

Research progress in neural regulatory mechanisms and targeted therapy of obesity (Review)

DEJIE KANG^{1*}, XIA LI^{2*}, YAOYOU ZHANG¹, YIHAN SUN¹,
YUHAN LI¹, ZHIYAN YAO¹ and YOULEI LI¹

¹Department of Physiology, Yan'an Medical College, Yan'an University, Yan'an, Shaanxi 716000, P.R. China;

²Yan'an Key Laboratory of Obesity Prevention and Treatment, Department of Endocrinology and Metabolism, Yan'an University Affiliated Hospital, Yan'an, Shaanxi 716000, P.R. China

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Abstract. Obesity is a multifactorial chronic metabolic disease driven by disrupted energy homeostasis and excessive adipose tissue (AT) deposition under genetic, environmental and central neural regulation. Sustained energy surplus triggers AT

hypertrophy, endocrine dysfunction and low-grade inflammation, elevating risks of type 2 diabetes mellitus, cardiovascular diseases and multiple cancers while impairing physical-mental well-being. Hypothalamic central neural circuits integrate peripheral metabolic signals to govern feeding and systemic energy balance and serve as core pathological drivers of obesity. Conventional interventions including bariatric surgery, calorie restriction and exercise yield only transient weight loss with poor long-term outcomes, as they fail to reverse obesity-related neural-circuit dysfunction and thus produce high weight-regain rates. Translational obstacles remain for neuromodulatory therapies, including poorly defined cell-type-specific neural control and limited blood-brain barrier penetration of candidate agents. The present review systematically outlined obesity-associated hierarchical neural networks centered on hypothalamic arcuate nucleus pro-opiomelanocortin and agouti-related peptide neurons and the leptin-melanocortin axis. The present review summarized recent progress in hypothalamic neurons, key neuro-transmitters and downstream cascades controlling energy metabolism; characterized gut-microbiota-vagus-nerve gut-brain signaling and dual appetite-regulatory roles of short-chain fatty acids; and delineated pathological links between gut dysbiosis and hypothalamic pro-opiomelanocortin neuronal injury, distinguishing confirmed mechanisms from unvalidated hypotheses. Three neural-targeted anti-obesity modalities (GLP-1R agonists, MC4R agonists and NMU-R2 small-molecule candidates) are comparatively assessed, covering preclinical evidence for NMU-R2, adverse-effect profiles, target populations and animal-to-human translational gaps. The present study further addresses multimodal combined interventions and balanced pros-and-cons of neuromodulation techniques. This multi-system overview provided theoretical support for developing novel precision anti-obesity strategies.

Correspondence to: Dr Youlei Li, Department of Physiology, Yan'an Medical College, Yan'an University, 580 Shengdi Road, Baota, Yan'an, Shaanxi 716000, P.R. China
E-mail: liyoulei@yau.edu.cn

*Contributed equally

Abbreviations: AgRP, agouti-related protein; α -MSH, α -melanocyte-stimulating hormone; ARC, arcuate nucleus; AT, adipose tissue; BAT, brown adipose tissue; BBB, blood-brain barrier; BP, blood pressure; CCK, cholecystokinin; CNS, central nervous system; DA, dopamine; FA, fatty acids; FDA, Food and Drug Administration; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; GCG, glucagon; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor; GLP-1Ras, GLP-1 receptor agonists; GPCR, G protein-coupled receptor; GPR41, G protein-coupled receptor 41; GPR43, G protein-coupled receptor 43; GHS-R1a, growth hormone secretagogue receptor 1a; HPA, hypothalamic-pituitary-adrenal axis; HR, heart rate; LEP, leptin; LEPR, leptin receptor; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; MC1R, melanocortin 1 receptor; MC4R, melanocortin 4 receptor; NAcc, nucleus accumbens; NMU-R1, neuromedin U receptor 1; NMU-R2, neuromedin U receptor 2; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; ROS, reactive oxygen species; RYGB, roux-en-Y gastric bypass; SCFAs, short-chain fatty acids; SG, sleeve gastrectomy; T2DM, type 2 diabetes mellitus; TLR4, toll-like receptor 4; TNF- α , tumor necrosis factor- α ; UCP1, uncoupling protein 1; VTA, ventral tegmental area; WAT, white adipose tissue

Key words: obesity, hypothalamus, gut-brain axis, oxidative stress, energy homeostasis, appetite regulation

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1. Introduction

Obesity represents a global epidemic metabolic disorder characterized by an imbalance between energy intake and expenditure, leading to ectopic adipose tissue (AT) accumulation and multiple life-threatening comorbidities, including type 2 diabetes mellitus (T2DM), metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular disorders and malignant tumors, all of which markedly increase all-cause mortality. During recent decades, the global incidence of obesity has continued to rise, with the prevalence of severe obesity increasing sixfold. According to published projections indicate that 20% of the global population will be affected by obesity by 2030 (1).

Obesity-associated chronic low-grade inflammation disrupts insulin signaling in AT, the liver, skeletal muscle and the central nervous system (CNS), thereby establishing a vicious cycle of insulin resistance and excessive fat accumulation (2).

Growing neurobiological evidence shows that central neural circuits play a dominant role in the initiation and progression of obesity by integrating peripheral metabolic cues to regulate appetite and energy expenditure (3). Nevertheless, existing reviews have largely examined hypothalamic regulation, gut microbiota signaling and inflammatory injury separately and lack a comprehensive multisystem framework that integrates neural dysfunction, gut-brain communication, oxidative stress and metabolic inflammation. Current clinical weight-loss strategies mainly rely on surgical interventions and lifestyle modifications, yet their long-term effectiveness remains limited because of poor patient adherence and frequent weight regain. Consequently, neuron-targeted therapies based on obesity-related neuroregulatory mechanisms have emerged as a promising research area. However, key translational challenges, including blood-brain barrier (BBB) penetration, target selectivity and long-term safety, remain insufficiently addressed.

The present review systematically summarized the multi-layer neural regulatory network underlying obesity (Fig. 1), clarified bidirectional communication along the gut-brain axis and discussed inflammation- and oxidative stress-mediated neuronal injury. It also highlighted recent preclinical and clinical advances in neural-targeted anti-obesity therapies, aiming to address these research gaps and provide a theoretical foundation for obesity prevention and precision treatment.

2. Hypothalamic neuromodulation network: the central hub of energy balance

Arcuate nucleus (ARC): The integrated center of peripheral signaling and central regulation. The hypothalamus is widely recognised as the principal regulatory centre for appetite and serves as an essential component in maintaining systemic energy homeostasis (4). It integrates peripheral nutrient and

endocrine signals to coordinate feeding behaviour and metabolic activity through both neuroendocrine and neuronal pathways (5). As the primary integrative hub for peripheral metabolic inputs, the ARC possesses an incomplete BBB, enabling direct sensing of circulating metabolic factors and bidirectional signal transmission between peripheral tissues and the CNS (6). Within the central homeostatic network, the ARC functions as a key relay centre, integrating afferent signals from peripheral tissues with descending cerebral inputs. This unique anatomical characteristic has established the ARC as a key focus for investigating the mechanisms that maintain energy balance (7). Two functionally antagonistic neuronal populations reside within the ARC: Pro-opiomelanocortin (POMC) neurons and agouti-related protein (AgRP)/neuropeptide Y (NPY) neurons. The dynamic interplay between these neuronal populations is essential for maintaining whole-body energy homeostasis (8).

After translation, the POMC precursor protein undergoes proteolytic processing to generate melanocortin peptides, which suppress appetite and increase energy expenditure by activating central melanocortin receptors. Among these cleavage products, melanocortins play a pivotal role in regulating food intake and systemic energy metabolism through interactions with specific CNS receptors. During energy deprivation, POMC neuronal activity decreases, accompanied by reduced c-FOS expression and α -melanocyte-stimulating hormone (α -MSH) secretion (9).

In mammals, AgRP neurons synthesize and secrete AgRP while co-expressing NPY, a key component of the neural circuitry regulating feeding behavior (10). The NPY peptide family comprises three evolutionarily related proteins, pancreatic polypeptide, peptide YY (PYY) and NPY, which exhibit substantial conservation in both molecular structure and biological function. The nucleus accumbens (NAcc) functions as a central reward-processing region. NPY participates not only in interactions with reward-related neural pathways but also in networks regulating emotional behavior, substance dependence, alcohol consumption and dietary fat intake (11). As the most abundant neuropeptide in the brain, NPY exerts its effects through four distinct Y-receptor subtypes, thereby influencing feeding behavior, stress responses, anxiety regulation and memory formation. NPY acts on postsynaptic Y1 and Y5 receptors to counteract POMC signaling, whereas chronic overactivation of NPY pathways promotes hyperphagia and adiposity, contributing to metabolic disorders and mood disturbances (12).

During states of energy deficiency, AgRP/NPY neurons become activated. AgRP and NPY both rapidly stimulate feeding behavior (13). AgRP neurons extend widespread axonal projections throughout the neuraxis, enabling them to regulate food intake and a variety of hunger-associated behaviors, including food-seeking activity and anxiety-related responses (13). AgRP and POMC neurons exert opposing effects on metabolic regulation. Under negative energy balance, AgRP neuron activation promotes food consumption. Conversely, when energy intake exceeds energy expenditure, resulting in positive energy balance, POMC neuronal activity increases, suppressing appetite and enhancing energy expenditure. Together, these opposing mechanisms constitute a key negative-feedback system for maintaining energy

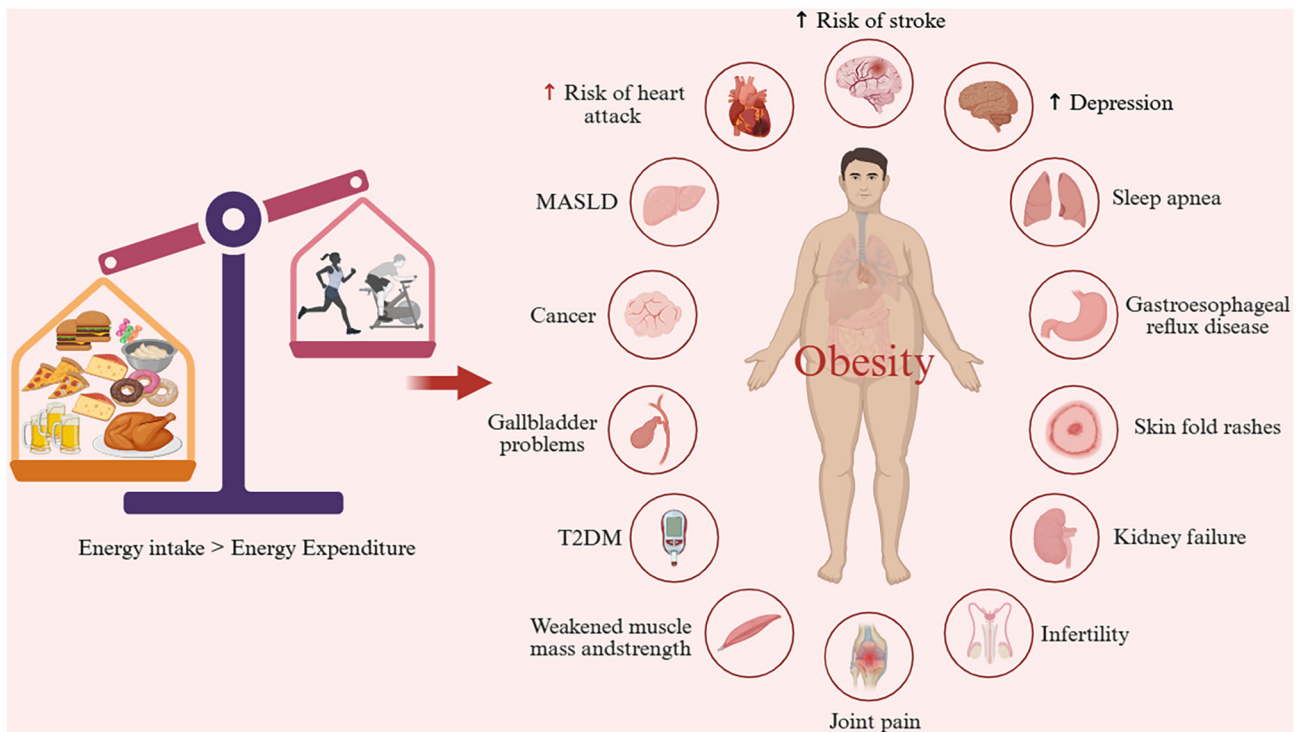


Figure 1. Core etiological mechanism and multisystem complications of obesity. Left panel: Obesity originates from chronic positive energy balance, defined as energy intake surpassing energy expenditure. Right panel: Multisystem comorbidities triggered by obesity. Apart from morphological changes, obesity drives systemic metabolic dysfunction and predisposes individuals to numerous disorders, including T2DM, MASLD, stroke, myocardial infarction, multiple malignancies, chronic kidney disease, obstructive sleep apnea, gastroesophageal reflux disease, gallbladder diseases, intertriginous dermatitis, joint pain, sarcopenia, infertility and depression. Created in BioRender. Peng, C (2026) <https://BioRender.com/3ai466d>. T2DM, type 2 diabetes mellitus; MASLD, metabolic dysfunction-associated steatotic liver disease.

homeostasis. The antagonistic POMC-AgRP/NPY circuit therefore represents the core regulatory network governing energy balance (14).

Core neurons and key regulatory pathways. Melanocortin peptides are key neurochemical mediators of energy homeostasis. They maintain metabolic balance through three principal mechanisms: Suppressing appetite, enhancing thermogenesis and modulating sympathetic nervous system activity (15). The leptin-melanocortin signalling axis represents the central pathway through which the hypothalamus regulates appetite. Disruption of key downstream components of this pathway, including leptin (LEP), leptin receptor (LEPR) and melanocortin 4 receptor (MC4R), results in severe early-onset obesity. As illustrated in Fig. 2, LEP activates POMC neurons, promoting the synthesis and release of α -MSH. MC4R is regulated by two endogenous ligands with opposing actions. α -MSH acts as an agonist to activate MC4R, whereas AgRP functions as an inverse agonist that not only suppresses constitutive receptor activity but also competitively inhibits α -MSH-mediated signalling (16,17).

Disruption of LEP-melanocortin pathway homeostasis dysregulates feeding behavior, neuroendocrine function and autonomic nervous system activity. As the neuronal populations involved have extensive neural projections and broad inter-regional connectivity, impairment of this pathway results in widespread physiological consequences (18). Melanocortin peptides exert their biological effects through five receptor subtypes, designated MC1R-MC5R. Among these, melanocortin 4 receptor (MC4R) is most strongly associated with

monogenic obesity and serves as the principal downstream effector regulating food intake and energy homeostasis within the melanocortin signaling network (19).

MC4R is highly expressed in the hypothalamus, particularly within neurons of the paraventricular nucleus (PVN). Clinical and genetic studies have demonstrated that loss-of-function mutations in MC4R account for the largest proportion of monogenic obesity cases. Such mutations promote excessive food intake while reducing thermogenesis-associated energy expenditure, thereby establishing a self-reinforcing pathological cycle that drives obesity development (18,20). As a key center for regulating feeding behavior, metabolism and neuroendocrine activity, the PVN rapidly senses and responds to alterations in adiposity and energy stores (21). Collectively, the MC4R system functions as a central regulatory node that integrates appetite control with systemic metabolic homeostasis through a broad network of downstream signaling pathways (21).

Melanocortins also function beyond energy regulation. In the skin, melanocortins regulate pigmentation and immune responses through melanocortin 1 receptor (MC1R)-dependent signaling. In the pituitary-adrenal axis, POMC is processed into adrenocorticotrophic hormone, which binds melanocortin 2 receptor in the adrenal cortex to regulate cortisol secretion. Within the hypothalamus, melanocortin 3 receptor signaling appears to play a more prominent role in regulating fat metabolism than appetite control. In key metabolic tissues, including AT, the liver and skeletal muscle, melanocortin peptides influence inflammatory responses and thermoregulatory

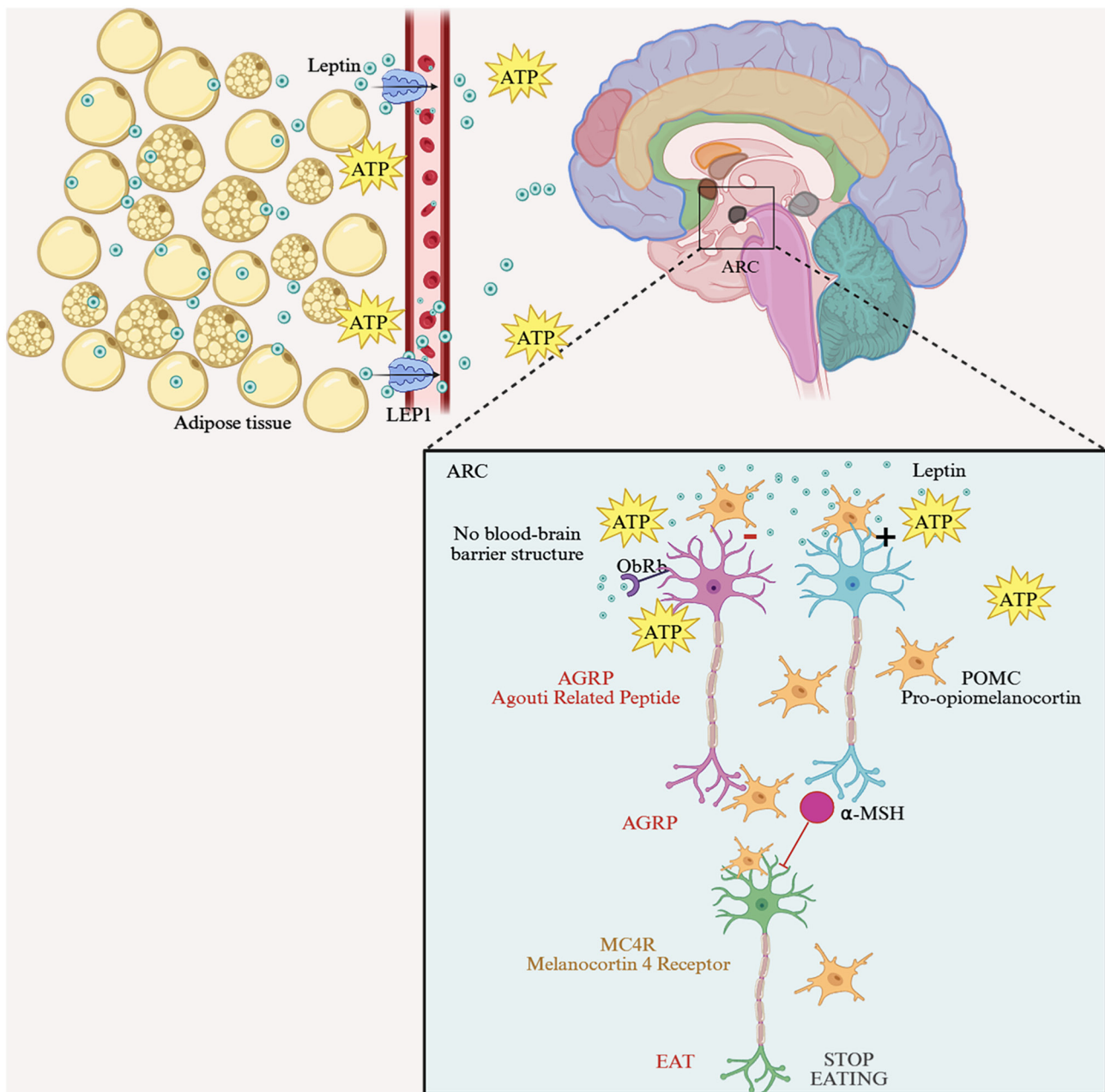


Figure 2. Molecular mechanisms underlying feeding regulation mediated by the LEP-MC signaling pathway. Schematic illustrating the core signaling cascade whereby the hypothalamic ARC governs feeding behavior via the LEP-MC axis. LEP, secreted by AT, enters the ARC via LRP1-mediated transport. Owing to the deficient blood-brain barrier structure within the ARC, circulating leptin directly targets two functionally antagonistic neuronal subsets in this nucleus. LEP excites anorexigenic POMC neurons, stimulating α -MSH release. α -MSH subsequently activates MC4R to propagate satiety signals and suppress food intake. Conversely, LEP inhibits orexigenic AgRP neurons. AgRP acts as an endogenous antagonist of MC4R, blocking receptor activation, counterbalancing α -MSH-mediated anorexigenic effects and triggering hunger signals to promote feeding. Created in BioRender. Peng, C (2026) <https://BioRender.com/3jateczg>. ARC, arcuate nucleus; LEP, leptin; MC, melanocortin; AT, adipose tissue; LRP1, low-density lipoprotein receptor-related protein 1; POMC, pro-opiomelanocortin; α -MSH, α -melanocyte-stimulating hormone; MC4R, melanocortin 4 receptor; AgRP, agouti-related peptide.

processes through pathways involving melanocortin 5 receptor (MC5R) (18,22,23).

Key hormones in appetite regulation

Targeting central regulatory hormones. LEP is a 167-amino-acid peptide hormone secreted by adipocytes. It plays a central role in regulating neural circuits involved in energy balance and is essential for maintaining systemic metabolic homeostasis (24). As illustrated in Fig. 3, LEP directly modulates neural circuits within the CNS,

thereby reducing overall energy expenditure (25). This adipose-derived hormone crosses the BBB and binds to the LEPR, enabling direct neurochemical regulation of hypothalamic regions characterized by an incomplete BBB (26). LEP also modulates mesolimbic dopamine (DA) neuron activity, primarily regulating reward-driven feeding and promoting adaptive food-seeking behaviors during energy deficiency (18). LEP deficiency results in uncontrolled appetite and impaired function of both POMC and AgRP neuronal populations. These functionally antagonistic

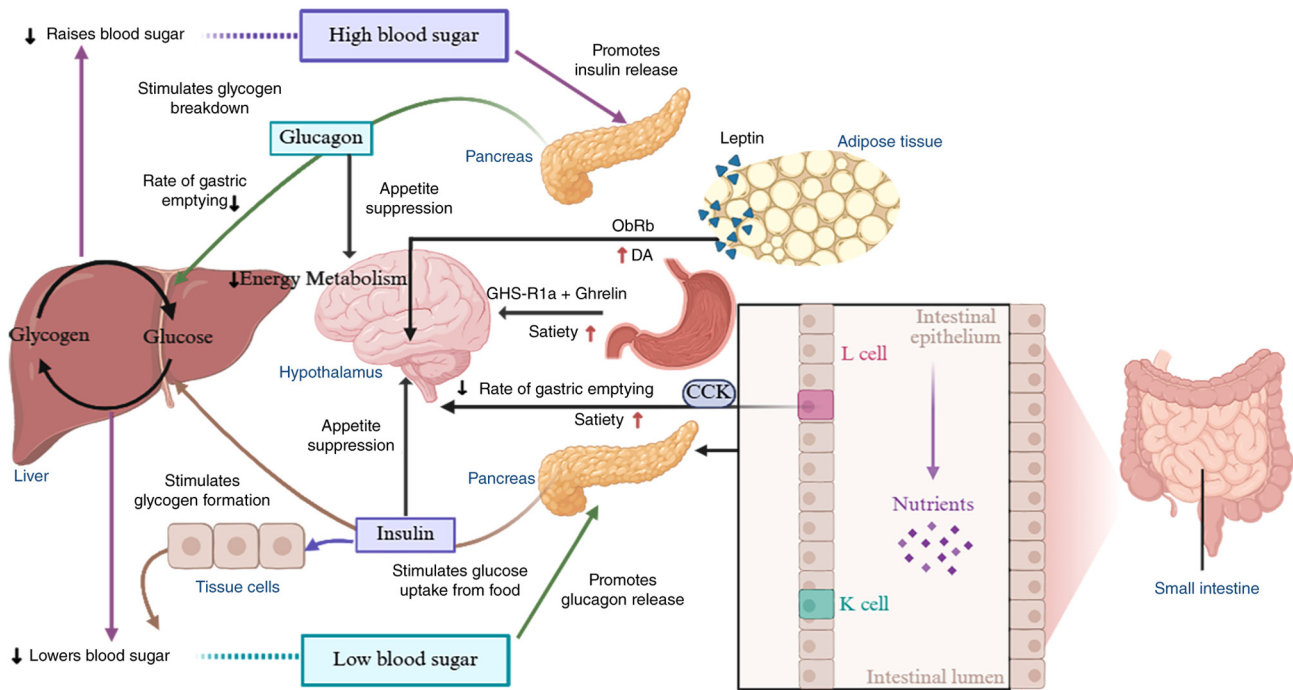


Figure 3. Molecular mechanisms of appetite and energy homeostasis regulated by central hormones and gut-brain axis signaling. Schematic summarizing the integrated regulatory network in which adipokines, pancreatic hormones and gut-derived hormones coordinately control appetite, gastric emptying, systemic glucose balance and energy metabolism. Circulating LEP, secreted by adipose tissue, targets hypothalamic ObRb receptors to trigger anorexigenic signaling and suppress feeding. Pancreatic insulin lowers blood glucose by stimulating hepatic glycogen synthesis and peripheral glucose uptake; insulin also relays satiety signals to the hypothalamus to inhibit appetite. By contrast, pancreatic glucagon elevates blood glucose by promoting hepatic glycogen breakdown, while concurrently suppressing appetite and slowing gastric emptying. Hormones of the gut-brain axis transmit peripheral nutrient information to the central nervous system. Ghrelin from the stomach binds hypothalamic GHS-R1a to elicit orexigenic responses. Intestinal L/K cells secrete CCK upon nutrient exposure; CCK mediates satiety, decelerates gastric emptying and relays inhibitory signals to the hypothalamus. DA modulates reward-related feeding behavior. Collectively, these circulating hormonal signals converge on hypothalamic nuclei to orchestrate food intake, gastrointestinal motility and hepatic glucose metabolism, maintaining whole-body energy homeostasis. Created in BioRender. Peng, C (2026) <https://BioRender.com/w6rbeqx>. LEP, leptin; ObRb, leptin receptor b; GHS-R1a, growth hormone secretagogue receptor 1a; CCK, cholecystokinin; DA, dopamine; CNS, central nervous system; L/K cells, enteroendocrine L/K cells.

neurons project convergent fibers to the PVN. This signaling pathway enhances sympathetic nervous system activity in both white AT and brown AT (BAT), thereby influencing feeding behavior (25,27). As AT mass increases, circulating LEP concentrations rise proportionally, signaling to the CNS to suppress hunger and reduce food intake. In obesity, however, the CNS exhibits markedly diminished responsiveness to LEP signaling, a pathological state known as leptin resistance (28). At the cellular level, persistent peripheral inflammation, excessive reactive oxygen species (ROS) accumulation and chronic nutrient overload collectively induce mitochondrial dysfunction, endoplasmic reticulum stress, dysregulated lipid metabolism and impaired autophagic flux in ARC neurons. Sustained exposure to these pathological alterations gradually leads to central leptin resistance. Notably, this pathological cascade has been extensively validated in rodent models of obesity; however, direct histological and signaling evidence from human hypothalamic tissue remains limited and such findings should not be indiscriminately extrapolated to human obesity (29).

As a key regulator of glucose and lipid homeostasis, insulin precisely controls systemic metabolic activity and cellular energy balance by activating the PI3K/Akt signaling pathway in peripheral tissues (13). In response to elevated blood glucose levels, pancreatic β -cells secrete insulin,

which binds to insulin receptors and initiates metabolic processes that promote glucose uptake and utilization in adipocytes, myocytes and hepatocytes. Excessive expansion of AT induces lipid accumulation in multiple organs, leading to endoplasmic reticulum stress and chronic inflammation, which ultimately disrupt normal insulin signaling and its downstream actions (30). Progressive insulin resistance further impairs insulin's ability to suppress lipolysis. Consequently, the release of free fatty acids (FA) from adipocytes increases, resulting in abnormal FA accumulation in tissues not specialized for fat storage (31). Within the CNS, insulin exerts highly specific actions through receptors expressed on the membranes of brain microvascular endothelial cells at the BBB (32). Following transport across the BBB, insulin activates PI3K/Akt-dependent satiety pathways in ARC POMC neurons, thereby suppressing food intake. In chronic obesity, ectopic lipid deposition and persistent hypothalamic microglial inflammation impair central insulin signal transduction, attenuating its anorexigenic effects and exacerbating hyperphagia. Substantial evidence from neuron-specific insulin receptor knockout mouse models supports this regulatory model. However, the epigenetic mechanisms underlying cell-selective insulin desensitization remain largely hypothetical and have not yet been validated in human tissues (33).

This metabolic dysregulation promotes adipocyte expansion and hypertrophy, progressively reducing cellular sensitivity to insulin signaling while increasing susceptibility to inflammatory activation. Through the coordinated action of these interconnected processes, systemic metabolic dysfunction gradually develops (34).

ADP is an adipocyte-derived protein that shares several functional properties with insulin. It suppresses gluconeogenesis, promotes glucose uptake and facilitates FA esterification. Reduced ADP levels contribute to pathological alterations, including insulin resistance and excessive lipid accumulation. ADP secretion decreases as adipocyte size increases. Conversely, during periods of nutritional restriction, adipocyte-derived ADP levels rise substantially, promoting lipid storage within AT (35). ADP exerts tissue-specific effects through adiponectin receptor 1, which is predominantly expressed in skeletal muscle and adiponectin receptor 2, which is highly expressed in the liver. Through these receptors, ADP enhances lipid oxidation, suppresses hepatic gluconeogenesis and promotes peripheral glucose utilization. Epidemiological studies have demonstrated a strong inverse association between circulating ADP concentrations and both BMI and total body fat mass. Furthermore, ADP production is markedly suppressed in individuals consuming high-carbohydrate diets and in patients with obesity, resulting in markedly reduced circulating ADP levels (36-38).

In summary, LEP, insulin and ADP represent three principal adiposity-associated hormones involved in central and peripheral metabolic regulation. LEP and insulin exert anorexigenic effects that limit excessive food intake, whereas ADP primarily improves peripheral metabolic sensitivity without directly acting on central appetite-regulating neurons. In obesity, reduced ADP secretion, together with central leptin and insulin resistance, disrupts this homeostatic hormonal feedback network. Within the ARC, insulin signaling through the PI3K/Akt pathway produces distinct regulatory effects on the two key neuronal populations. In POMC neurons, insulin signaling enhances anorexigenic output and increases leptin sensitivity. However, in chronic obesity, insulin-mediated suppression of AgRP neuronal activity becomes impaired, resulting in cell-type-specific insulin resistance that contributes to persistent hyperphagia (26,28,31,35).

Gut-brain axis-related hormones. Ghrelin, an orexigenic peptide hormone produced by X/A-like endocrine cells in the gastric mucosa, is a potent stimulator of appetite. It promotes food intake and energy consumption by activating growth hormone secretagogue receptor 1a (GHS-R1a), a seven-transmembrane receptor (39). GHS-R1a belongs to the G protein-coupled receptor (GPCR) superfamily and is widely expressed in diverse tissues, including the pancreas, spleen, heart, kidneys, gonads, thyroid gland, adrenal glands, AT, vascular tissues and the CNS. Within the hypothalamus, GHS-R1a is predominantly expressed in the ARC and PVN, where it serves as a key target of ghrelin signaling and initiates neuroendocrine pathways involved in appetite regulation (40). Ghrelin production and secretion are strongly influenced by nutritional status. Circulating ghrelin concentrations typically rise 1-2 h before meals and decline markedly within the first hour after food intake due to the suppressive effects of postprandial hormone release (41).

Glucagon-like peptide-1 (GLP-1), a gut-derived peptide that plays a central role in glucose and lipid homeostasis as well as appetite regulation, is primarily secreted by intestinal L cells in the distal ileum and by neurons in the nucleus tractus solitarius (NTS) (39). The NTS serves as a key satiety center that suppresses feeding behavior. When enteric sensory inputs exceed the activation threshold of gut-gut communication pathways, NTS-specific microcircuits can induce conditioned taste aversion, thereby limiting food intake (42). As a key incretin hormone, GLP-1 is widely expressed in the gastrointestinal tract, brainstem nuclei and various endocrine tissues. Its physiological actions are mediated primarily by the GLP-1 receptor (GLP-1R), a highly specific cell-surface receptor (43).

GLP-1 promotes insulin secretion through actions on pancreatic islet cells and enhances insulin sensitivity in peripheral target tissues. Although GLP-1 has been reported to stimulate preadipocyte maturation, evidence also suggests that it may contribute to lipid accumulation within the brain under certain experimental conditions, potentially inducing neuroinflammatory responses that impair insulin sensitivity (44,45). In addition to stimulating glucose-dependent insulin secretion, GLP-1 suppresses glucagon (GCG) release from pancreatic α -cells and delays gastric emptying (46). Following nutrient intake or consumption of a high-calorie diet, GLP-1-producing neurons become activated. Central administration of GLP-1 or GLP-1R agonists into the hypothalamus markedly reduces food intake and body weight and these effects occur independently of alterations in blood glucose homeostasis (47). Although pancreatic islets represent the primary site of GLP-1 action, this incretin hormone also regulates systemic glucose metabolism through receptors expressed on neuronal and peripheral cells, thereby contributing to whole-body glucose homeostasis. Furthermore, selective activation of GLP-1R within the ventral tegmental area (VTA) attenuates excitatory synaptic transmission in dopamine (DA) neurons projecting to the NAcc, suppressing reward-driven feeding behavior (48).

Cholecystokinin (CCK) is an important gastrointestinal satiety peptide that exerts its effects by activating CCK1 receptors located on vagal sensory afferent neurons. This mechanism enables peripheral satiety signals to be transmitted to the CNS, thereby eliciting corresponding behavioral responses (49). CCK receptors are broadly distributed throughout the body and are particularly abundant in the CNS, peripheral nerves, glial networks and gastrointestinal tissues (49). In addition to delaying gastric emptying through activation of vagal afferent pathways, CCK enhances sustained satiety signaling during and after food consumption (36).

Crosstalk between hypothalamic circuits, gut-brain axis and inflammatory signaling. The hypothalamus functions as a central integrative hub that receives dual upstream inputs from gut microbiota-derived metabolites and systemic inflammatory mediators, thereby forming a closed tripartite pathological regulatory network involving hypothalamic neural circuits, the gut microbiota-gut-brain axis and inflammation-oxidative stress pathways. This network operates through three interconnected bidirectional crosstalk mechanisms, within which well-established consensus pathways can be distinguished from emerging hypotheses that require further validation.

The first mechanism involves central-to-peripheral efferent signaling. ARC POMC and AgRP neurons regulate

gastrointestinal hormone secretion, intestinal motility and mucosal barrier integrity through vagal efferent projections. These neuronal outputs directly influence the abundance of short-chain fatty acid (SCFA)-producing commensal microorganisms and the expression of intestinal tight junction proteins, thereby reshaping the intestinal SCFA production profile (50).

The second mechanism comprises peripheral-to-central afferent feedback. Circulating short-chain fatty acids (SCFAs), ghrelin and GLP-1 convey hunger and satiety signals to hypothalamic neurons through both vagal sensory pathways and the systemic circulation. Simultaneously, microbial metabolites, adipokines, lipopolysaccharide and pro-inflammatory cytokines reach the ARC from peripheral tissues. Intestinal barrier dysfunction, commonly referred to as a 'leaky gut', amplifies the influx of these inflammatory signals. Given the BBB surrounding the ARC is incomplete, these mediators can access hypothalamic tissue, triggering microglial activation and central neuroinflammation (51).

The third mechanism is the inflammation-oxidative stress positive-feedback loop. This pathway has been extensively validated in preclinical models, although direct evidence in humans remains largely indirect. Peripheral M1-polarised macrophages secrete TNF- α and interleukin-6 (IL-6), which cross the BBB and stimulate excessive ROS production within hypothalamic microglia. Accumulated ROS suppresses POMC transcriptional activity, disrupts LEP-MC satiety signaling and insulin signaling pathways and promotes the development of central hormone resistance. Impaired hypothalamic neuronal function subsequently exacerbates visceral adiposity and peripheral inflammatory infiltration. Concurrently, persistent hypothalamic neuroinflammation further compromises intestinal mucosal barrier integrity, aggravating gut microbial dysbiosis and chronic peripheral low-grade inflammation. Together, these alterations establish a self-perpetuating pathological cycle that progressively worsens obesity-associated metabolic dysfunction (52).

In summary, the hypothalamus acts as the central integration node of this regulatory network, gut microbiota-derived signals provide key peripheral metabolic inputs and chronic inflammation together with oxidative stress serve as pathological amplifiers. The dynamic interplay among these three systems jointly contributes to the initiation and progression of obesity.

3. Gut-brain axis: Mutual interplay between gut commensal microbiota and the central and peripheral nervous systems

The gut microbiome functions as a metabolic regulator. Gut commensal microbiota comprises a taxonomically diverse community of microorganisms that plays a fundamental role in nutrient metabolism, long-term dietary adaptation, host responses to pharmacological interventions and interactions with the host genetic background (53). Increasing evidence indicates that the gut microbiota contributes substantially to the development and progression of metabolic diseases by regulating tissue inflammation, lipid storage, glucose homeostasis, insulin sensitivity and endocrine metabolic signalling pathways (54).

Notably, the gut microbiota is a key regulator of appetite control. Microbiota-derived SCFAs exert bidirectional effects

on appetite regulation rather than exclusively promoting satiety. The physiological outcome depends on luminal SCFA concentration, intestinal receptor distribution and the host's metabolic status. At physiological micromolar concentrations generated through balanced dietary fiber fermentation, SCFAs activate free fatty acid receptor 2 (FFAR2) and G protein-coupled receptor 43 (GPR43) on enteroendocrine L cells, stimulating the secretion of GLP-1 and PYY. These peripheral satiety signals are subsequently transmitted through vagal afferent pathways to the NTS and hypothalamic ARC, suppressing excessive food intake (55).

By contrast, sustained millimolar-level SCFA accumulation associated with highly fermentable fiber diets or microbial dysbiosis may exert orexigenic effects through two distinct mechanisms. First, elevated circulating SCFA concentrations may cross the incomplete BBB around the ARC, selectively increasing AgRP/NPY neuronal firing while reducing POMC neuronal excitability. Second, excessive SCFA signaling through FFAR3 and GPR41 in pancreatic islets may suppress insulin secretion, thereby attenuating central insulin-mediated satiety signaling. Notably, recolonization studies in germ-free mice have produced conflicting findings. SCFAs derived from certain *Bifidobacterium* species have been reported to reduce food intake, whereas Firmicutes-enriched microbial communities generating large SCFA pools have been associated with exacerbated diet-induced obesity. These observations suggest that the overall metabolic effects of SCFAs cannot be universally regarded as anorexigenic and that further human intervention studies are required to resolve these inconsistencies observed in preclinical models (55,56).

SCFAs regulate host metabolism through multiple signaling pathways. On the one hand, they activate ghrelin-associated pathways and stimulate FFAR3/GPR41 signaling in pancreatic islets, thereby inhibiting insulin secretion. On the other hand, they bind FFAR2 and GPR43, triggering downstream cascades that promote the release of GLP-1, PYY and LEP (57). Consequently, disturbances in gut microbiota composition or function can adversely affect key metabolic organs, including white AT, skeletal muscle and the liver, ultimately contributing to systemic metabolic dysfunction (58).

The gut microbiota also communicates bidirectionally with the CNS through the gut-brain axis, enabling coordinated regulation of neural function and host behavioral responses (53). Current evidence suggests that microbiota-mediated regulation of obesity involves four principal mechanisms. First, the gut microbiota enhances nutrient extraction and absorption, thereby disrupting energy balance. Second, it promotes lipid synthesis and storage. Third, it regulates feeding behavior through gut-brain axis signaling. Finally, it contributes to chronic low-grade inflammation, which promotes systemic insulin resistance and excessive fat accumulation. Together, these processes drive obesity development and progression (59).

The majority of mechanistic insights into gut microbiota-mediated metabolic regulation have come from germ-free mouse models. Translation to humans remains limited by substantial inter-individual variability in microbial composition, dietary confounding factors and ethical constraints. These limitations currently restrict the clinical application of microbiota-targeted therapeutic strategies (60).

Overall, accumulated preclinical evidence demonstrates that SCFAs exert context-dependent effects on appetite regulation that are strongly influenced by concentration, receptor distribution and host metabolic status. While physiological SCFA production appears to support satiety signaling and metabolic homeostasis, excessive SCFA accumulation under dysbiotic conditions may promote hyperphagia and obesity. Further well-controlled human intervention studies are required to clarify these complex and potentially opposing effects (61).

Vagus nerve: Fast track for gut-brain communication. The vagus nerve is a central component of the gut-brain axis and serves as a primary communication pathway between the gastrointestinal tract and the CNS. Its extensive sensory terminals are distributed throughout the intestinal mucosa and muscular layers, enabling the accurate detection and transmission of chemical and mechanical signals associated with food intake to central neural circuits (62). The vagus nerve comprises functionally distinct branches, including a visceral regulatory component that governs organ function and a brainstem-projecting component that facilitates communication with higher neural centres. Through its role as a key anatomical interface linking the enteric nervous system and the CNS, the vagus nerve provides a direct pathway for bidirectional communication between the gut and the brain (6).

As the largest and most widely distributed cranial nerve, the vagus nerve exerts extensive regulatory effects on multiple physiological systems, particularly the respiratory and digestive systems. Its fibers are abundantly distributed throughout the duodenum, jejunum and other intestinal regions, where they detect signals generated by the gut microbiota and their metabolites. These sensory inputs can directly influence CNS activity, thereby modulating host behavior and metabolic responses (55).

The vagal fibers innervating the small intestine are predominantly pseudounipolar sensory neurons. Their peripheral axons extend into the submucosal and muscular layers of the gastrointestinal tract, forming specialized sensory endings. Some of these fibers express mechanosensitive receptors, including intramuscular arrays and intraganglionic laminar endings, which detect mechanical stimuli and relay this information through ascending neural pathways to central sensory processing regions (63). Through these mechanisms, the vagus nerve contributes to the regulation of food intake and helps prevent excessive energy consumption that may lead to obesity. Conversely, prolonged caloric restriction may disrupt normal metabolic homeostasis and alter vagal signaling pathways (64).

Individuals with obesity exhibit substantial alterations in gut microbial composition and metabolic pathway abundance. Dysregulation of the gut-brain axis resulting from these microbiota-associated changes is closely linked to abnormal feeding behavior, metabolic dysfunction and weight gain. Microbiota-derived metabolites influence appetite-regulating neural circuits and neuroendocrine pathways governing energy metabolism through multiple gut-brain communication mechanisms, thereby contributing to the regulation of food intake and body weight (65).

Evidence further suggests functional lateralization between the left and right vagal branches. The right vagus nerve

predominantly innervates the small intestine and transmits nutrient-related information to the ventromedial hypothalamic nucleus, which subsequently relays these signals to the medial parabrachial nucleus and the substantia nigra pars compacta. This right vagus-parabrachial-nigrostriatal circuit plays an important role in regulating feeding reward and nutrient preference. Experimental studies indicate that activation of this pathway is required for nutrient sensing, reward-driven behavior and preference formation. In obesity, particularly when accompanied by gut microbial dysbiosis, this neural circuit appears to be functionally impaired. Diet-induced alterations in the gut microbiota may therefore contribute to dysfunction of vagal reward pathways, further promoting maladaptive feeding behaviors and excessive weight gain (Fig. 4) (66,67).

Full causal cascade of gut dysbiosis-hypothalamic neuro-inflammation-POMC neuronal dysfunction. Gut microbiota dysbiosis initiates a sequential pathological cascade that impairs anorexigenic ARC POMC neurons and ultimately establishes a self-perpetuating vicious cycle. This pathway comprises six successive stages characterized by distinct molecular events and biomarkers. The majority of evidence for this mechanism comes from rodent models, whereas direct validation in humans remains limited to indirect neuroimaging and biomarker-based observations (68).

The first stage involves disruption of intestinal barrier integrity. Dysregulated gut microbial communities suppress the expression of key tight junction proteins, including occludin and zonula occludens-1, increasing intestinal permeability, commonly referred to as a 'leaky gut'. This barrier dysfunction facilitates the translocation of bacterial products, including lipopolysaccharide (LPS) and peptidoglycans, into the circulation, thereby initiating peripheral low-grade inflammation characterized by elevated serum TNF- α and IL-6 (69).

The second stage involves disruption of BBB integrity. Circulating pro-inflammatory cytokines impair tight junctions surrounding the ARC, increasing permeability and permitting peripheral inflammatory mediators to access the hypothalamic parenchyma (70).

The third stage is characterized by activation of hypothalamic microglia. Infiltrating LPS activates toll-like receptor 4 (TLR4) signaling in resident microglia, promoting their polarization towards the pro-inflammatory Iba1-positive M1 phenotype (71).

The fourth stage involves the development of central neuro-inflammation and oxidative stress. Activated M1 microglia secrete IL-6 and induce excessive production of ROS, together with endoplasmic reticulum stress in ARC neurons. These pathological stimuli enhance NF- κ B activity within POMC neurons, directly suppressing POMC transcription while simultaneously inhibiting leptin-induced signal transducer and activator of transcription 3 phosphorylation. This process constitutes a principal mechanism underlying central leptin resistance (72).

The fifth stage impairs melanocortin signaling. Reduced POMC activity decreases the synthesis and release of α -MSH, weakening MC4R-dependent satiety signaling within the PVN. Concurrently, AgRP/NPY-mediated orexigenic pathways become overactivated, promoting hyperphagia and AT accumulation (17).

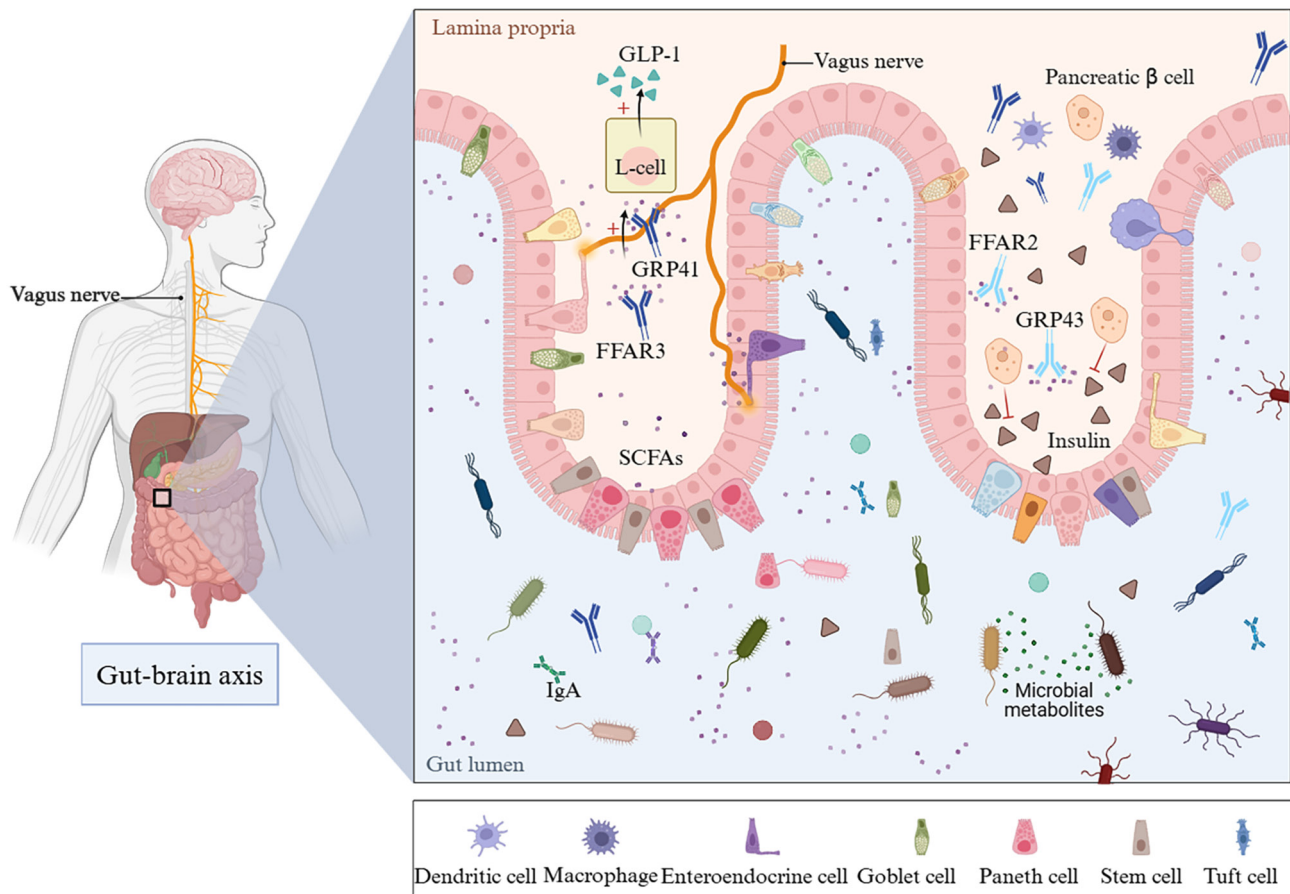


Figure 4. Molecular mechanisms of bidirectional crosstalk between gut microbiota and the central nervous system via the gut-brain axis. This schematic depicts the vagus nerve-centric gut-brain axis circuit that mediates reciprocal communication between gut microbiota and the CNS to regulate feeding behavior and systemic energy metabolism. Intestinal microbiota generate microbial metabolites including SCFAs. SCFAs activate free fatty acid receptors FFAR2 and FFAR3 expressed on intestinal epithelial and enteroendocrine cells, which stimulates L-cells to secrete GLP-1. Gut-derived chemical signals, together with enter hormones, are sensed by vagal afferent nerve terminals within the intestinal lamina propria. These peripheral signals propagate along the vagus nerve to brainstem nuclei and are further relayed to hypothalamic appetite-regulating centers. Meanwhile, intestinal immune cells (dendritic cells, macrophages) and secretory IgA help maintain the intestinal barrier and microbial homeostasis. Dysregulated gut microbiota disrupts gut-brain axis signaling, triggering abnormal feeding patterns and metabolic dysfunction. Reciprocally, the CNS modulates intestinal motility, epithelial secretion and immune function through autonomic vagal output, thereby sustaining gut microbiota equilibrium and completing this bidirectional regulatory loop. Created in BioRender. Peng, C (2026) <https://BioRender.com/thkvb2y>. CNS, central nervous system; SCFAs, short-chain fatty acids; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; GLP-1, glucagon-like peptide-1; IgA, immunoglobulin A.

The sixth and final stage completes the pathological feedback loop. Expanded adipocytes secrete more pro-inflammatory adipokines, which further exacerbate gut microbial dysbiosis and peripheral inflammation. This, in turn, reinforces the upstream pathological processes, establishing a self-amplifying cycle that progressively worsens obesity-associated metabolic dysfunction (73).

Importantly, direct evidence for this complete sequential cascade comes primarily from diet-induced obesity models and germ-free microbiota transplantation studies in rodents. Longitudinal human investigations integrating cerebrospinal fluid inflammatory profiling with hypothalamic functional magnetic resonance imaging have not yet confirmed this exact stepwise pathway in patients with obesity (74-76).

4. Pathological amplifiers of obesity: Systemic inflammation and oxidative stress

AT inflammation and metabolic dysfunction. Obesity-associated inflammation refers to a persistent systemic

inflammatory state driven by abnormal expansion and dysfunction of AT (77). As obesity progresses, multiple tissues and organs, including AT, skeletal muscle, the liver, small intestine, pancreatic islets and the CNS, exhibit clear features of inflammatory activation (78). Inflammatory mediators disrupt insulin signaling pathways, impair glucose uptake and disturb lipid metabolic homeostasis, creating a self-reinforcing cycle that links excessive fat accumulation with insulin resistance (2).

Obesity is characterized by chronic inflammation within AT, largely driven by the recruitment and infiltration of pro-inflammatory macrophages (79). In individuals with obesity, inflammatory signaling is markedly amplified across multiple tissues through interactions between innate and adaptive immune cells, accompanied by a predominance of type 1 immune responses. Intestinal mucosal inflammation and the accumulation of pro-inflammatory macrophages within local tissues are recognized pathological features of obesity (63). Macrophages represent the most abundant innate immune cell population in white AT, accounting for 40-50% of the total

cellular content. During obesity, resident adipose macrophages preferentially polarize towards the M1 phenotype, producing large quantities of pro-inflammatory mediators that disrupt insulin signaling cascades and contribute to metabolic dysfunction (80).

Obesity also promotes pathological expansion of WAT, accelerating adipocyte hypertrophy, tissue hypoxia, inflammation and hormone resistance. WAT functions as both a metabolic and an immunological organ through the secretion of adipokines, including LEP and ADP, which regulate food intake and peripheral insulin sensitivity. In addition, WAT releases numerous pro-inflammatory cytokines, including IL-6 and TNF- α (81). Consequently, AT expansion not only increases energy storage but also amplifies inflammatory signaling throughout the body.

Among these inflammatory mediators, IL-6 possesses particularly complex physiological functions. IL-6 and its receptor are both expressed in the hypothalamus. A high-fat diet can induce hypothalamic inflammation and disrupt systemic energy metabolism. Notably, IL-6 appears to exert context-dependent effects within the CNS. Experimental studies show that physical activity stimulates hypothalamic IL-6 release, which contributes to regulating obesity-associated neuroinflammation. Under these conditions, IL-6 suppresses chronic inflammatory responses induced by high-fat feeding, helps restore normal feeding behavior and supports the maintenance of systemic energy balance (82,83).

Collectively, obesity-associated inflammation represents a key pathogenic mechanism linking AT dysfunction, immune activation, insulin resistance and metabolic disturbances. Through sustained interactions among AT, immune cells, peripheral metabolic organs and the CNS, chronic low-grade inflammation drives the initiation and progression of obesity-related metabolic disease.

Oxidative stress and neuronal damage. Oxidative stress is a key pathogenic driver of obesity that contributes to disease progression by promoting preadipocyte differentiation into mature adipocytes, suppressing FA β -oxidation and enhancing adipogenesis (84). Obesity-induced metabolic disturbances in AT alter the expression and biological activity of numerous bioactive molecules, including adipokines, inflammatory mediators, growth factors, enzymes and free FA (85). As the primary energy storage organ, AT plays an essential role in regulating systemic energy metabolism, maintaining metabolic homeostasis and preserving insulin sensitivity (86). Under chronic energy excess and metabolic stress, AT undergoes pathological expansion through hypertrophy and hyperplasia, characterized by impaired adipogenic differentiation, enlarged adipocytes, increased immune-cell infiltration, persistent low-grade inflammation and reduced insulin sensitivity (87).

AT is broadly classified into white AT and BAT. White AT primarily functions as an energy storage depot, whereas BAT dissipates energy through thermogenesis by uncoupling oxidative phosphorylation, a process facilitated by its high mitochondrial density and abundant uncoupling protein 1 (UCP1) expression (88). A defining characteristic of white AT is its rapid expansion in response to nutritional surplus and metabolic stress (87). During obesity, both adipocyte

hypertrophy and hyperplasia contribute to progressive tissue dysfunction, accompanied by increased immune-cell infiltration, chronic inflammation and impaired insulin responsiveness (89).

In obesity, mitochondrial oxidative capacity within white AT becomes compromised. Metabolic stress-related factors can activate TLR4 on macrophages, initiating NF- κ B signaling and stimulating the production of pro-inflammatory cytokines and mediators. This process promotes chronic inflammation and further disrupts metabolic homeostasis (88). In addition to their role in lipid storage, adipocytes function as endocrine cells that secrete hormones and cytokines, including LEP and ADP, which regulate metabolism and inflammatory responses (80). Excess caloric intake promotes adipocyte hypertrophy and stimulates the differentiation of precursor cells into mature adipocytes within the extracellular matrix. Adequate vascularization is essential for this process. As adipocytes enlarge, they secrete pro-angiogenic factors and extracellular matrix-remodeling mediators that support tissue growth and meet increasing metabolic demands (90).

ROS play a central role in regulating lipid metabolism. Excessive ROS production impairs the electron transport chain, suppresses FA oxidation and favors lipid storage over lipid utilization (91). In obesity, elevated ROS levels arise from mitochondrial dysfunction in both peripheral AT and hypothalamic ARC neurons. Increased ROS selectively suppresses POMC peptide secretion and attenuates downstream melanocortin-mediated satiety signaling. Simultaneously, ROS activates NF- κ B-dependent inflammatory pathways, creating a synergistic pathological interaction between oxidative stress and inflammation that exacerbates metabolic dysfunction (92).

Importantly, the majority of mechanistic evidence associating ROS with hypothalamic neuronal dysfunction comes from primary neuronal culture studies and rodent models of diet-induced obesity. Direct quantitative assessment of ROS and functional validation in hypothalamic tissues from patients with obesity remain extremely limited. Therefore, interpret conclusions about ROS-mediated hypothalamic dysfunction within these evidential constraints and do not universally extrapolate them to all forms of human obesity (93-95).

Excessive ROS accumulation induces oxidative damage to neuronal membrane lipids and mitochondrial DNA, impairs synaptic communication between ARC neurons and downstream PVN circuits and further aggravates central LEP and insulin resistance. The interplay between oxidative stress and chronic inflammation represents a fundamental mechanism underlying AT dysfunction during obesity development. Mitochondrial dysfunction and endoplasmic reticulum stress within adipocytes drive excessive ROS production, which in turn activates inflammatory pathways. The resulting inflammatory response further amplifies oxidative damage, establishing a self-perpetuating cycle that promotes lipid accumulation and metabolic impairment (Fig. 5) (31).

Mechanistically, excessive intracellular ROS suppresses POMC synthesis through at least two pathways validated in *ex vivo* hypothalamic slice models. First, ROS-induced endoplasmic reticulum stress activates the protein kinase RNA-like endoplasmic reticulum kinase/eukaryotic initiation factor 2 α

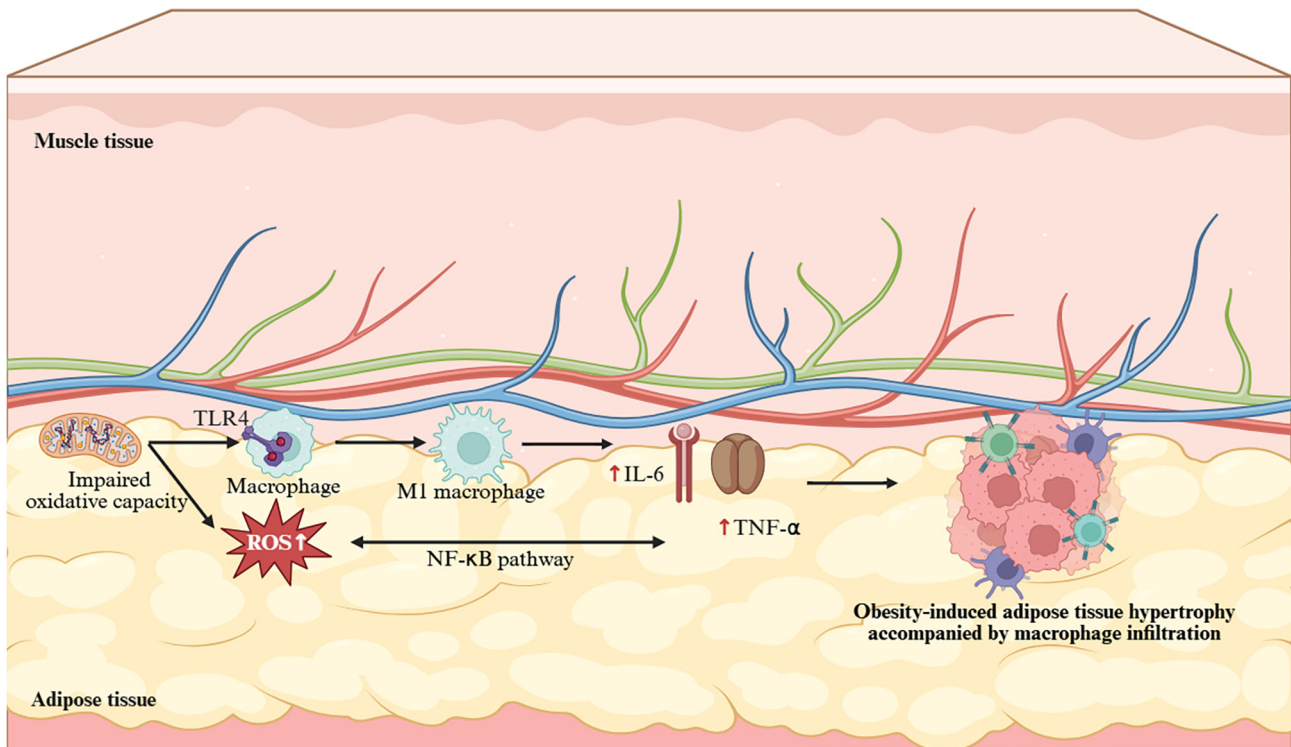


Figure 5. Molecular mechanisms linking adipose tissue hypertrophy to obesity-induced inflammation and oxidative stress. This schematic depicts the self-amplifying feedback loop between inflammation and oxidative stress established within hypertrophic adipose tissue under obese conditions. Obesity drives pathological WAT expansion, which facilitates macrophage recruitment into adipose depots. Recruited macrophages undergo polarization toward the pro-inflammatory M1 phenotype. Through TLR4-dependent activation of the NF- κ B signaling cascade, M1 macrophages produce abundant pro-inflammatory cytokines, including IL-6 and TNF- α . Adipocyte hypertrophy impairs mitochondrial oxidative capacity and triggers excessive ROS accumulation. Elevated ROS further potentiates NF- κ B-mediated inflammatory signaling. This bidirectional interaction sustains a vicious cycle linking oxidative stress and chronic low-grade inflammation within adipose tissue. Created in BioRender. Peng, C (2026) <https://BioRender.com/495grys>. WAT, white adipose tissue; M1, classically activated macrophage phenotype; TLR4, toll-like receptor 4; ROS, reactive oxygen species.

pathway, repressing POMC translation (96). Second, ROS promotes NF- κ B nuclear translocation, enabling NF- κ B to bind directly to the POMC promoter and inhibit its transcription. Although preclinical cellular and animal studies strongly support these ROS-mediated mechanisms, current imaging technologies do not permit real-time monitoring of endogenous ROS-POMC transcriptional interactions in the living human hypothalamus. This limitation considerably restricts translating these experimental findings to clinical obesity research and patient populations (93,97,98).

5. Neural targeted anti-obesity strategies: From mechanism to clinical

Existing research has confirmed a clear association between obesity progression and genetic variations, with specific genes regulating key processes such as appetite, energy expenditure and fat accumulation. Targeted interventions based on these genes can address obesity at its underlying cause while minimizing adverse effects on the patient's body (16).

GLP-1 receptor is a relatively mature target for obesity treatment. GLP-1 receptor agonists (GLP-1RAs) exhibit a notable association with stress, anorexic phenotypes, hypothalamic-pituitary axis function and central neuroinflammatory processes within the brain. GLP-1RAs represent an important therapeutic target for obesity prevention and treatment. These

compounds act through multiple mechanisms, including promoting insulin secretion, enhancing cellular insulin sensitivity, reducing hepatic glucose production, suppressing appetite and increasing satiety. Their multi-target regulatory properties facilitate effective weight management (99).

As a bona fide GLP-1RA, liraglutide has received Food and Drug Administration (FDA) approval for managing obesity in adolescents aged 12-17 years. This FDA-approved treatment helps patients achieve weight-management goals by suppressing hunger signals and improving physiological appetite regulation (100,101). Liraglutide shares >97% sequence homology with native human GLP-1 and acts through a mechanism analogous to that of endogenous GLP-1. It exerts dual effects on appetite suppression and weight reduction by stimulating GLP-1R localized in the CNS, thereby achieving its therapeutic effects (102). Liraglutide activates hypothalamic POMC neurons and VTA dopaminergic neurons through specific neuronal signaling mechanisms (103). Liraglutide increases peripheral fatty acid oxidation and enhances systemic energy expenditure by reducing chronic caloric excess and lipid accumulation in AT. Preclinical evidence indicates that liraglutide indirectly alleviates adipose oxidative stress by reducing chronic caloric overload and central inflammatory infiltration. However, no direct experimental evidence demonstrates that liraglutide functions as a primary antioxidant that scavenges intracellular ROS. Liraglutide's rapid hypothalamic effects depend on specific transport and activation pathways.

Within seconds of administration, erythrocytes take up the drug and, within minutes, it activates corresponding neurons in BBB-protected nuclei (104). However, liraglutide has several limitations in clinical practice, particularly gastrointestinal adverse effects and treatment intolerance. In addition, it may be associated with serious complications, including pancreatitis and malignant tumors (105).

Semaglutide, a GLP-1RA approved for subcutaneous administration in individuals with chronic obesity, demonstrates substantial weight-loss efficacy but may carry a risk of acute systemic shock. Its biological effects are mediated through both CNS pathways and enteric neural circuits (106). As a recently developed antidiabetic agent, semaglutide lowers glucose through two principal mechanisms. First, it enhances insulin sensitivity and promotes glucose transporter 4 translocation, thereby increasing cellular glucose uptake. Second, it delays gastric emptying, allowing more gradual intestinal glucose absorption into the bloodstream. This reduces postprandial glucose excursions and helps maintain stable postprandial glycemic control (107). Oral semaglutide can bidirectionally regulate appetite-related pathways by reducing preference for high-fat foods while enhancing endogenous feeding-regulatory mechanisms. This action suppresses excessive food-seeking behavior and facilitates weight control (99,108). Gastrointestinal adverse events are the most common side effects associated with GLP-1RAs. Semaglutide-induced nausea and vomiting arise through both peripheral and central mechanisms. Peripherally, activation of GLP-1R by semaglutide slows gastric emptying and prolongs gastric distension, thereby inducing early satiety and nausea. Within the CNS, semaglutide reaches the area postrema and influences the brainstem vomiting center, activating GLP-1 signaling pathways in the VTA and NTS. This process triggers cellular signaling pathways associated with nausea and vomiting (109).

Tirzepatide, a novel dual GLP-1/GIP receptor agonist, has received FDA approval for obesity management. It simultaneously activates GLP-1R and the glucose-dependent insulinotropic polypeptide receptor, producing more potent anorectic effects and greater long-term weight-loss efficacy than single-target GLP-1RAs. Multi-receptor co-agonists targeting GLP-1, GIP and glucagon receptors are currently in phase II-III clinical trials and represent a key research focus in developing next-generation anti-obesity peptide therapeutics (110).

Some emerging molecular targets

MC4R agonists. Loss-of-function MC4R mutations constitute a key aetiological factor in the development of obesity. Targeting MC4R with receptor agonists modulates food intake and energy expenditure by directly activating downstream signaling pathways.

Setmelanotide, an MC4R agonist, promotes body weight reduction while avoiding severe adverse effects. Setmelanotide is a highly potent and selective MC4R agonist that binds MC4R and restores its function. Selective modulation of the MC4R pathway circumvents upstream genetic defects associated with obesity resulting from LEP deficiency. Reduced caloric intake, increased energy expenditure and activation of MC4R signaling are key mechanisms underlying weight loss. Together,

these effects reduce hunger drive and promote weight reduction (111,112). In high-fat diet-fed and leptin receptor-deficient mice, setmelanotide markedly suppresses food intake and body weight gain. Unlike other MC4R agonists, setmelanotide does not induce acute or chronic increases in blood pressure (BP) or heart rate (HR) in either obese non-human primates or humans (113).

NMU-R2 agonist. The *Nmu* gene is expressed in the hypothalamus and encodes a neuromodulatory peptide that exerts its biological effects through two GPCRs, neuromedin U receptor 1 (NMU-R1) and neuromedin U receptor 2 (NMU-R2). Global *Nmu* knockout mice spontaneously develop severe obesity characterized by hyperphagia, reduced BAT thermogenesis and impaired glucose tolerance (114). Longitudinal studies have demonstrated progressive hyperglycemia, hyperinsulinemia and ectopic lipid accumulation in these animals. Notably, exogenous LEP supplementation fails to reverse this metabolic phenotype, indicating that NMU-R2 signaling regulates energy homeostasis through a leptin-independent mechanism (114-116).

Selective CNS-specific deletion of NMU-R2 recapitulates the obese phenotype, whereas peripheral deletion of NMU-R1 has no effect on feeding behavior, confirming that the anti-obesity effects of NMU signaling are mediated predominantly through central NMU-R2. Preclinical pharmacological studies further support the therapeutic potential of NMU-R2. Central administration of NMU peptide markedly suppresses food intake and enhances UCP1-mediated thermogenesis in both wild-type and leptin receptor-deficient *db/db* mice. In addition, synthetic small-molecule NMU-R2-selective agonists effectively attenuate weight gain in rodents with high-fat diet-induced obesity without inducing NMU-R1-mediated gastrointestinal smooth muscle contraction or related visceral adverse effects (117-119).

NMU-R2 is highly expressed in ARC and PVN hypothalamic neurons. Activation of this receptor suppresses AgRP neuronal activity, enhances POMC neuronal signaling and modulates mesolimbic dopaminergic reward pathways to reduce preference for highly palatable, high-fat foods. However, several translational challenges remain. Native NMU peptide ligands cannot readily cross the BBB, prompting extensive efforts to develop lipophilic, subtype-selective, non-peptide small-molecule agonists. Current research focuses on optimizing BBB permeability while evaluating chronic organ toxicity and potential neuropsychiatric effects associated with stress and circadian rhythm regulation (120).

Consequently, NMU-R2 has emerged as a promising therapeutic target for obesity treatment. Developing highly selective, non-peptide small-molecule agonists targeting NMU-R2 is expected to suppress appetite effectively and provide new strategies for obesity management and prevention. Multiple research groups are currently engaged in the discovery and optimization of NMU-R2 agonists, with efforts directed towards improving molecular structures, evaluating *in vivo* efficacy, overcoming BBB penetration limitations and characterizing potential adverse effects that may affect clinical translation (120).

Although NMU-R2 agonists have considerable potential to address the unmet therapeutic needs of individuals with

obesity and severe LEP resistance who respond poorly to GLP-1RAs and MC4R agonists, their clinical development remains constrained by two key obstacles: Inadequate BBB penetration of small-molecule candidates and unintended peripheral activation of NMU-R1, which may lead to gastrointestinal adverse effects (121). Accumulating evidence from structural pharmacology and genetic studies supports NMU-R2 as an independent anti-obesity target distinct from the leptin-melanocortin axis. Lead small-molecule candidates with optimized lipophilicity have demonstrated improved BBB penetration and chronic oral administration has increased BAT UCP1 expression and reduced cumulative food intake in db/db LEP-resistant mice without altering systolic BP. Furthermore, genetic rescue experiments have confirmed the central metabolic role of NMU-R2. Selective re-expression of NMU-R2 within the ARC of global Nmu knockout mice completely reverses hyperphagia and obesity, whereas tissue-specific restoration of NMU-R1 provides no metabolic benefit (117,120,122).

Despite these advances, numerous key barriers to clinical translation persist. In particular, long-term toxicological data regarding the effects of sustained central NMU-R2 activation on the hypothalamic-pituitary-adrenal (HPA) axis remain unavailable. Given the established role of NMU signaling in HPA axis regulation, this unresolved issue represents an important consideration for future clinical trial design. At present, no oral small-molecule NMU-R2 agonist has entered phase I clinical trials (123).

Horizontal comparative analysis of GLP-1RAs, MC4R agonists and NMU-R2 targeted drugs. GLP-1R, MC4R and NMU-R2 agonists all modulate central appetite-regulating circuits, but differ substantially in target distribution, weight-loss efficacy, adverse-effect profiles, target populations and stages of clinical development. GLP-1RAs are currently the most mature and widely used first-line pharmacological therapies for obesity. MC4R agonists have demonstrated specific efficacy in monogenic forms of obesity arising from defects in the LEP-MC pathway. By contrast, NMU-R2 agonists represent emerging preclinical therapeutic targets with potential applicability in leptin-resistant obesity, although their efficacy and safety have not yet been validated in human clinical trials. The principal advantages, limitations and target populations associated with these therapeutic strategies are summarised in Table I (102,106,113,117).

Translational medicine barriers of neural targeted drugs

Stratified applicable population analysis. Current neuron-targeted anti-obesity therapies exhibit substantial interindividual variability in treatment response, reflecting differences in central neural circuit function, gut microbiota composition and LEP signaling sensitivity. In addition to genotype-based stratification among individuals with obesity, patients receiving these three classes of agents require personalized treatment strategies and clearly defined contraindications.

GLP-1RAs are contraindicated in individuals with a personal or family history of medullary thyroid carcinoma, severe gastroparesis, recurrent acute pancreatitis or during pregnancy and lactation (124). The MC4R agonist setmelanotide is currently indicated only for individuals with biallelic

loss-of-function MC4R mutations, congenital LEP deficiency or POMC mutations (125). Preclinical evidence suggests that NMU-R2 agonists may exacerbate anxiety and sleep disturbances; therefore, individuals with chronic psychiatric disorders may not be suitable candidates for these therapies.

Mechanistic interpretation of adverse drug reactions. Neuromodulatory anti-obesity therapies exhibit distinct adverse-effect profiles and continue to face unresolved long-term safety concerns. The gastrointestinal adverse effects commonly associated with GLP-1RAs arise through both peripheral and central mechanisms. Peripherally, delayed gastric emptying and prolonged intestinal distension contribute to symptom development, whereas centrally, activation of GLP-1R within the area postrema vomiting center following drug penetration across the BBB further promotes nausea and vomiting. These adverse effects are generally transient during the first 1-3 months of treatment and gradual dose escalation substantially reduces their incidence (126). By contrast, MC4R agonists may induce pigmentation-related adverse effects through unintended activation of peripheral melanocytic MC1R, thereby reducing cosmetic acceptability, particularly among younger patients receiving long-term therapy. All emerging centrally acting small-molecule candidates share a major translational limitation: Although BBB penetration enables sustained neuronal exposure within the hypothalamus and brainstem, none of these novel targets currently have comprehensive CNS safety data extending beyond 5 years, representing a significant barrier to clinical development (127).

Differences in adverse-event profiles between rodent preclinical studies and human clinical trials are partly attributable to species-specific receptor distribution patterns. For GLP-1RAs, phase III clinical trials have reported nausea rates of 30-40%, whereas mouse studies typically demonstrate only mild symptoms, reflecting interspecies differences in GLP-1R expression within the area postrema (128-130). In addition, therapeutic heterogeneity associated with individual gut microbiota composition presents a further translational challenge. Individuals enriched with short-chain fatty acid-producing commensal bacteria may achieve comparable satiety at lower GLP-1RA doses, whereas those with gut dysbiosis often exhibit reduced therapeutic responsiveness and a greater risk of vomiting (131).

Translational gap between preclinical animal models and human obesity. Rodent models of diet-induced obesity typically rely on simple high-fat dietary interventions, whereas human obesity is a complex multifactorial disorder influenced by polygenic susceptibility, hedonistic eating behaviors, gut microbiota dysbiosis and chronic psychological stress. The majority of preclinical studies of NMU-R2 agonists have been conducted in young male mice, with limited validation in female, aged or multi-comorbidity models. In addition, species-specific differences in MC4R structure and downstream signaling pathways further restrict the translation of findings from animal studies into clinical efficacy, thereby reducing the predictive value of preclinical outcomes for human therapeutic responses (132-134).

Multimodal combined intervention strategies for obesity. Sustained long-term weight loss is rarely achieved through single neural-targeted pharmacotherapy, lifestyle modification or bariatric surgery alone because compensatory feedback

Table I. Horizontal comparison of three representative neural-targeted anti-obesity agents.

Target	Representative drugs	Core advantages	Main adverse effects and deficiencies	Applicable populations	Clinical translation stage
GLP-1R	Liraglutide, semaglutide and tirzepatide	1. Dual central/ peripheral regulation; 2. Improve T2DM, MASLD and cardiovascular risk; 3. Approved for adolescents 12-17 y	1. Nausea, vomiting and diarrhea (most common); 2. Rare pancreatitis, thyroid tumor risk; 3. Partial patients develop long-term tolerance	General obesity, T2DM combined overweight, adolescent obesity	Mature first-line clinical drug
MC4R	Setmelanotide	1. Directly restore melanocortin satiety signaling; 2. No elevated BP/HR	1. Only effective for monogenic obesity; 2. Skin pigmentation due to MC1R off-target	MC4R mutation, patients with congenital leptin deficiency	Approved for rare genetic obesity
NMU-R2	Selective small-molecule candidates (preclinical)	1. Independent of LEP axis, effective for LEP resistance; 2. No gastrointestinal side effects induced by NMU-R1	1. No human clinical data; 2. Potential HPA axis/ sleep disturbance risks	Leptin-resistant obese animal models	Preclinical optimization

GLP-1R, glucagon-like peptide-1 receptor; T2DM, Type 2 diabetes mellitus; MASLD, metabolic dysfunction-associated steatotic liver disease; MC4R, melanocortin 4 receptor; BP/HR, blood pressure/heart rate; MC1R, melanocortin 1 receptor; NMU-R2, neuromedin U receptor 2; LEP, leptin; NMU-R1, neuromedin U receptor 1; HPA, hypothalamic-pituitary-adrenal axis.

mechanisms within central energy-regulating circuits counteract therapeutic effects. Consequently, multimodal combination approaches have emerged as a key translational research focus, with regimens combining GLP-1RAs and metabolic bariatric surgery supported by the strongest clinical evidence (135). In addition to Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG) is among the most commonly performed metabolic bariatric procedures worldwide and both operations demonstrate distinct synergistic effects when combined with GLP-1RAs (136). Short-term preoperative semaglutide treatment reduces baseline body weight and BMI, thereby lowering the risk of perioperative complications, wound infection and fatty liver decompensation. Postoperatively, continued GLP-1RA therapy enhances gut-brain axis-mediated satiety signaling, suppresses ARC AgRP/NPY-driven compensatory hyperphagia and attenuates mesolimbic dopaminergic circuit-mediated hedonistic feeding, thereby improving long-term weight maintenance. Clinical studies have shown that RYGB combined with semaglutide achieves total body weight reductions of 18-25% within 2 years, markedly exceeding those achieved with surgery alone (137-139). Similarly, phase III studies have demonstrated that patients undergoing SG who receive postoperative semaglutide achieve an additional 7-10% reduction in total body weight over 24 months compared with surgery alone. Mechanistically, bariatric surgery remodels gut microbiota composition and accelerates nutrient delivery to the distal intestine, thereby enhancing endogenous GLP-1 secretion and producing synergistic anorexigenic effects when

combined with exogenous GLP-1RAs. Nevertheless, ~40% of patients undergoing SG experience progressive weight regain within 3-5 years because of compensatory central regulatory mechanisms (140-142).

Beyond GLP-1RA-surgery combinations, novel unimolecular dual- and triple-receptor peptide agonists co-targeting GLP-1R, GCG and MC4R integrate appetite suppression, thermogenesis promotion and hepatic lipid regulation. In preclinical studies, these agents demonstrate greater weight-loss efficacy than single-target GLP-1RAs. Triple GLP-1/GCG/MC4R co-agonists currently in phase II clinical evaluation may also serve as effective adjunctive therapies after bariatric surgery, helping overcome limitations of single-target interventions, although long-term cardiovascular and CNS safety assessments remain ongoing. Furthermore, low-intensity vagus nerve stimulation combined with low-dose GLP-1 analogues, such as tirzepatide, has been shown to enhance gut-brain satiety signaling while reducing gastrointestinal adverse effects, providing a potential therapeutic strategy for individuals unable to tolerate full-dose GLP-1RA treatment. In addition, dietary fiber-derived prebiotics can modulate intestinal short-chain fatty acid production and restore gut-brain axis homeostasis, functioning as adjunctive interventions that enhance the efficacy of neuromodulatory therapies while reducing dosage requirements (143-146).

Balanced advantages and limitations of neuromodulation anti-obesity techniques. Neuromodulation approaches, including invasive vagus nerve stimulation (VNS),

hypothalamic deep brain stimulation (DBS) and non-invasive transcranial neuromodulation, represent non-pharmacological neural-targeting strategies, each with distinct advantages and unresolved translational challenges that warrant balanced discussion rather than unilateral criticism (22).

Unique advantages of neuromodulation. Neuromodulation avoids the systemic adverse effects associated with GLP-1RAs, including gastrointestinal discomfort, thyroid-related risks and pancreatic toxicity, making it a potential option for patients with severe drug intolerance or contraindications to peptide-based therapies (147). It permits cell-type-specific and neural-circuit-specific regulation, as DBS targeting the ARC/PVN selectively modulates orexigenic and anorexigenic pathways without unintended effects on peripheral organs. It also offers potential for synergistic use, as low-intensity VNS may reduce the clinical dose required for GLP-1 receptor agonists, thereby decreasing the incidence of nausea and vomiting while maintaining weight-loss efficacy. Furthermore, implantable devices provide sustained long-term neuromodulation, helping to address poor medication adherence during chronic weight management (148).

Major translational limitations and clinical drawbacks. Several key limitations continue to hinder the clinical application of neuromodulatory therapies for obesity. Intracranial DBS carries risks of hemorrhage, intracranial infection and neural injury, whereas cervical VNS implantation is commonly associated with hoarseness, dysphagia and persistent throat discomfort. Another challenge is the marked interindividual variability in stimulation parameters. Standardized optimal stimulation protocols for patients with obesity have not been established and highly variable weight-loss responses contribute to inconsistent clinical outcomes across phase II and phase III trials. Moreover, prolonged stimulation over 1-2 years may induce adaptive remodeling of hypothalamic reward circuits through long-term neural plasticity, resulting in a gradual decline in therapeutic efficacy and subsequent weight regain. Economic barriers further limit clinical translation, as the high costs of implantable devices and long-term monitoring constrain widespread implementation in primary care settings. In addition, the mechanisms underlying non-invasive transcranial stimulation require further validation. Existing human fMRI studies have not consistently demonstrated signal transmission from prefrontal regions to hypothalamic appetite circuits; therefore, this concept remains an emerging but unconfirmed hypothesis (149-153).

6. Conclusions and outlook

Obesity now constitutes a notable global public health challenge that requires urgent attention. Its development is closely associated with multiple factors, including high-fat and high-sugar diets, sedentary lifestyles, genetic predisposition, socioeconomic status and other contributing factors (154). Although obesity research has advanced substantially, current therapeutic strategies remain limited by the lack of anti-obesity medications that provide both high efficacy and a favorable safety and tolerability profile (155).

Obesity results from complex interactions among hypothalamic neural circuits, gut microbiota-gut-brain axis signaling, chronic inflammation and oxidative stress (156).

The antagonistic ARC POMC/AgRP/NPY neuronal network and the downstream LEP-MC-MC4R pathway represent the central regulatory system governing energy homeostasis. Gut microbiota-derived SCFAs influence gastrointestinal hormone secretion and vagal afferent signaling, whereas AT inflammation and ROS impair central neuronal function and promote insulin resistance, thereby accelerating the progression of obesity.

Current neuron-targeted anti-obesity therapies face three key translational challenges. First, the cell-type-specific regulatory mechanisms of heterogeneous hypothalamic neurons remain incompletely understood, limiting the development of precise neuromodulatory strategies. Second, the signal transduction cascades linking gut microbial metabolites to neural pathways have not been systematically validated *in vivo*, restricting the advancement of microbiota-based adjunctive interventions. Third, the majority of peptide agonists exhibit poor BBB permeability, are associated with systemic adverse effects and are prone to weight regain after treatment discontinuation. In addition, the long-term safety of novel small-molecule targets, such as NMU-R2, requires further longitudinal clinical evaluation. Future interdisciplinary research integrating neuroscience, microbiology and clinical pharmacology is expected to facilitate the development of selective, BBB-permeable neuron-targeted therapeutics. Combined agonists that simultaneously target multiple appetite-regulating receptors, together with non-invasive neuromodulation approaches, may overcome the limitations of single-agent therapies and provide new strategies for the global management of obesity.

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Availability of data and materials

Not applicable.

Authors' contributions

YLL conceived the present study, provided direction and guidance on the whole project. DJK and XL wrote and edited the manuscript. YYZ, YHS, YHL and ZYY performed the literature search and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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