous system (Hyun and Sohn, 2022). The pancreas uses insulin and its other hormones to send signals to the central nervous system, which controls glucose metabolism and appetite regulation, and the pancreas receives neural signals that control its hormone production (Ruud et al., 2017). The gut transmits hunger and satiety signals to the brain through hormonal pathways and vagus nerve pathways, which help control eating patterns and meal size (Sun et al., 2023). The body uses its complex system of hormonal and neural signals to control energy intake and energy output, while any disruptions in these signals will lead to metabolic disorders that include obesity and diabetes. Table 1 shows the interconnected, allowing the brain to coordinate hormonal responses to internal and external stimuli, and disruptions can impact health and disease.

## 3. Hypothalamic control of appetite and energy expenditure

The hypothalamus has a network of nuclei that control hunger and energy use. The three main nuclei of this network system include the arcuate nucleus (ARC), the paraventricular nucleus (PVN) and the lateral hypothalamus (LH) (Lau et al., 2018). The ARC uses its main sensor ability to detect metabolic and hormonal signals which circulate in the body, including leptin, insulin and ghrelin, to create a system that controls food intake and energy conservation (Yousefvand and Hamidi, 2022). The ARC contains two different types of neurons which produce orexigenic signals through NPY and AgRP, and anorexigenic signals through POMC and CART to their respective projection targets in the PVN and LH to establish opposing effects on appetite and metabolic processes (Yousefvand and Hamidi, 2020).

Fig. 2 shows the hypothalamic appetite regulatory circuit, emphasizing the opposing roles of NPY/AgRP and POMC/CART neurons in controlling feeding behavior and energy spending. The PVN serves as

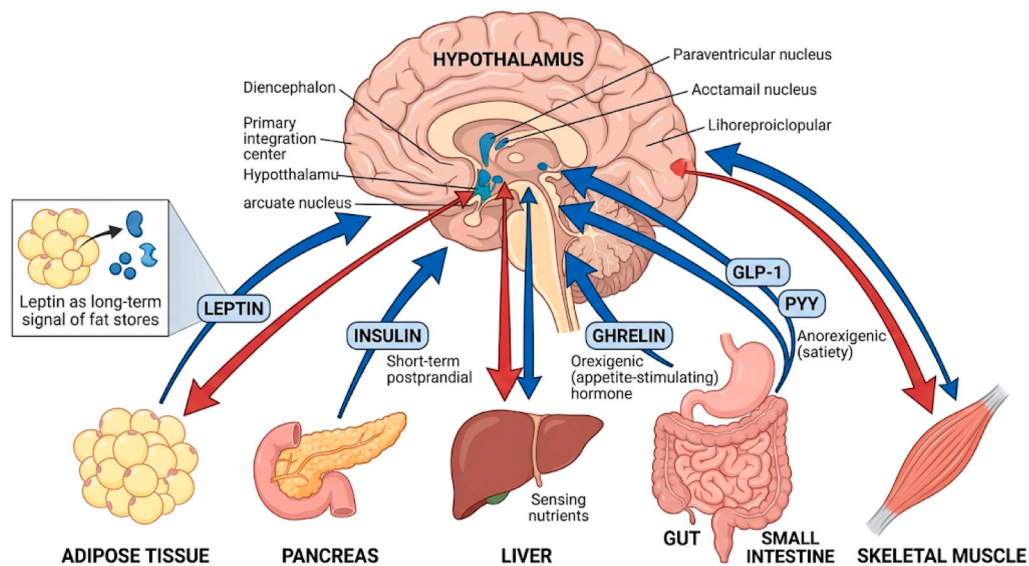


Fig. 1. Neuroendocrine communication between the brain and peripheral organs regulates energy balance.

**Table 1**  
Interconnected Brain–Hormone Signaling and Its Role in Health and Disease.

| Neuroendocrine Axis                            | Main Components                                         | Primary Function                                                                                                           |
|------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| Hypothalamic-Pituitary-Adrenal (HPA) Axis.     | Pituitary Gland, Hypothalamus, Adrenal Glands           | Regulates stress response, immune function, metabolism, and circadian rhythms via cortisol release (Sheng et al., 2021)    |
| Hypothalamic-Pituitary-Gonadal (HPG) Axis      | Pituitary Gland, Gonads (ovaries/testes), Hypothalamus, | Controls reproductive function, sexual development, and fertility via sex hormone regulation (Phumsattitpong et al., 2021) |
| Hypothalamic-Pituitary-Thyroid (HPT) Axis      | Hypothalamus, Pituitary Gland, Thyroid Gland            | Regulates metabolism, growth, and energy balance via thyroid hormone production (Van Den Berghe, 2016)                     |
| Hypothalamic-Pituitary-Somatotropic (HPS) Axis | Hypothalamus, Pituitary Gland, Liver/Body Tissues       | Governs growth and development through growth hormone and IGF-1 secretion (Van Den Berghe, 2016)                           |
| Hypothalamic-Pituitary-Prolactin (HPP) Axis    | Hypothalamus, Pituitary Gland, Mammary Glands           | Controls lactation and reproductive behaviors via prolactin release (Van Den Berghe, 2016)                                 |

the main output center which links direct input from ARC neurons to create signal that control food consumption and energy burning through the melanocortin system and MC4R-expressing neurons. The LH functions as the hunger center because it receives signals from the ARC and PVN to control feeding behavior and reward-based eating (Zhang and Van Den Pol, 2016). These nuclei establish two-way communication while their functions depend on peripheral signals to create a vital circuit which sustains energy balance. Disrupted function or connectivity of the ARC, PVN, and LH leads to abnormal appetite control and energy expenditure, resulting in obesity and metabolic disorders (Siemian et al., 2021).

The ventromedial hypothalamus (VMH), along with the ARC, PVN, and LH, is involved in controlling energy balance. In addition to controlling satiety, energy expenditure, glucose metabolism, and adaptive reactions to variations in energy availability, the VMH combines hormonal and metabolic data. The activities of ARC-based orexigenic and anorexigenic pathways are complemented by interactions between VMH neurons and other hypothalamic and peripheral metabolic circuits.

Impaired energy balance and aberrant eating behavior have been linked to VMH signaling dysfunction (Zhu et al., 2023; Loid et al., 2020).

Two functionally antagonistic neuronal groups in the arcuate nucleus (ARC) of the hypothalamus are critical for the control of hunger and energy balance. The orexigenic NPY/AgRP neurons drive food intake, energy conservation, and weight gain, and are maximally activated during an energy deficit (Krashes et al., 2016). These neurons are involved in the anabolic control of energy balance by promoting eating behavior and reducing energy expenditure (Sohn, 2015). By contrast, anorexigenic POMC/CART neurons are preferentially recruited when energy levels are sufficient. POMC neurons produce  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), which participates in catabolic control of energy balance via appetite suppression and promotion of energy expenditure (Wei et al., 2018). These two neuronal populations are also modulated by peripheral signals of the metabolic status of the body (e.g. insulin, ghrelin, leptin), allowing the hypothalamus to collect information about the energy balance of the body and to modulate food intake accordingly.

One of the major downstream pathways through which ARC neurons regulate hunger and energy expenditure is the melanocortin system. One such receptor is the melanocortin-4 receptor (MC4R), which integrates opposing signals from AgRP and POMC neurons. POMC neurons produce  $\alpha$ -MSH, which promotes satiety and increases energy expenditure by activating MC4R on second-order hypothalamic neurons, especially in the paraventricular nucleus (PVN). In contrast, AgRP inhibits  $\alpha$ -MSH-mediated receptor activation, thus facilitating food intake and energy conservation as an endogenous antagonist of MC4R (Paeger et al., 2017). Thus, while MC4R antagonism or genetic deficiency is associated with hyperphagia, decreased energy expenditure, and obesity in human and animal models, central administration of MC4R agonists enhances satiety and weight loss (Butler, 2006).

Thus, the balance between two types of neurons, which include orexigenic NPY/AgRP neurons and anorexigenic POMC/CART neurons, needs to be maintained for proper appetite control and energy usage.

4. Peripheral hormonal signals and their central integration

Peripheral hormones control appetite through their energy status signals which they send to the brain, which uses the information to control food intake and energy burning (Sahu, 2004). Leptin acts on hypothalamic neurons primarily through the long form leptin receptor (LepRb), which is highly expressed in ARC neurons. Leptin binds to

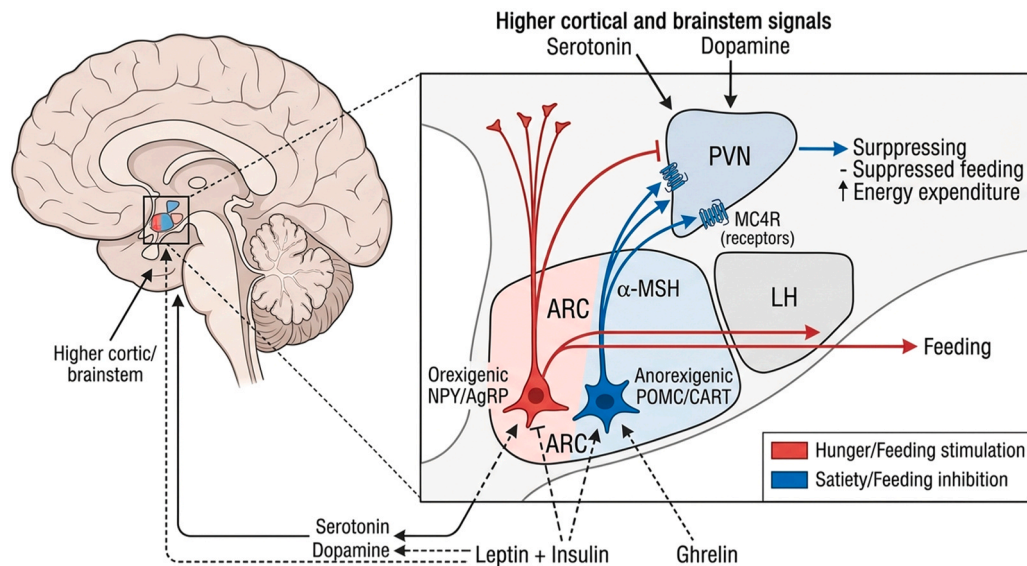


Fig. 2. Hypothalamic neural circuits regulating appetite and energy expenditure.

LepRb and activates receptor-associated Janus kinase 2 (JAK2). This causes phosphorylation and activation of signal transducer and activator of transcription 3 (STAT3). STAT3-dependent signaling inhibits NPY/AgRP neurons and activates POMC/CART activity to decrease food intake and increase energy expenditure. Negative feedback processes involving suppressor of cytokine signaling 3 (SOCS3) can lead to central leptin resistance in the setting of chronically elevated leptin levels as occurs in obesity (Tucker et al., 2024; Camilleri, 2015; Obradovic et al., 2021). The pancreatic  $\beta$ -cells produce insulin, which can enter the brain through the blood-brain barrier to create appetite control through its action on hypothalamic circuits (Hewson et al., 2002). The condition of brain insulin resistance which occurs in obesity, leads to decreased anorexigenic effects of leptin and results in disrupted energy balance. Ghrelin which serves as the sole orexigenic hormone in circulation originates from stomach secretions and rises before meals to create hunger. The substance connects to NPY/AgRP neurons in the hypothalamus while it controls GH release to connect energy consumption with growth development (Steinert et al., 2017). After people eat their meals, their bodies release gut-derived hormones which include peptide YY and glucagon-like peptide-1 and cholecystokinin to create feelings of fullness. The intestinal L-cell secretions of PYY and GLP-1 reduce appetite and food consumption because they target central appetite control centers, while their combined use creates an additive effect (Vijayashankar et al., 2024). CCK which the small intestine releases functions as a well-established bodily signal of fullness which prevents stomach contents from leaving while decreasing the amount of food people eat (Park et al., 2025). The system uses hormones to create feedback mechanisms which leptin and insulin use for long-term body fat assessment while ghrelin triggers hunger and PYY, GLP-1 and CCK promote meal termination and fullness (Geary, 2004). The hormonal disruption through altered sensitivity and secretion pathways leads to leptin and insulin resistance development in obesity which creates problems for central appetite control while also driving the progression of metabolic disorders.

## 5. Gut-brain axis in appetite regulation

The gut-brain axis is involved in hunger and energy balance regulation through coordinated interactions between enteroendocrine cells (EECs), microbiota-derived metabolites, gastrointestinal hormones and neurological pathways such as vagal afferents (Barton et al., 2023). EECs are specialized epithelial cells that are found throughout the

gastrointestinal system. They detect nutrients and microbial metabolites and secrete hormones such as GLP-1, PYY and CCK to regulate appetite and food intake (Moțăiaianu et al., 2023). The hormones have two pathways to produce their effects because they function through the body's endocrine system and through direct nerve connections that use neuropods to link EECs with vagal afferent fibers which enable fast gut-brain communication (Pizarroso et al., 2021). This process requires the gut microbiota to produce short-chain fatty acids (SCFAs), particularly acetate. SCFAs activate G-protein-coupled receptors on the enteroendocrine cells to stimulate release of anorexigenic hormones (eg, GLP-1 and PYY). These gut signals communicate with the brain via the vagus nerve and circulation to modulate hypothalamic neuropeptide activity and appetite regulation (O'Riordan et al., 2022; Asadi et al., 2022). The hormones send their signals to the brain through the vagus nerve and blood circulation, which leads to changes in hypothalamic neuropeptide production and appetite control. The SCFAs can travel through the blood-brain barrier to directly influence the production of central neuropeptides and brain functions (Asadi et al., 2022). The microbiota alters bile acids which become another type of metabolites that activates EECs through their gut-brain communication pathway which produces metabolic control effects (Masse and Lu, 2023). The vagus nerve serves as an essential pathway that transmits hormonal signals from the gastrointestinal system to the brainstem and hypothalamus, which connects peripheral and central appetite control systems. Enteroendocrine cells (EECs) can create direct synaptic links to vagal afferents, which enables them to send particular signals at high speeds. The interruption of this signaling pathway through vagotomy results in changes to appetite control mechanisms that promote weight gain (Longo et al., 2023).

Dysbiosis, which means an uneven distribution of gut bacteria, occurs in individuals with metabolic diseases like obesity and type 2 diabetes. The production of short-chain fatty acids and bile acids gets disrupted by dysbiosis, which also harms EEC function and alters gut hormone levels, leading to problems in gut-brain communication, increased hunger, and metabolic imbalance (Wang et al., 2020). The scientific community has developed new methods to treat metabolic disorders, which involve restoring microbial balance and regulating EEC-microbiota-vagal pathways.

## 6. Reward system and hedonic eating

Dopaminergic reward pathways drive hedonic "wanting" of palatable

foods. The pathways function as addiction precursors that operate together with hypothalamic centers that control body weight. The pathways undergo measurable changes because of continuous high-fat and sugar food consumption, which results in obesity development. Mesolimbic dopamine neurons in the ventral tegmental area (VTA) project to the nucleus accumbens (NAc), amygdala and prefrontal cortex to encode the motivational value of palatable food and its prediction error (Coccurello and Maccarrone, 2018). Palatable high-fat/high-sugar foods increase dopamine release in NAc through the same mechanism as drugs of abuse, which leads to food addiction symptoms that include cravings, increased consumption of food, and loss of control (Leung and Lutfy, 2025). Chronic overconsumption leads to decreased dopamine D2 receptor signaling in reward circuits, which results in a "hypodopaminergic" state that decreases reward sensitivity while driving people to eat more food to achieve their previous level of pleasure (Yu et al., 2022). Chronic overeating causes dopamine D2 receptors in reward pathways to become less active which leads to a state of reduced reward sensitivity. This results in increased food intake because people need to eat more to feel the same pleasure (Wu et al., 2017). The post-mortem and imaging results demonstrate that people with obesity have decreased dopamine transporter and synthesis markers together with reduced dopamine response to food, which supports the existence of reward deficiency (Gupta et al., 2020). Eating in a hedonic manner can override satiety, leading to binge-like or compulsive eating (Agustí et al., 2021). Rewards and homeostatic systems overlap anatomically and functionally rather than being separate (Rossi and Stuber, 2018). The hypothalamic nuclei, particularly the lateral hypothalamus and arcuate nucleus, transmit orexin, MCH, GABA, and glutamate pathways to the VTA/NAc, which enables energy state signals, leptin, insulin, and ghrelin to modify dopamine-driven motivation (Wallace and Fordahl, 2022). Conversely, dopaminergic and cortical reward circuits feed back to the hypothalamus and extended amygdala to alter feeding drive, and cue-triggered seeking (Alhadeff et al., 2019). The hormones leptin, insulin, ghrelin, GLP-1 and nesfatin 1 operate in both VTA and NAc and in the hypothalamus to connect homeostatic and hedonic control through their shared biochemical pathways (Kim et al., 2026). Chronic high-fat/sugar diets reduce tonic dopamine release, alter phasic dopamine signaling, and downregulate D2-related synaptic and gene markers in NAc and midbrain, changes linked to increased caloric intake, binge-like behavior, and weight gain (Plaza-Briceño et al., 2023). These diet-induced dopamine alterations are interpreted as both a driver and consequence of obesity, locking individuals into a "delicious circle" where weakened reward and disrupted homeostatic signaling jointly promote persistent hedonic overeating (Leung and Lutfy, 2025). Dopaminergic reward pathways encode the motivational pull of palatable foods, and with repeated exposure can shift into an addiction-like, hypodopaminergic state that encourages overeating. These reward circuits are tightly interwoven with hypothalamic homeostatic centers via shared hormones and projections. The integrated network of the body gets disrupted through the consumption of highly palatable energy dense diets which leads to both compulsive eating and obesity.

## 7. Circadian rhythms and appetite regulation

Circadian timing systems control our eating times, metabolic food processing, and hunger hormone levels. Disruption (sleep loss, shift work, mistimed meals) impairs this coordination and promotes metabolic risk. The suprachiasmatic nucleus (SCN) is the master biological clock and light exposure is the primary time-giving signal to the SCN. It coordinates the daily cycles of eating and fasting, activity and relaxation, waking and sleeping. These circadian eating patterns are altered and the typical temporal arrangement of energy expenditure is compromised when the SCN is experimentally disrupted in mice (Pickel and Sung, 2020). SCN outputs (autonomic, hormonal, and behavioral) synchronize clocks in hypothalamic appetite centers (ARC, PVN, DMH) and peripheral tissues, aligning hunger with the appropriate active

phase (Panda, 2016). Core clock genes (CLOCK, BMAL1, PER, CRY) form transcriptional loops present in SCN and metabolic tissues, rhythmically regulating thousands of metabolic genes (Schrader et al., 2024). Hypothalamic clocks in ARC and PVN generate daily variations in hunger, leptin signaling, and energy expenditure (Schrader et al., 2024). Genetic disruption of these clocks or of BMAL1 in the SCN alters AgRP/NPY and POMC expression, impairs energy balance, and promotes obesity phenotypes that can be rescued by restoring BMAL1 or imposing time-restricted feeding (Chaix et al., 2019). Sleep deprivation, circadian misalignment, and shift work disrupt both central and peripheral biological clocks which results in increased obesity risk (Maury, 2019). Human circadian misalignment studies show that it decreases both leptin and PYY levels while increasing postprandial active ghrelin levels which results in higher energy consumption and stronger desire for high-calorie foods (Chaput et al., 2023). Sleep loss and circadian disruption also alter leptin receptor sensitivity and clock gene expression in the hypothalamus, contributing to leptin resistance and dysregulated appetite (Halder and Melkani, 2025). Endocannabinoids and ghrelin display circadian rhythms which increase through sleep deprivation to boost appetite and sweet high-calorie food consumption (Du et al., 2024). The SCN establishes all daily feeding times whereas circadian clock genes within the hypothalamus and metabolic organs precisely regulate both hunger signals and energy consumption patterns. Circadian misalignment from sleep loss, shift work, or mistimed meals disrupts leptin, ghrelin, and their downstream signaling pathways which leads to decreased ability to control appetite and higher risk of developing metabolic diseases.

## 8. Neuroendocrine dysregulation in obesity

The central leptin resistance in obesity involves several mechanisms. First, leptin transport across the blood–brain barrier may be impaired, resulting in reduced accessibility of circulating leptin to hypothalamic neurons despite high peripheral leptin concentrations. Secondly, chronic hyperleptinemia can lead to overstimulation of leptin-dependent STAT3 signaling and negative feedback via SOCS3. Increased SOCS3 activity blocks leptin signaling, and can also block insulin signaling. Finally, the obesity-induced hypothalamic inflammation and endoplasmic reticulum stress also prevent further leptin and insulin responsiveness in appetite-regulating neurons (Obradovic et al., 2021; Sonnefeld et al., 2023). Insulin activates POMC neurons in the mediobasal hypothalamus while it disables AgRP/NPY neurons to decrease food consumption and enhance glucose and lipid metabolism (Dimitri, 2022). Diet-induced central insulin resistance disrupts this balance, leading to hyperphagia, obesity, and systemic insulin resistance (Chen et al., 2024). Tanycyte insulin receptors gate insulin access to arcuate neurons; loss of this signaling or palatable diet-induced tanycyte insulin resistance increases AgRP activity and impairs systemic insulin sensitivity (Pornie Kumar et al., 2021). High-fat diets rapidly induce hypothalamic gliosis, activation of NF- $\kappa$ B/JNK and chemokine pathways, and microglial/mast-cell activation before overt weight gain (Tian et al., 2025). The neuroinflammation results in ER stress which leads to neuronal damage and selective damage of POMC neurons, causing an imbalance that increases orexigenic drive while decreasing energy expenditure (Gaspar and Velloso, 2018). The inflammatory process inhibits leptin and insulin signaling through JAK/STAT and PI3K-Akt pathways in these neurons which leads to increased appetite control problems and obesity development (Prévost et al., 2025). Leptin and insulin normally control food consumption while they help the body spend energy through the hypothalamic POMC/AgRP networks. Obesity causes central hormone resistance because dietary hypothalamic inflammation ER stress and barrier/access mechanism changes lead to central hormone resistance for both structural and functional damage to key brain nuclei, which results in permanent excessive appetite and reduced metabolic control.

9. Appetite dysregulation in Type 2 diabetes

The integrated gut-brain-pancreas axis relies on incretin hormones, leptin and insulin together with other appetite-related signals. Type-2 diabetes (T2D) disrupts this axis which results in impaired functioning of both appetite control and glucose homeostasis systems. After meals, intestinal L and K cells release GLP-1 and GIP which enhance insulin secretion through glucose stimulation while they represent the main source of postprandial insulin release that maintains blood glucose levels (Boer and Holst, 2020). GLP-1 causes weight loss by its ability to slow gastric emptying while reducing appetite and food consumption. GIP functions mainly to increase insulin secretion and create fat storage while providing only limited short-term appetite suppression in humans (Nauck and Müller, 2023). The incretin effect is significantly diminished in T2D because GIP loses its ability to produce insulin and  $\beta$  cells become less responsive to both incretins and GLP-1 secretion which can decrease in particular during obesity (Holst et al., 2021). The hyperglycemic condition leads to incretin resistance which disrupts the normal glycolytic process in both enteroendocrine cells and beta cells according to proposed mechanisms (Rabbani and Thornalley, 2024). The hypothalamic circuits receive energy sufficiency signals from both adipose tissue leptin and insulin to decrease appetite while increasing insulin sensitivity (Rausch et al., 2025). In obesity/T2D, high leptin with central leptin resistance leads to hyperphagia together with weight gain plus inflammation which results in worsened insulin resistance (Ernesto et al., 2025). The experimental T2D condition demonstrates disrupted hypothalamic leptin signaling because the disease results in increased orexigenic NPY/AgRP pathways together with decreased anorexigenic POMC/CART pathways, which exercise can partially restore to its normal state (Khoramipour et al., 2023). Impaired incretin action together with insulin-leptin resistance causes people to eat more food which results in less feeling full and increased body fat and worse post-meal blood sugar control that strengthens their T2D metabolic disorder (Grespan et al., 2022). The combined effects of impaired GLP-1/GIP signaling and insulin-leptin axis malfunction in T2D lead to appetite and glucose control problems which result in excessive eating, weight increase and worsening insulin resistance; metabolic balance can be achieved through therapies that restore incretin and leptin-insulin signaling.

10. Anorexia and cachexia in metabolic diseases

Chronic metabolic diseases lead to anorexia and cachexia because cytokines cause brain changes which disrupt the neuroendocrine systems that control both appetite and metabolism. The persistent elevation of inflammatory cytokines IL-6, TNF- $\alpha$ , IL-1 $\beta$  and IL-8 in cancer cachexia establishes a connection between weight loss and anorexia (Paval et al., 2022). The long-term administration of cytokines could develop cachexia and prevent overconsumption of food (Suzuki et al., 2013). Cytokines function in hypothalamic nuclei ARC and PVN because IL-1 receptors located on POMC/CART neurons stimulate  $\alpha$ -MSH release which results in melanocortin-4 receptor MC4R activation that causes ongoing loss of appetite together with increased energy expenditure (Malla et al., 2022). The hypothalamic-pituitary axis development of neuroinflammation through IL-1 $\beta$  pathways results in increased muscle protein breakdown and fat tissue breakdown of adipose tissue (Braun and Marks, 2010). The process of inflammation creates changes in hypothalamic feeding centers through neuropeptide balance alterations which activate anorexigenic pathways via POMC/CART and CRH while inhibiting orexigenic pathways through NPY/AgRP, orexin and ghrelin signaling pathways (Braun and Marks, 2010). Angiotensin-II which usually rises during heart and kidney failure conditions decrease food consumption through its action of decreasing hypothalamic NPY and orexin levels via AMPK dephosphorylation (Yoshida et al., 2012). The melanocortin system comes forward as a common final pathway for an anorexia and cachexia stimulating effect of inflammation (Lechan and

Tatro, 2001). Because uremic toxins, chronic inflammation, circulating cytokines, amino acid imbalance, and altered serotonergic signaling increase satiety pathways and reduce appetite, anorexia can arise in chronic kidney disease (CKD). Poor appetite among dialysis patients frequently results in a higher inflammatory load, worse nutritional status, and worse clinical outcomes (Cheung et al., 2010). Table 2 shows major inflammatory and neural drivers of cachexia.

Chronic diseases like cancer and CKD cause systemic inflammation and metabolic derangements that damage hypothalamic neuropeptide and melanocortin pathways which then produce appetite suppression and weight loss through increased catabolic activity that results in anorexia-cachexia and deteriorating health conditions that shorten life span.

11. Sex hormones and energy balance

Body fat distribution, energy expenditure, and hunger are all affected by sex hormones in a significant way. Estrogen, particularly 17 $\beta$ -estradiol, through ER $\alpha$  signaling in hypothalamic POMC and VMH neurons increases energy expenditure and promotes satiety (Zhu et al., 2023; Lizcano, 2022). In POMC neurons, ER $\alpha$  activation leads to an increase in melanocortin MC4R activity and a reduction in the effect of NPY and ghrelin orexigenic action (Lizcano, 2022). Independently from that, increased visceral fat development, energy expenditure reduction, and cardiometabolic risks are connected with estrogen level reduction after menopause (Ko and Jung, 2021; Kozakowski et al., 2017). Neuro-estrogens which the hypothalamus makes through Cyp19a1 aromatase activation lead to increased MC4R expression, decreased food consumption and enhanced leptin sensitivity which occurs without any need for ovarian estrogen (Nguyen et al., 2025). Estrogens and androgens both affect the hypothalamic centers which control hunger and satiety as well as which body regions store fat. Androgen excess in women of reproductive age leads to obesity and insulin resistance together with heightened appetite because it changes hypothalamic appetite regulation and decreases energy spending while causing insulin resistance in peripheral body parts (Iwasa et al., 2023). The Mendelian randomization results in men show that increased bioavailable testosterone levels lead to reduced body fat and improved glucose metabolism, while obesity causes testosterone levels to decrease (Loh et al., 2022). Women worldwide experience severe obesity at higher rates because their biological makeup drives weight gain more than social circumstances. Estradiol decreases food consumption during the follicular and peri-ovulatory phases while progesterone and testosterone lead to increased hunger, which creates fluctuations in eating patterns throughout the menstrual cycle (Leeners et al., 2017). The premenopausal women demonstrate higher levels of leptin and insulin satiety sensitivity and increased thermogenic capacity compared to men which contributes to their decreased risk of weight gain and cardiometabolic disorders (Koceva et al., 2024). Menopause causes sharp estrogen decline together with relative hyperandrogenemia which results in greater visceral fat accumulation and decreased energy burning while increasing cardiometabolic risk all without extra calorie consumption. Estrogen therapy can partially reverse these changes (Ko and Jung, 2021; Kozakowski et al., 2017). Estrogen centrally promotes satiety and higher energy expenditure, while testosterone effects depend on both sex and environmental conditions. The hormonal mechanisms induce

Table 2  
Major inflammatory and neural drivers of cachexia.

| Mechanism                                | Appetite effect                        | Disease contexts                                       |
|------------------------------------------|----------------------------------------|--------------------------------------------------------|
| IL-6, TNF- $\alpha$ , IL-1 $\beta$ /IL-8 | Anorexia, muscle/fat loss              | Cancer, CKD, systemic illness (Braun and Marks, 2010)  |
| Hypothalamic melanocortin activation     | Sustained appetite loss, $\uparrow$ EE | Cancer cachexia, chronic disease (Suzuki et al., 2013) |
| Uremic toxins & hyperserotonergic state  | Satiety, reduced intake                | CKD/dialysis (Lechan and Tatro, 2001)                  |

specific sex differences which affect both appetite control and obesity development, whereas postmenopausal weight gain results from menopausal estrogen loss.

## 12. Therapeutic targets and pharmacological interventions

GLP-1 receptor agonists (GLP-1 RAs) use complimentary peripheral and central pathways to prevent obesity. Activation of GLP-1 receptors, which are expressed in brainstem and hypothalamus circuits implicated in appetite control, increases satiety while decreasing food-seeking and hedonic responses to appetizing food (Moiz et al., 2025; Drucker, 2018). GLP-1 receptor activation modifies neuronal activity in circuits that regulate hunger at the cellular level by increasing intracellular cyclic AMP and activating downstream protein kinase A and associated signaling pathways. Furthermore, GLP-1 RAs reduce food intake and improve metabolic regulation by delaying stomach emptying, increasing glucose-dependent insulin secretion, and decreasing incorrect glucagon secretion (Drucker, 2018). Further experimental data suggests that GLP-1 receptor-expressing glutamatergic neurons are involved in the weight-loss effects of liraglutide, underscoring the significance of central neuronal circuits in hunger suppression (Adams et al., 2018). GLP-1 RAs provide significant therapeutic advantages, but they can also have side effects, most frequently gastrointestinal symptoms as nausea, vomiting, diarrhea, constipation, and pain in the abdomen. Gallbladder disease and pancreatitis are less frequent but clinically significant side effects, and side effects may become more noticeable when dosage is increased (Drucker, 2018). Crucially, the advantages of GLP-1 RA therapy may not always persist after medication is stopped. Within a year of stopping semaglutide, individuals in the STEP 1 extension trial recovered around two-thirds of their prior weight reduction, along with a partial reversal of cardiometabolic benefits (Wilding et al., 2022). These results suggest that obesity is a long-term illness and that stopping GLP-1 RA treatment may allow biological processes that promote weight increase to resume. For long-term benefits, systematic weight-maintenance techniques and long-term therapy may be necessary. ManuscriptsManuscript

Obesity causes hyperleptinemia with central leptin resistance which prevents people from receiving effective treatment through exogenous leptin therapy (Pena-Leon et al., 2024). Preclinical "leptin sensitizers" (e. g., celastrol, withaferin A, some phenolics, amylin/pramlintide, GLP-1, HSP-90 inhibitors) restore leptin signaling pathways while decreasing food consumption and resulting in 20–25% weight reduction for diet induced obese mice (Garfield et al., 2015). The mechanisms involve blocking negative regulators which include SOCS3 PTP1B and they reduce leptin levels while they enhance BBB transport and activate IL-6/STAT3 pathway in hypothalamic LepR neurons (Kühnen et al., 2019). Human translation remains limited. MC4R uses POMC ( $\alpha$ -MSH) and AgRP signals to regulate hunger because its PVH(MC4R) neuron activation results in strong feeding suppression while producing weight reduction (Heyder et al., 2021). The drug setmelanotide functions as a biased MC4R agonist which enables patients with POMC or LEPR deficiencies to achieve significant weight loss and reduced appetite while experiencing less cardiovascular side effects than previous MC4R medications (Chapela et al., 2025). Structural studies show ligand-specific MC4R activation mechanisms that guide design of safer, more selective agonists (Ramassamy, 2024). Bariatric procedures rapidly increase GLP-1 and PYY and decrease ghrelin, shifting the gut–brain axis toward strong satiety signaling (Kellett et al., 2025). Vagal and central reward-circuit changes reduce cravings and alter food preference, contributing to durable intake reduction beyond mechanical restriction (Douglass et al., 2017). Pharmacologic "surgery mimetics" (GLP-1 analogues, MC4R agonists, recombinant leptin) seek to reproduce these endocrine and neural effects (Valdearcos et al., 2017). GLP-1 RAs, emerging leptin-sensitizing strategies, MC4R agonists, and bariatric surgery all act on overlapping gut–brain and melanocortin circuits to suppress appetite and improve energy balance, with surgery currently providing the most durable effects and drugs increasingly mimicking its neuroendocrine profile.

## 13. Emerging research and future directions

Neuroinflammation, genetic variation, and new gut–brain signals are reshaping future neuroendocrine appetite therapies. High-fat diet and other insults trigger microgliosis and astrocyte activation in the medio basal hypothalamus, altering neuronal control of energy balance (Fernández-Arjona et al., 2022). Selective inhibition or depletion of microglia blunts diet-induced microgliosis and greatly limits hyperphagia and weight gain, whereas forced NF- $\kappa$ B activation in microglia is sufficient to reduce energy expenditure, increase intake, and cause obesity even without dietary excess (Li et al., 2025). Prior neuro-inflammatory events can "prime" hypothalamic microglia, leading to enhanced microgliosis, loss of POMC neurons, and long-term disturbances of energy balance under later obesogenic diets (Gan et al., 2024). Epigenetically driven PI3K/Akt-linked neuroinflammation and apoptosis in ventromedial hypothalamus also contribute to disordered appetite signaling in high-fat-exposed rats (Loid et al., 2020). Rare pathogenic variants in leptin-POMC/CART-MC4R, BDNF-TrkB and related hypothalamic genes cause severe early-onset obesity, underscoring the central role of this circuit (Valassi et al., 2008). In early-onset severe obesity, about 8% of children carried rare likely-pathogenic variants in hypothalamic developmental or melanocortin-pathway genes (Alcantara et al., 2022). DNA methylation changes in hypothalamus (elevated 5-mC) can directly alter expression of galanin and IGF signaling genes, reshaping orexigenic networks and conferring weight-gain-resistant or disordered appetite phenotypes (Howick et al., 2017). Dozens of gut and brain peptides beyond GLP-1—ghrelin/GHSR-1a, PYY, CCK, amylin, CART, BDNF, orexin, MCH, endocannabinoids are being mapped into detailed "wiring diagrams" of appetite control using cell-specific genetics and circuit tools (Ueno and Nakazato, 2016). Emerging drug strategies include: amylin and dual amylin–calcitonin receptor agonists, PYY and CCK analogues, ghrelin antagonists or GOAT inhibitors, MC4R agonists, and multi-target peptide combinations that better mimic bariatric-like gut–brain signaling. Glial-targeted anti-inflammatory approaches, vagal-nerve-based devices, and circuit-level interventions to bypass damaged hypothalamus are highlighted as future avenues, especially for hypothalamic obesity (Wilding et al., 2022). Neuroinflammation (especially microglial activation), rare gene variants, and epigenetic remodeling of hypothalamic circuits are now seen as major drivers of appetite dysregulation. The next generation of therapies which combine anti-inflammatory treatment with multiple hormone therapies and neuromodulation techniques, relies on gut-brain peptide research and advanced circuit technology to develop their treatment methods.

## 14. Conclusion

The process of neuroendocrine control which governs appetite and energy balance requires multiple systems because brain structures, hormonal signaling and peripheral metabolic processes all interact with each other. The hypothalamus processes hormonal signals from leptin, insulin and ghrelin to control hunger, satiety and energy expenditure. Scientists can manipulate these pathways to study appetite control mechanisms which may help researchers understand how metabolic diseases develop. The neuroendocrine dysregulation which includes hormonal resistance, inflammation and altered reward signaling results in metabolic disorders which include obesity and type-2 diabetes and cachexia. The disturbances disrupt the brain's ability to control energy balance together with the body's peripheral organs. Scientists discovered the mechanisms that underlie energy balance control which led to the creation of GLP-1 receptor agonists and melanocortin receptor agonists and bariatric surgery as medical treatments. Research studies at future dates will discover new methods to prevent and treat metabolic disorders through their investigation of neuroinflammation, genetic regulation and new neuropeptides.

## CRediT authorship contribution statement

**Mst. Mohona Khatun:** Writing – original draft, Visualization, Data curation. **Md. Nazmul Ahsan Sarker:** Writing – original draft, Visualization, Investigation. **Mohammad Shahangir Biswas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Conceptualization. **Munna Kumar Podder:** Writing – review & editing, Visualization, Validation, Data curation. **Sabrina Akter:** Writing – review & editing, Validation, Data curation.

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Declaration of Generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the author used ChatGPT (version 5.5, «thinking» model) solely for language-related assistance, including grammatically accurate translation, lexical refinement, and adaptation of the text to academic English. All translated and edited text was carefully reviewed and verified by the author and was confirmed to be fully consistent with the original content and the research conducted by the author. The study design, data analysis, interpretation of results, and all scientific conclusions were performed independently by the author, who takes full responsibility for the content of the published article.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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## Data availability

Not applicable

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