



Neuroendocrine regulation of appetite

Nikolay Botushanov¹, Aleksandar Botushanov¹, Albena Botushanova¹

¹ Department of Endocrinology and Metabolic Diseases, Medical University of Plovdiv, Plovdiv, Bulgaria

Corresponding author: Nikolay Botushanov, Department of Endocrinology and Metabolic Diseases, Medical University of Plovdiv, 15A Vassil Aprilov Blvd., 4002 Plovdiv, Bulgaria; Email: nbotush@gmail.com

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Abstract

Appetite is primarily regulated by complex neuroendocrine pathways that integrate peripheral and central signals to maintain energy homeostasis. Two principal systems govern feeding behavior: the homeostatic system, which responds to metabolic needs, and the hedonic system, which is driven by reward and sensory inputs. The gastrointestinal tract, one of the largest endocrine organs, plays a pivotal role by secreting appetite-regulating hormones in response to nutrients. These signals act on central circuits, particularly within the hypothalamus, involving first-order neurons such as neuropeptide Y/agouti-related peptide and pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript. In addition, gut-derived hormones like ghrelin, peptide YY, glucagon-like peptide 1, cholecystokinin, and others modulate central and vagal pathways. This review provides a detailed account of the molecular and anatomical mechanisms underlying appetite regulation, focusing on the neuroendocrine interactions between the gut and the brain.

Keywords

appetite regulation, hypothalamus, neuroendocrine, feeding behavior, gut-brain axis

Introduction

Appetite is primarily regulated through two mechanisms: homeostatic and hedonic. The gastrointestinal tract (GIT) is the first point of contact with food; it plays a key role in linking nutrient composition and energy content to brain centers that regulate energy homeostasis. The GIT is one of the largest endocrine organs in the body, containing populations of enteroendocrine cells (EECs) throughout its length that synthesize and secrete multiple metabolically active peptides in response to ingested nutrients. These gut hormones regulate digestive function, feeding behavior, energy expenditure (EE), and glucose homeostasis through autocrine, paracrine, and endocrine actions.^[1] In addition to the GIT, peripheral signals reflecting current energy availability also come from adipose tissue, bone, and the pancreas, all of which participate in appetite regulation. There is a close connection between factors released from peripheral tissues under altered energy balance and feeding behavior. These contribute to three motivational processes

that provide the fundamental, unconditioned control over meal initiation and portion size^[2]: 1) Hunger: the drive that initiates food seeking and meal onset, closely linked with desire and motivation to consume specific types of food; 2) Satiety: the process leading to meal termination, influenced by the physical feeling of fullness in the stomach; and 3) Postprandial satiety: suppresses further intake and extends the intermeal interval. Hedonic liking—based on pleasure associated with food stimuli—and prospective consumption (how much an individual expects to eat) also play a role. The timing, size, and content of meals give insights into what, when, and how much a person consumes. Eating patterns are regulated by species-specific physiological processes. In humans, however, additional social and cultural factors influence eating behavior. In eating disorders, this control is disrupted, and it no longer aligns with the body's current energy needs.^[3] Individuals with overweight or obesity typically consume more than those with a normal BMI (18.5-25 kg/m²).^[4] Therefore, understanding the physiological processes that accompany and

regulate meals is essential for recognizing normal and abnormal feeding behavior, including chronic overeating that contributes to the global obesity epidemic.^[5] In this context, highlighting the role of central regulation in shaping feeding behavior, Smith proposed a “paradigm shift from nutritional homeostasis to behavioral neuroscience”.^[6]

Hypothalamic regulation of appetite

Appetite is a central component of energy balance and is tightly regulated by neuroendocrine feedback loops that integrate peripheral and central signals. Two key regulatory systems operate in concert: the homeostatic system, driven by internal metabolic cues, and the hedonic system, driven by external sensory and reward-related cues.^[7] The hypothalamus and other regions of the central nervous system (CNS) integrate peripheral signals indicating energy availability (**Table 1**). These signals are processed by distinct neuronal circuits. Homeostatic regulation primarily involves two opposing pathways: an anorexigenic pathway that suppresses appetite and an orexigenic pathway that promotes food intake. These pathways converge in the arcuate nucleus (ARC) of the hypothalamus and transmit signals to other regions such as the lateral hypothalamus and the paraventricular nucleus (PVN) to modulate feeding behavior.^[8] The ARC contains first-order neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are activated during energy deficit and stimulate feeding. In contrast, pro-opiomelanocortin (POMC) neurons produce alpha-melanocyte-stimulating hormone (α-MSH), which activates melanocortin-4 receptors (MC4R) in the PVN to promote satiety and energy expenditure. POMC neurons

also co-express cocaine- and amphetamine-regulated transcript (CART). Ghrelin stimulates NPY/AgRP neurons, increasing hunger—especially during fasting—while polypeptide Y (PYY), glucagon-like peptide 1 (GLP-1), and oxyntomodulin activate POMC neurons.^[2] In energy surplus, POMC activity predominates, enhancing satiety. MC4R activation improves insulin sensitivity and energy expenditure, whereas AgRP antagonizes this pathway under energy deficit conditions.^[9] Mutations in MC4R are associated with hyperphagia, obesity, and altered glucose metabolism. MC4R is also expressed in EECs and may influence gut hormone secretion.^[10] Ascending hypothalamic projections reach higher-order centers that process sensory and motivational aspects of feeding. Functional MRI (fMRI) studies show that circulating gut hormones like ghrelin, PYY, and GLP-1 modulate neural activity in regions such as the amygdala, orbitofrontal cortex (OFC), insula, and striatum, which are involved in food reward and decision making.^[11,12] Ghrelin enhances sensitivity to food cues, increasing activation in these reward centers, even in the fed state.^[13] Conversely, postprandial PYY and GLP-1 reduce the rewarding value of food and suppress appetite-related brain activity.^[12]

Peripheral signals from the gastrointestinal tract regulating energy balance

Signals originating from the GIT and directed toward appetite and satiety centers function in two directions depending on the body’s current energy needs: 1) orexigenic (appetite-stimulating) and 2) anorexigenic (appetite-suppressing) factors (**Table 2**).

Table 1. CNS regions involved in appetite and feeding regulation. Adapted from: Makaronidis JM, Batterham RL. Obesity, body weight regulation and the brain: insights from fMRI. *Br J Radiol* 2018; 91(1089):20170910

Brain region	Role in feeding behavior
Hypothalamus	Homeostatic control
Hippocampus	Learning and memory; connects energy balance with feeding stimuli
Amygdala	Emotional assessment; evaluates the value of food; links homeostatic and hedonic regulation; contributes to food enjoyment
Insular cortex (gustatory cortex)	Integrates sensory information from taste with feeding processes to form the final perception
Nucleus of the solitary tract (NTS)	Afferent terminal of the vagus nerve; key relay in visceral sensory signaling
Ventral tegmental area (VTA)	Assesses the nutritional and rewarding value of food; generates motivational signals
Cerebellum	Integrates and coordinates somatic-visceral responses during feeding
Nucleus accumbens	Determines motivational and reinforcing properties of food; encodes expected reward; connects motivation with behavior
Orbitofrontal cortex (OFC)	Processes reward; integrates sensory, cognitive, and reward-related information
Cingulate cortex	Involved in decision making
Prefrontal cortex	Translates internal and external cues into feeding behavior; responsible for decision making and behavioral execution

Table 2. Primary orexigenic and anorexigenic peripheral factors, site of secretion, site of action and primary action. (For details see the text)

Factor	Type	Primary action	Site of action	Site of secretion
Ghrelin	Orexigenic	Stimulates appetite and GH secretion	Hypothalamus, vagus nerve	Stomach (P/D1 cells), duodenum
Endocannabinoids	Orexigenic	Enhances reward-based feeding	CNS (mesolimbic reward system)	Brain and gut
NPY	Orexigenic	Stimulates appetite	Arcuate nucleus of hypothalamus (ARC)	Hypothalamus (ARC)
AgRP	Orexigenic	Inhibits melanocortin signaling	Arcuate nucleus of hypothalamus (ARC)	Hypothalamus (ARC)
Leptin	Anorexigenic	Suppresses appetite via ARC neurons	Hypothalamus, vagus nerve	Adipose tissue, stomach
PYY(3-36)	Anorexigenic	Suppresses NPY/AgRP via Y2R	Hypothalamus (ARC), vagus nerve	Distal intestine (L-cells)
GLP-1	Anorexigenic	Inhibits appetite, stimulates insulin	Hypothalamus, vagus nerve	Distal intestine (L-cells)
CCK	Anorexigenic	Delays gastric emptying, induces satiety	Brainstem, hypothalamus	Duodenum, jejunum (I-cells)

Orexigenic factors

Ghrelin is synthesized and secreted by P/D1 cells located in the stomach's antrum and fundus and in the duodenum^[14], both during fasting and at usual mealtimes. Its secretion increases immediately before a meal and declines rapidly postprandially.^[14] Ghrelin secretion is part of an integrated system involving various central nervous system (CNS) and GIT regions. Nutrient-related signals stimulate gastric ghrelin release, activating hypothalamic and dopaminergic feeding centers in the CNS, thereby increasing appetite. Chronic stress, negative energy balance, leptin, and insulin can modulate feeding motivation by stimulating or inhibiting ghrelin release.^[15] Ghrelin secretion is influenced by autonomic nervous system activation, involving cholinergic and adrenergic neurotransmitters. Evidence suggests that increased ghrelin levels under acute or chronic stress—unrelated to negative energy balance—are mediated by sympathetic nervous system activation via pi-adrenergic receptors on ghrelin-secreting cells.^[16] Ghrelin release is inhibited by gastrointestinal hormones released during digestion, such as somatostatin and gastrin. Ghrelin undergoes acylation via O-acyl-transferase, becoming acyl-ghrelin. In this form, it stimulates growth hormone (GH) secretion via growth hormone secretagogue receptor 1a (GHSR1a) and enhances appetite by activating agouti-related protein (AgRP) and neuropeptide Y (NPY) neurons in the hypothalamus. It exerts an orexigenic effect by inhibiting melanocortin receptor 4 (MC4R)^[14], increases the rewarding value of food, stimulates gastric emptying and HCl production, mirroring its secretion pattern. Ghrelin helps maintain energy balance during long-term deficits. Circulating ghrelin levels inversely correlate with weight gain, obesity, and insulin resistance^[17], and positively with

weight loss, anorexia nervosa, and cachexia related heart failure.^[18] Ghrelin also inhibits insulin secretion and stimulates endocannabinoid release.

Endocannabinoids, like ghrelin, have orexigenic effects. The endocannabinoid system plays a central role in homeostatic and non-homeostatic regulation of feeding behavior. Endocannabinoids bind to cannabinoid receptors in the CNS and peripheral tissues. Cannabinoid receptor 1 (CB1R) activation stimulates appetite; its blockade reduces intake. Dietary fatty acids stimulate oral chemosensory receptors and anandamide release.^[19] Anandamide levels increase with prolonged fasting and reflect plasma lipids^[19], activating dopaminergic circuits in the mesocorticolimbic system including the ventral tegmental area and nucleus accumbens, essential for hedonic feeding. Clinical trials have shown limited success for CB1R blockers in treating obesity, indicating that targeting a single appetite-regulating system is insufficient. Food-induced endocannabinoid changes depend on taste quality and are linked to food-related pleasure. The system's role in appetite regulation remains incompletely understood.

Anorexigenic factors

Peptide YY 3-36 (PYY) is secreted from enteroendocrine L-cells in response to protein and fatty acid contact.^[16] Its secretion is proportional to caloric content. Food intake is regulated via the hypothalamus, particularly the melanocortin and neuropeptide Y (NPY) systems in the arcuate nucleus (ARC). PYY binds to Y2 receptors (Y2R), which are widely expressed in the CNS and on afferent vagal terminals. Y2R is a presynaptic inhibitory receptor highly expressed on NPY neurons in the ARC and is accessible to

peripheral hormones. By interacting with Y2R in the hypothalamus, PYY suppresses first-order NPY/AgRP neurons in the ARC, thereby reducing the desire to eat.^[20] Locally, it activates afferent vagal fibers, helping to decrease appetite and feeding motivation. It also reduces the rewarding value of food. Peripheral injection of PYY inhibits food intake and weight gain in rats. This effect is absent in Y2R knockout mice, indicating that its anorexigenic effect depends on Y2R. Peripheral administration of PYY increases c-Fos immunoreactivity in the ARC and decreases hypothalamic NPY mRNA. Intra-ARC injection of PYY(3-36) inhibits food intake. It also suppresses electrical activity of NPY terminals, thus activating adjacent POMC neurons.^[21] In humans, postprandial infusion of PYY(3-36) significantly decreases appetite and food intake by 33% over 24 hours. Thus, postprandial elevation of PYY(3-36) suppresses eating by acting through Y2R in the ARC.^[20,21]

Glucagon-like peptide 1 (GLP-1), a widely studied incretin in clinical practice, has pleiotropic effects on glucose and energy homeostasis. It is secreted from L-cells in response to glucose and fatty acid contact. Its secretion is further stimulated by bile acids. GLP-1 receptors (GLP-1R) can be found throughout the body, including the hypothalamus, liver, pancreas, skeletal muscle, myocardium, and vagus nerve.^[22] GLP-1 stimulates insulin and inhibits glucagon secretion. In the hypothalamus, it activates vagal afferents in the paraventricular nucleus and suppresses appetite.^[21] It also reduces motivation to eat, lowers the rewarding value of food^[23], and delays gastric emptying.

Oxyntomodulin is co-secreted with GLP-1 from L-cells in response to food intake. It binds to both GLP-1 and glucagon receptors (GCGR). GLP-1R activation reduces appetite and energy intake, delays gastric motility and emptying, and promotes glucose-dependent insulin secretion. It centrally suppresses appetite via hypothalamic nuclei.^[24] Glucagon receptor activation boosts glucose production, but concurrent GLP-1R activation counteracts it. Oxyntomodulin infusion improves glucose tolerance in type 2 diabetes, supporting dual GCGR/GLP-1R agonists as a promising treatment for diabetes and obesity by reducing weight and blood glucose more effectively than GLP-1R monotherapy.

Cholecystokinin (CCK) is secreted by L- and I-cells in response to proteins and fatty acids via G-protein-coupled receptor GPR40 and calcium-sensing receptors. It interacts with CCK-1 receptors in the stomach, pancreas, gallbladder, and CCK-2 receptors in the CNS. It activates vagal afferents terminating in the nucleus tractus solitarius (NTS) and stimulates paraventricular nuclei of the hypothalamus. CCK reduces appetite and energy intake, delays gastric emptying, inhibits gastric HCl secretion, and stimulates insulin secretion.^[25] Its effects are potentiated by leptin and inhibited by ghrelin. Vagal afferent responses to CCK are blunted in obesity. fMRI shows activation of brainstem, hypothalamus, and motor cortex after fatty acid intake; these effects are blocked by CCK-2 antagonists. CCK also supports pancreatic P-cell mass and acts as an incretin in certain contexts.^[25]

Glucose-dependent insulintropic peptide (GIP) is secreted by enteroendocrine K-cells in the proximal small intestine in response primarily to glucose and fatty acids. It interacts with GIP receptors in pancreatic islets, the hypothalamus, and adipose tissue. In P-cells, it stimulates glucose-dependent insulin secretion. In the CNS, it promotes hippocampal progenitor cell proliferation and reduces caloric intake.^[26]

Gastric leptin, in addition to its adipose origin, is also synthesized and secreted by chief and parietal endocrine P-cells in the stomach in response to nutrients.^[27] Its secretion is stimulated by insulin and CCK.^[28] Gastric leptin modulates vagal afferent activity, enhancing postprandial satiety signals. In rats, gastric and duodenal vagal afferents express leptin receptors (Lep-R)^[29], many terminating in the stomach. Leptin inhibits vagal afferents during fasting and stimulates them postprandially, adjusting caloric intake based on nutrient status. Local gastric leptin amplifies the anorexigenic effects of circulating leptin.^[30] However, chronic high-fat diets reduce leptin responsiveness in vagal afferents.^[31] The gastric wall contains two mechanosensitive vagal afferent fiber classes. Those in the muscular layer respond to stretch and contraction, while mucosal fibers are activated by contact with larger food particles, contributing to particle size assessment. Mucosal afferent activation delays gastric emptying, enhancing mechanical digestion.^[32] The specific effects of leptin on each vagal afferent subtype, as well as whether they can be modified by dietary changes, remain unknown.^[33]

Uroguanylin is secreted by enterochromaffin cells in the duodenum and small intestine in response to ingested nutrients. It interacts with guanylyl cyclase 2C (GUCY2C) receptors in the gut epithelium and hypothalamus. In the gut, it regulates fluid and electrolyte balance; in the hypothalamus, it promotes satiety and reduces energy intake.^[34]

Neurotensin is produced by enteroendocrine cells in response to dietary lipids. It binds to neurotensin receptors (NTR1, NTR2, NTR3) in the CNS, pancreas, and GIT. It increases proopiomelanocortin (POMC) expression, activates the midbrain dopaminergic system, suppresses appetite, reduces gastrointestinal motility and acid secretion, and enhances glucose-dependent insulin secretion.^[35]

Leptin is secreted by white adipocytes and signals energy stores to the brain. It suppresses appetite by modulating ARC neurons, opposing ghrelin's effects.^[28] Leptin deficiency causes hyperphagia and severe obesity; treatment with leptin reduces ghrelin levels and increases insulin, GLP-1, and PYY postprandially.^[36] In individuals without leptin deficiency, exogenous leptin does not induce significant weight loss.^[37]

Growth differentiation factor 15 (GDF15), originally described as a stress- and inflammation-induced cytokine, also regulates appetite and weight. It acts via the area postrema and NTS and influences the ARC.^[38]

There is evidence that gut anorexigenic hormones work synergistically. Co-administration of GLP-1 and PYY suppresses appetite more effectively than either alone.^[39]

GLP-1, PYY, and OXM have additive effects on satiety and energy reduction.^[40] GIP and CCK enhance GLP-1's effects.^[41] Pancreatic hormones are also involved in appetite regulation. Insulin receptor activation in the ARC reduces appetite.^[42] Amylin, co-secreted with insulin in response to glucose and fats, binds to CNS receptors (especially in the area postrema), relaying signals to the NTS to inhibit feeding.^[43] It acts independently of the hypothalamic loop and is also found in the gastric fundus and bone. Amylin suppresses postprandial glucagon, appetite, energy intake, and delays gastric emptying.^[44]

Sensory, visual, gustatory, and olfactory stimuli regulating appetite

The chemosensory properties of food are among the primary determinants of eating behavior. Visual, gustatory, and olfactory signals strongly influence the decision to initiate a meal and the motivation to continue eating. Taste and smell are especially important in food preference and hedonic enjoyment. Ghrelin has been shown to modulate olfactory sensitivity by enhancing CNS responses to olfactory stimuli. Circulating ghrelin levels directly correlate with olfactory function.^[45] Gut hormones have also been detected in saliva, and their receptors are expressed in taste buds, suggesting a regulatory role in gustatory perception. Preclinical studies indicate that elevated salivary PYY levels alter taste preferences and reduce both energy intake and body weight. The oral cavity represents the initial site of food detection, and chemoreception via taste receptors is the first step in nutrient recognition and subsequent metabolic response.^[46] Several gut hormones—including PYY, ghrelin, insulin, and GLP-1—are present in saliva and influence taste signal modulation, particularly in response to sweet and fatty stimuli.^[47] GLP-1 is expressed in sweet- and umami-sensitive cells and modulates sweet sensitivity.^[47] In addition, taste receptors are found throughout the GIT and are involved in GLP-1 release following glucose ingestion.

Role of vagal stimulation in appetite regulation

The vagus nerve provides bidirectional communication between the brain and the GIT. Afferent vagal neurons serve as early integrators of peripheral energy-related signals, influenced by various gut hormones. Receptors for leptin, ghrelin, CCK, GLP-1, and PYY are located on vagal afferent neurons. These afferents transmit energy availability signals to the nucleus tractus solitarius. Furthermore, the vagus nerve receives direct synaptic input from EECs, which have synapse-like structures called neuropods. These structures can communicate with vagal afferents to rapidly relay nutrient-related signals to the brainstem.^[48] Efferent vagal fibers

originate from the dorsal motor nucleus of the vagus in the medulla, which contains parasympathetic efferent neurons and innervates the muscular and mucosal layers of gastrointestinal organs. Efferent fibers modulate enteric neurons, linking central and enteric nervous systems. Vagal afferents show inherent plasticity, adjusting their response to gut-derived signals during acute and chronic energy status changes. The regulation of gut hormone receptor expression is also dynamic. Ghrelin and CCK modulate vagal phenotype and sensitivity, potentially in opposite directions.^[48]

Genetic and epigenetic influences on appetite regulation

Both homeostatic and hedonic drives related to eating behavior are influenced by genetic and epigenetic predispositions. Population studies have shown that up to 85% of the variability in body mass index (BMI) can be attributed to heritable factors. One well-known obesity-associated variant, rs9939609 in the FTO gene, is linked to increased appetite and preference for high-calorie foods. Normal-weight adults homozygous for this risk allele exhibit higher postprandial ghrelin levels, elevated hunger, and altered reward responses in the brain compared to those carrying the low-risk variant.^[49] Environmental epigenetic influences—especially those passed through perinatal programming—can also significantly shape individual body weight trajectories.^[50] Although the exact extent to which genetic factors influence weight remains to be fully understood, individuals show wide interindividual variability in their propensity to gain weight, baseline appetite levels, food preferences, and biological responses to energy excess or restriction.

Conclusions

Appetite regulation is orchestrated through neuroendocrine interactions between the gut, CNS, and peripheral tissues. Gut hormones act via the hypothalamus and vagus nerve to modulate appetite-related circuits. Orexigenic signals such as ghrelin and endocannabinoids promote intake, while anorexigenic signals including PYY, GLP-1, and CCK induce satiety. Understanding these mechanisms provides insight into both physiological feeding and the pathophysiology of obesity and eating disorders. Targeting multiple components of this regulatory network may offer more effective therapeutic strategies for appetite-related disorders.

Ethical approval

Not applicable

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

Conflict of interest

The authors have declared that no competing interests exist.

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All authors have contributed equally.

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