

Review

The Bioenergetic Architecture of Metabolic Regulation: From Gut–Brain Signalling to Next-Generation Peptide Pharmacology

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Abstract

Energy homeostasis arises from a complex interplay between gut-derived hormones, the central nervous system, and pancreatic function. Beyond the classical incretin axis, a broad spectrum of gut peptides acts in concert to coordinate appetite regulation, nutrient sensing, gastric motility, and systemic bioenergetic balance. Perturbation of this network contributes to metabolic disorders such as obesity, type 2 diabetes, and cachexia, underscoring its pivotal role in physiological and pathological energy regulation. This review provides an integrated analysis of the mechanisms through which gut–brain–pancreas communication maintains metabolic homeostasis, with particular attention to the dynamic cross-talk between peripheral endocrine signals and central regulatory circuits. Alterations in these pathways are examined in relation to their impact on energy expenditure and substrate utilisation, alongside recent translational efforts exploiting multi-receptor peptide agonism and combinatorial hormonal modulation to restore metabolic equilibrium. Emerging therapeutic approaches increasingly aim to engage multiple bioenergetic pathways simultaneously, supported by advances in peptide engineering and molecular design. By conceptualising metabolic regulation as a coordinated network rather than a linear hormonal cascade, this article delineates a physiological and translational framework for next-generation interventions targeting bioenergetic dysfunction in human disease.

Keywords: gut–brain–pancreas axis; bioenergetic regulation; endocrine signalling; peptide hormones; multi-peptide strategies



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1. Introduction

Over the last twenty years, the treatment landscape for metabolic diseases has undergone remarkable evolution, primarily due to the advent of glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Originally developed to treat type 2 diabetes, these agents have demonstrated a wide range of pleiotropic effects, including significant weight loss, cardiovascular improvements, and regulation of systemic energy metabolism, thereby solidifying their role as a fundamental component of contemporary metabolic medicine (Figure 1) [1]. The clinical success of next-generation molecules such as liraglutide, semaglutide, and tirzepatide has led to new therapeutic approaches. Metabolic regulation is no longer viewed as a linear pathway but as an interconnected hormonal network that can be targeted pharmacologically [2]. Indeed, despite their high efficacy, therapeutic responses

exhibit significant variability among individuals, including weight-loss plateaus and the differential durability of metabolic benefits. These patterns emphasise that energy balance is sustained not by a single pathway but by an integrated system connecting the gut, brain, and pancreas [3–5].

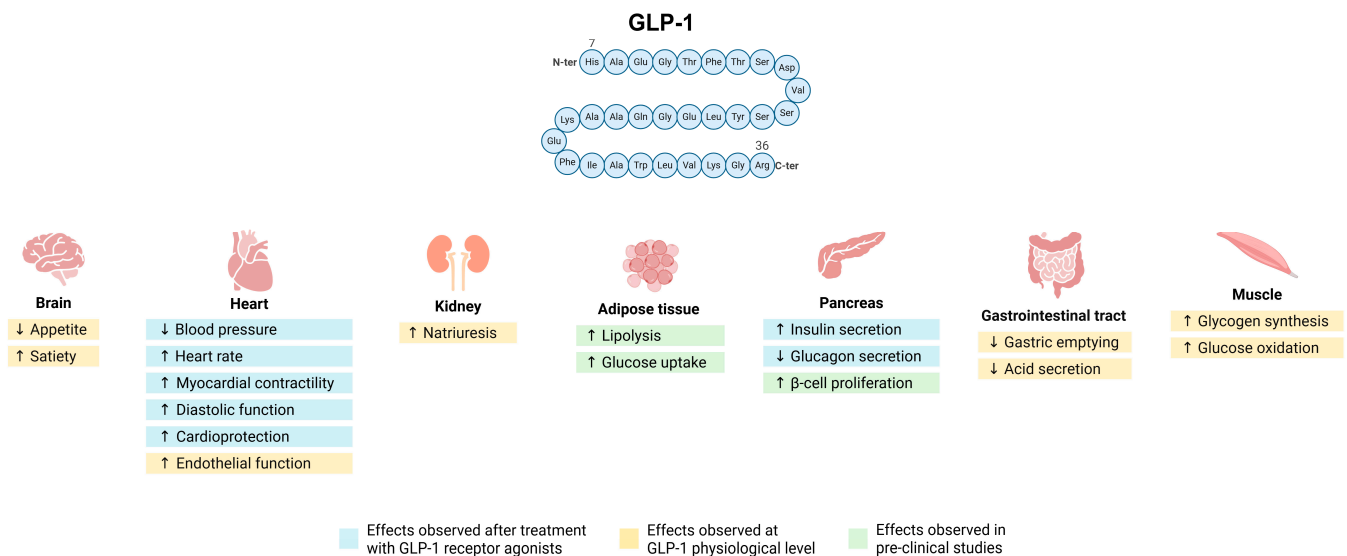


Figure 1. Systemic actions of GLP-1 across metabolic organs. GLP-1 exerts coordinated effects on the brain, pancreas, GI tract, heart, kidney, adipose tissue, and skeletal muscle through tissue-specific receptor activation and downstream signalling pathways, supporting nutrient sensing, glycemic control, cardiovascular regulation, and whole-body energy homeostasis. Upward arrows (↑) indicate up-regulation, while downward arrows (↓) indicate down-regulation. Numerical values at the N- and C-termini of GLP-1 indicate the specific positions of amino acid residues within the peptide sequence. Created with BioRender.com.

Within this framework, intestinal enteroendocrine cells (EECs) play a central role. Acting as nutrient-sensing sentinels, they release multiple peptides, including GLP-1, GIP (gastric inhibitory peptide), PYY (peptide tyrosine tyrosine), CCK (cholecystokinin), amylin, and ghrelin, in response to nutrient exposure. These hormones communicate via endocrine, paracrine, and neurocrine pathways to control satiety, food consumption, energy use, and substrate metabolism [6,7]. Convergence of these peripheral signals occurs within key central circuits, including hypothalamic POMC (proopiomelanocortin) and AgRP (agouti-related neuropeptide) neurons, brainstem NTS (nucleus of the solitary tract) pathways, and vagal afferents, which integrate hormonal inputs with autonomic and sympathetic outputs to coordinate metabolic responses [8,9]. The intestinal endocrine network operates through extensive functional overlap and counter-regulation, an evolutionary design that confers resilience to perturbations. Yet, this redundancy also poses therapeutic challenges: chronic stimulation of a single hormonal pathway, such as the GLP-1 axis, may trigger compensatory mechanisms that progressively attenuate treatment efficacy. To overcome these limitations, metabolic pharmacology is shifting toward multi-receptor approaches. Dual and triple agonists that co-activate GLP-1, GIP, and/or glucagon receptors have demonstrated more robust and durable improvements in metabolic outcomes than traditional GLP-1 RAs [10]. These observations suggest that therapeutic benefit results not only from combined receptor activation but also from the resynchronisation of the integrated hormonal network, mimicking endogenous physiology more closely [11,12]. Receptors for GLP-1, amylin, and ghrelin are expressed in mitochondria-rich tissues such as skeletal muscle and brown adipose tissue, where they modulate mitochondrial biogenesis, mitochondrial dynamics, and energetic efficiency [13]. Through modulation of

pathways such as AMPK (AMP-activated protein kinase), mTOR (mechanistic target of rapamycin), and PGC-1 α (peroxisome proliferator-activated receptor-gamma coactivator), these peptides directly influence mitochondrial respiration, substrate selection, and ATP (adenosine triphosphate) generation [14,15]. Perturbations in gut–brain signalling can therefore induce redox imbalances, shifts in substrate preference, and mitochondrial dysfunction, providing a direct mechanistic bridge between neuroendocrine communication and bioenergetic homeostasis. From a pathophysiological standpoint, these integrated networks help explain the broad spectrum of metabolic phenotypes. In obesity, for instance, blunted postprandial responses of GLP-1, PYY, and CCK coexist with hyperactive ghrelin signalling and hypothalamic leptin and insulin resistance [16,17]; conversely, in catabolic conditions such as cachexia, excessive suppression of orexigenic signals and increased energy expenditure predominate [18,19]. These alterations are often accompanied by systemic inflammation and receptor dysregulation, reinforcing a vicious cycle of impaired energy homeostasis [20]. This systems-level perspective carries important translational implications: future metabolic therapies should shift from single-target strategies toward coordinated modulation of the entire peptide network governing appetite and energy balance. Activating one receptor alone is insufficient; rather, the goal is to restore the functional coherence of the gut–brain–pancreas axis, thereby reestablishing a more physiological and sustainable bioenergetic balance. Accordingly, this review aims to integrate current molecular, physiological, and clinical insights into the gut–brain–pancreas axis and to explore its therapeutic implications. Moreover, we discuss how multi-hormonal modulation, via dual or triple agonists, may represent a promising strategy for treating metabolic diseases, targeting not only clinical endpoints but also recalibrating the entire energy-regulatory network.

2. The Gut–Brain Axis

The gut–brain axis is a bidirectional communication system. Signals travelling from the brain to the gut, mediated by the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, regulate gastrointestinal motility, secretion, and digestive processes [21,22]. The largest body surface in contact with the external environment, the gastrointestinal tract, acts as a true sensory organ, responding to mechanical, nutritional, microbial, pathogenic, and toxic stimuli to maintain homeostasis [23]. Following nutrient ingestion, luminal contents reach the duodenum and jejunum, stimulating enteroendocrine cells. These cells secrete bioactive peptides that exert paracrine effects on vagal afferents, enteric neurons, and immune cells, as well as endocrine actions on central nervous system targets [24,25]. Although EECs constitute less than 1% of the epithelial population, they form the largest endocrine organ in the body, producing stomach hormones such as ghrelin, gastrin, histamine, and somatostatin [26], along with intestinal peptides including GLP-1, PYY, neurotensin, OXM (oxyntomodulin), CCK, GIP, motilin, secretin, and GLP-2 [27,28]. Together, these hormones regulate nutrient assimilation, satiety, glycemic control, and multiple aspects of systemic physiology.

2.1. Enteroendocrine Cell Function and Local-Systemic Signalling Integration

Hormone secretion relies on nutrient detection through G protein-coupled receptors (GPCRs) and channels; for instance, glucose stimulates L (GLP-1) and K (GIP) cells via sodium-glucose co-transporter 1 (SGLT1) [29,30]. Circulating concentrations reflect both the site and timing of nutrient absorption, as illustrated by the rapid GIP peak originating from duodenal K cells [31].

However, increasing evidence suggests that the relative contribution of endocrine versus paracrine signalling varies substantially across peptides. EECs secrete high con-

centrations of GLP-1, GLP-2, CCK, SCT, and neurotensin, whose receptors are widely expressed on neighbouring endocrine cells, ENS (enteric nervous system) neurons, vagal afferents, immune cells, and mesenchymal populations [32,33], indicating that many physiological effects arise from local circuits. This interpretation is consistent with the extremely short half-life of GLP-1 in circulation (2–3 min), of which only 10–15% reaches the systemic bloodstream [34]. Nonetheless, GLP-1 and GIP receptors are also expressed on pancreatic β -cells and accessible regions of the brain, including the area postrema and specific hypothalamic nuclei, ensuring endocrine actions remain physiologically relevant. This distinction between local and systemic effects is crucial for designing therapeutic strategies to stimulate endogenous peptide release [35–37]. Hormones co-released from EECs frequently display overlapping and cooperative functions: GIP and GLP-1 synergistically stimulate insulin secretion [38]; CCK, OXM, neurotensin, and PYY reduce food intake by modulating vagal and hypothalamic circuits [39]; CCK and secretin promote pancreatic secretion; and GLP-1, PYY, and CCK all slow gastric emptying to optimise nutrient absorption and enhance satiety [40–42].

Region-specific receptor expression along the gastrointestinal tract further diversifies EEC responsivity, yet how signals from discrete gut segments are integrated into unified metabolic responses remains incompletely understood. Selective stimulation of specific EEC subtypes is emerging as a strategy to clarify these mechanisms and to design targeted interventions [43,44].

2.2. Central and Pancreatic Integration of Peptide-Derived Signals

Within the central nervous system, the hypothalamus functions as the principal core for metabolic integration. Neurons in the arcuate nucleus detect circulating hormones and vagal-derived inputs, with anorexigenic POMC/CART (cocaine and amphetamine-regulated transcript) neurons and orexigenic neuropeptide Y (NPY)/AgRP neurons exerting opposing influences on energy intake and expenditure [45]. These first-order neurons transmit signals to downstream nuclei in two steps: first, to the paraventricular (PVN), ventromedial (VMH), and lateral hypothalamus (LH) to coordinate neuroendocrine outputs, autonomic tone, glucose homeostasis [46], and motivational aspects of feeding; second, rapid integration occurs in the brainstem via the nucleus tractus solitarius, modulating parasympathetic activity through the dorsal motor nucleus of the vagus [47,48]. The islets of Langerhans operate at the intersection of these regulatory loops. β -cells and α -cells respond to combinations of blood glucose, incretin and non-incretin peptides, vagal neurotransmission, and sympathetic signals to regulate insulin and glucagon secretion [49,50]. Through these integrated mechanisms, the pancreas translates central and peripheral cues into metabolic action, stabilising glucose levels and coordinating nutrient storage and mobilisation (Figure 2) [51].

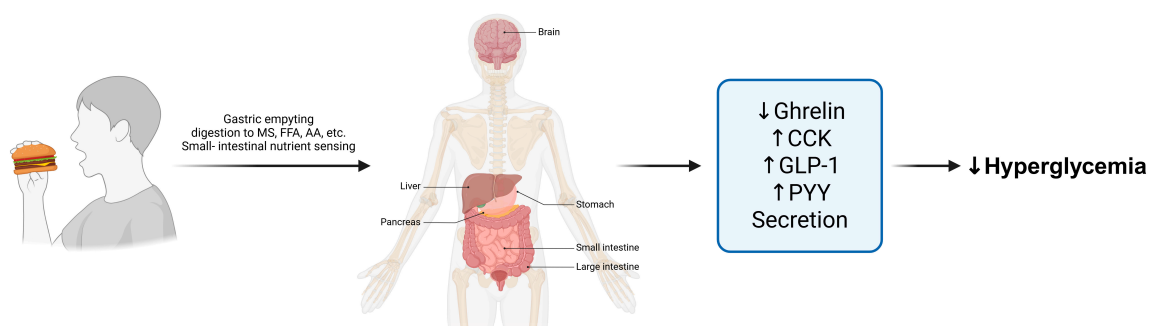


Figure 2. Integrated physiological response to meal ingestion and small-intestinal nutrient sensing. Upward arrows (↑) indicate up-regulation, while downward arrows (↓) indicate down-regulation. Created with BioRender.com.

2.3. Bioenergetic Regulation and Pathophysiological Disruption of the Gut–Brain–Pancreas Axis

Beyond neuroendocrine and autonomic regulation, the gut–brain–pancreas axis exerts a profound influence on cellular energy metabolism, linking hormonal signalling to mitochondrial and substrate-level adaptation [52,53]. The hypothalamus itself serves as a nutrient and energy sensor, responding to glucose, fatty acids, ketone bodies, and hormonal cues to orchestrate systemic metabolic adaptation [54]. Energy homeostasis, therefore, emerges from the coordinated interplay of orexigenic (hunger-promoting) and anorexigenic (satiety-promoting) signals, which dynamically alternate according to nutritional state and bioenergetic demand [45]. Under physiological conditions, redundancy and cross-talk among these pathways enhance robustness. However, in pathological contexts, such as obesity, chronic inflammation, insulin and leptin resistance, or ageing, this redundancy may become maladaptive [55]. Impaired central sensing can distort the perception of energy availability, attenuate satiety responses, promote persistent activation of orexigenic circuits, and uncouple pancreatic hormone secretion from real metabolic needs [56,57]. Given the ongoing rise in obesity and its associated comorbidities, including type 2 diabetes, cardiovascular disease, osteoarthritis, and specific cancers, there is an urgent need for safe and effective metabolic therapies [58]. Pharmacological interventions directly targeting the brain to suppress appetite or increase energy expenditure have historically been limited by modest efficacy or unacceptable side effects [59,60]. In contrast, therapies based on gut-derived hormones have demonstrated substantial clinical success, providing a compelling rationale for harnessing the gut–brain axis in the treatment of metabolic disease [61].

3. Key Peptides Beyond the Incretins

Energy homeostasis depends on the integration of multiple peripheral and central signals. These signals continuously convey information on nutrient availability, energy demand, and metabolic efficiency. Incretin hormones such as GLP-1 and GIP have revolutionised treatment approaches to metabolic disease, but they represent only a fraction of the extensive peptidergic network that regulates the gut–brain–pancreas axis. These peptides serve as real-time biochemical translators between nutrient flux and energy expenditure. They modulate appetite, digestion, and substrate utilisation in response to peripheral metabolic states and central neuroenergetic needs. Moreover, in recent years, a new concept emerged, “microgenderome”, which suggests that sex hormones and gut microbiota composition influence enteroendocrine peptides, such as GLP-1, PYY and CCK, secretion and responsiveness. The secretion of these peptides is affected by variations in microbiota profiles between genders, as well as by changes associated with puberty, menopause, and ageing [62]. Nevertheless, human studies investigating postprandial physiological roles of such peptides (e.g., ghrelin, GLP-1, PYY and CCK) show marked heterogeneity, with conflicting results between obese and normal individuals. Many studies suggest postprandial responses of peptides, involved in the gut–brain–pancreas axis, vary significantly and are often affected by factors such as study design, nutrient composition, adiposity, insulin sensitivity, behavioural factors, and individual metabolic and environmental conditions [63].

3.1. Ghrelin: The Hunger Hormone

Ghrelin is a 28-amino-acid brain–gut peptide hormone. It is mainly produced in the stomach, with smaller amounts in the hypothalamus, pituitary, and peripheral organs [64]. Ghrelin is released in pulses that anticipate meals, mirroring the fasting–feeding cycle [65,66]. Its plasma levels rise before meals and drop rapidly within an hour after eating [67]. Besides stimulating appetite via NPY/AgRP neurons in the arcuate nucleus, ghrelin has broad metabolic and energy-related roles. Ghrelin activates hypothalamic AMPK in arcuate and ventromedial

nuclei, enhancing neuronal energy sensing and plasticity in orexigenic circuits [64,68]. In the periphery, ghrelin increases hepatic glucose output [69,70] and reduces glucose-stimulated insulin secretion by modulating pancreatic β -cell activity in humans [71]. This peptide also shifts substrate use by promoting adipogenesis and lipid storage in adipocytes, thereby helping conserve glucose for essential oxidative tissues such as the brain [72]. Conversely, it decreases PKA (protein kinase A) activity in vagal afferents and increases hepatic glucose production along the gut–brain–liver axis [73]. Indeed, it was shown that the anorexigenic effects of PYY and GLP-1 require an intact vagus nerve, suggesting that multiple gut peptides converge on shared vagal circuits [74]. Knockdown and knockout studies of glucagon-like peptide-1 receptors (GLP-1R) indicate that the glucose-lowering effects of GLP-1 depend on GLP-1R expression in peripheral neurons [75,76]. In addition, truncally vagotomized humans do not exhibit normal reductions in food intake, gastric emptying, or glucagon secretion in response to GLP-1R agonists and display diminished insulinotropic effects [44,77]. Dysregulation of ghrelin signalling contributes to several metabolic disorders. In obesity, reduced postprandial ghrelin suppression and altered ghrelin dynamics are frequently observed, which are often interpreted as indicators of decreased ghrelin responsiveness [67,78]. In contrast, elevated ghrelin levels are typical of cachexia and anorexia nervosa, suggesting compensatory activation of hunger-promoting pathways [79]. Ghrelin also functionally interacts with key satiety and incretin peptides, such as GLP-1 and PYY [78]. Therapeutic modulation of the ghrelin receptor (GHS-R1a) is being explored for appetite suppression in obesity and for anabolic support in wasting conditions, highlighting the dual clinical potential of targeting this pathway.

3.2. Peptide YY and Obestatin: The Postprandial Restraint Signals

Peptide YY, secreted from enteroendocrine L-cells predominantly located in the distal ileum and colon in response to nutrient ingestion, functions as a key postprandial satiety hormone [80,81]. After food intake, circulating PYY₃₋₃₆ rises rapidly. It preferentially activates presynaptic Y₂ receptors (Y₂R) on NPY/AgRP neurons in the arcuate nucleus, leading to disinhibition of anorexigenic POMC neurons and, subsequently, reduced food intake [82,83]. In humans, infusion of physiological postprandial concentrations of PYY₃₋₃₆ suppresses appetite and decreases 24 h energy intake by approximately 30% [82,84]. Physiological effects attributed to PYY include slowing of intestinal transit [85,86], inhibition of gastrointestinal anion and electrolyte secretion [87]. Peripherally, PYY slows gastric emptying and intestinal motility, prolonging nutrient absorption and contributing to sensations of fullness [83]. PYY interacts strongly with GLP-1 within the gut–brain axis, and co-infusion studies in humans demonstrate synergistic reductions in energy intake when PYY₃₋₃₆ is combined with GLP-1 compared with either hormone alone [88]. This complementary action has inspired the development of dual- and multi-agonist therapeutics combining PYY-like activity with GLP-1 receptor agonism, with early-phase studies reporting promising effects on weight reduction and glycemic control [89,90]. Obestatin is a 23-amino-acid peptide derived from the preproghrelin precursor, similar to ghrelin. It was originally identified as an anorexigenic counterpart to ghrelin, based on its reported inhibition of food intake and gastric motility in rodents [91]. However, subsequent studies failed to reproduce these effects consistently, and the proposed initial receptor, GPR39, was not confirmed as a physiological target [92–95]. Thus, the role of obestatin in appetite regulation remains controversial. In human islets, obestatin promotes β -cell survival, reduces apoptosis, and induces expression of genes involved in maintaining β -cell mass and function [96]. It also enhances the in vitro generation and survival of β -like cells from pancreatic precursors [97]. In cellular and animal models, obestatin exerts cytoprotective actions, improving mitochondrial integrity and reducing oxidative stress under metabolic stress conditions [98,99].

Together, PYY and obestatin constitute feedback components of the gut–brain–pancreas axis: PYY primarily functions as a postprandial “nutrient sufficiency” signal that integrates gastrointestinal and hypothalamic satiety pathways. In contrast, obestatin mainly acts as a cellular protective factor supporting β -cell viability and mitochondrial stability during metabolic overload. Both peptides aid in the coordinated regulation of energy intake, nutrient handling, and metabolic resilience.

3.3. Amylin: The Synchronizer of Metabolic Timing

Amylin, also known as islet amyloid polypeptide (IAPP) or diabetes-associated peptide, is a member of the calcitonin (CT) family of peptides [100]. Amylin exerts its biological effects by activating amylin receptors (AMYRs) [101]. These receptors are composed of the calcitonin receptor (CTR), a classic GPCR, combined with one of three receptor activity-modifying proteins (RAMPs): AMY1R, AMY2R, and AMY3R [102]. AMYRs are widely distributed in the CNS, including the hypothalamus and nuclei of the dorsal-vagal complex such as the area postrema and nucleus tractus solitarius [103]. Amylin, acting via its receptors, regulates glucose appearance through three coordinated mechanisms [104]. First, it slows gastric emptying, delaying nutrient delivery to the small intestine and thereby attenuating the postprandial rise in blood glucose. Second, it suppresses meal-induced glucagon secretion, reducing glucagon-stimulated hepatic glucose output. Third, amylin induces meal-ending satiation by activating the area postrema and the nucleus tractus solitarius, which project to hypothalamic circuits controlling energy intake. In addition to its acute glycemic effects, amylin reduces adiposity and increases energy expenditure [105]. Amylin can be viewed as a “metabolic synchronizer,” aligning nutrient flux with mitochondrial oxidative capacity. Preclinical studies suggest that amylin may influence hypothalamic AMPK signalling and promote lipid oxidation in peripheral tissues, thereby improving energy partitioning and limiting ectopic fat deposition. Altered amylin production, aggregation, and signalling dynamics have been implicated in obesity, insulin resistance and type 2 diabetes [104,106,107]. Notably, human IAPP is the major constituent of islet amyloid deposits, tightly linking dysregulated amylin biology to progressive β -cell dysfunction [108,109]. Furthermore, amylin also appears to play a role in lipid metabolism by potentially modulating chylomicron uptake [110]. This effect may be mediated through direct regulation of lipoprotein receptors or indirectly via modulation of insulin activity [111]. As amylin plays a critical role in glucose regulation and energy balance, it is a promising target for therapeutic intervention. However, the clinical application of native amylin is limited by its short half-life, structural instability, and propensity to form amyloid aggregates [112]. Starting from amylin, some compounds have been synthesised: davalintide [113], PEGylated or glycosylated amylin [114]. The next-generation amylin-targeted drugs include: amycretin, an unimolecular GLP-1 agonist, and an amylin oral receptor agonist, where the combination of amylin and GLP-1 agonism has shown additive or synergistic benefits for weight loss and metabolic efficiency. Eloralintide (LY3841136), a potent, long-acting once-weekly amylin receptor agonist, is designed to have minimal calcitonin activity, unlike other amylin agonist molecules [115–117].

3.4. Cholecystokinin: The Rapid Satiation Trigger

Cholecystokinin, also known as CCK, is a neuropeptide released from intestinal L cells and cerebral neurons after nutrient consumption [118]. This peptide belongs to a family of regulatory peptides that includes also gastrin, which is a ligand for the CCK₁ and CCK₂ receptors [119]. Beyond its classical digestive functions, CCK is among the most potent short-latency satiation signals, activating within minutes of nutrient entry into the duodenum. Its anorexigenic effects are primarily mediated by activation of CCK-A

receptors on vagal afferents, which relay signals to the NTS and onward to hypothalamic targets [120,121]. CCK is involved in metabolic regulation and lipid absorption: regulates the release of pancreatic exocrine enzymes which plays a role in the digestion of fats, proteins, and carbohydrates; causes contraction and relaxation of the gallbladder via the sphincter of Oddi in response to food; regulates the release of bile acid to aid in further fat digestion in the small intestine and interacts with leptin and GLP-1 pathways to amplify satiety and enhance postprandial thermogenesis [122]. The introduction of long-chain fatty acids stimulates the release of CCK, which links CCK₁ receptors and activates vagal efferent neurons, increasing intracellular calcium. CCK initially activates the afferent fibres in the small intestine via a paracrine mechanism. CCK can inhibit gastric emptying by relaxing the proximal stomach, thereby increasing tension in the pyloric sphincter and contributing to satiety [123]. CCK signalling engages hindbrain-forebrain pathways and may interface with limbic and reward-related circuits. However, its contribution to hedonic processing is less clearly defined than that of peptides such as GLP-1 [124]. Synergistic interactions with leptin and GLP-1 further reinforce this integrative role: leptin markedly potentiates CCK-induced vagal activation and satiation, amplifying meal-related negative feedback [125,126] (Table 1).

Table 1. Overview of common gut–brain peptides. Upward arrows (↑) indicate up-regulation, while downward arrows (↓) indicate down-regulation.

Peptide	Origin	Main Receptor(s)	Central Effects	Peripheral Effects	Therapeutic Relevance
Ghrelin	Stomach, hypothalamus, pituitary	GHS-R1a	Activates NPY/AgRP neurons; hunger signal	↑ hepatic glucose output; ↓ insulin secretion; ↑ adipogenesis	Obesity (antagonism); cachexia/anorexia (agonism) [69–73]
PYY (PYY₃₋₃₆)	L-cells in distal ileum and colon	Y2R	Reduces appetite; disinhibits POMC neurons	↓ gastric emptying; ↓ intestinal motility	Obesity; Metabolic syndrome [85–87,127,128]
Obestatin	Preproghrelin-derived peptide	GPR39 (not confirmed)	Controversial anorexigenic effect	↑ β-cell survival; ↑ β-like cell generation (in vitro)	Metabolic resilience; β-cell protection [96–98]
Amylin (IAPP)	β-cells	AMYRs	Activates AP/NTS → hypothalamic satiety pathways	↓ gastric emptying; ↓ postprandial glucagon; ↓ adiposity; ↑ energy expenditure;	T2DM; Obesity [103–111]
CCK	Intestinal L-cells and neurons	CCK1R CCK2R	Rapid satiation; integrates hindbrain-forebrain pathways	Regulates pancreatic enzyme secretion; gallbladder contraction; inhibits gastric emptying; postprandial thermogenesis	Obesity; Digestive regulation [122–126,129,130]

3.5. Other Emerging Peptides: Beyond Classical Gut Hormones

Beyond the classical gut–brain hormone repertoire, several additional peptides have emerged as modulators of energy balance, linking gastrointestinal nutrient sensing with central and peripheral metabolic responses. Neurotensin, secreted from N-cells in the distal small intestine in response to intraluminal lipids, exerts both local and central actions [131,132]. Neurotensin slows intestinal transit and facilitates lipid digestion through effects on pancreatic secretion and small-bowel motility [133]. Centrally, it modulates dopaminergic and other neuromodulatory circuits implicated in feeding behaviour and thermoregulation [134]. More recent data indicate that neurotensin signalling also influences adaptive thermogenesis and energy expenditure in rodents, in part via adipose-

derived neurotensin, which acts as an anti-thermogenic factor [135]. Neurotensin exerts a robust anorectic effect in animal models, whereas its relevance to human appetite regulation remains less consistent and not yet fully established [132,136]. Oxyntomodulin, a proglucagon-derived peptide co-secreted with GLP-1 from intestinal L-cells, functions as a dual agonist at GLP-1 and glucagon receptors [137,138]. This dualism translates into both appetite suppression and increased energy expenditure in humans, making oxyntomodulin an early prototype for modern GLP-1/glucagon co-agonists [139]. Secretin, classically known for stimulating pancreatic bicarbonate secretion, has recently re-emerged as a gut-derived activator of brown adipose tissue. In rodents, postprandial secretin robustly activates brown adipose tissue (BAT) and increases energy expenditure, while early human studies suggest a potential BAT-activating effect, although data remain preliminary [140,141]. These findings reposition secretin as a short-acting effector of nutrient-coupled thermogenic responses rather than a purely exocrine hormone. Nesfatin-1, derived from nucleobindin-2 and expressed in both the gastrointestinal tract and hypothalamus, reduces food intake via melanocortin-dependent pathways [142,143]. In rodent models, central and peripheral nesfatin-1 improve glucose homeostasis and insulin sensitivity, acting on the liver, skeletal muscle and adipose tissue [144]. Experimental data also support anti-inflammatory and anti-oxidant actions of nesfatin-1, together with modulation of cellular stress responses, although these cytoprotective effects are only partially characterised in humans [145,146]. Growth differentiation factor 15 (GDF15), a stress-induced mitokine, is upregulated by mitochondrial dysfunction and nutrient overload and has emerged as a potent regulator of systemic energy homeostasis [147,148]. Acting via the GFRAL-RET receptor complex in the area postrema and nucleus tractus solitarius, GDF15 strongly suppresses appetite in rodents and non-human primates, while human physiology appears broadly consistent, although long-term metabolic effects are still being defined [149,150]. Unlike classical nutrient-triggered gut hormones, GDF15 secretion primarily reflects cellular stress, functioning as a long-range negative-feedback signal that limits metabolic overload and links mitochondrial integrity to whole-body energy regulation [148]. The mechanisms described above highlight the importance of gastrointestinal peptides as active regulators of postprandial physiology. The transition from food intake to nutrient absorption triggers a coordinated sequence in which gastric emptying, intestinal nutrient detection, and targeted secretion of gut-derived hormones occur as interconnected events (Table 2).

Table 2. Overview of emerging peptides in gut–brain axis. Upward arrows (↑) indicate up-regulation, while downward arrows (↓) indicate down-regulation.

Peptide	Origin	Main Receptor(s)	Central Effects	Peripheral Effects	Therapeutic Relevance
Neurotensin	N-cells in distal small intestine	NTRs	Modulates dopaminergic and neuromodulatory feeding circuits; thermoregulation	↓ intestinal transit; ↑ lipid digestion	Metabolic regulation [131–135]
Oxyntomodulin (OXM)	L-cells, proglucagon-derived; co-secreted with GLP-1	GLP-1R GCGR	Appetite suppression	↑ energy expenditure;	Obesity [137–139]
Secretin	S-cells	Secretin-R	BAT activation; increases energy expenditure	↑ pancreatic bicarbonate secretion	Metabolic modulation; Thermogenesis [140,141]

Table 2. Cont.

Peptide	Origin	Main Receptor(s)	Central Effects	Peripheral Effects	Therapeutic Relevance
Nesfatin-1	Nucleobindin-2 (GI tract and hypothalamus)	Not fully defined	Reduces food intake via melanocortin pathways; improves glucose homeostasis centrally	Anti-inflammatory and antioxidant (in rodents)	Obesity; Insulin resistance [142–144]
GDF15	Stress-induced mitokine	GFRAL-RET	Strong appetite suppression (in rodents); stress-related energy regulation (in non-human primates)	Long-range negative-feedback on metabolic overload	Obesity; Metabolic stress [147–149]

These peptides act as essential messengers connecting the gastrointestinal tract with the brain, pancreas, liver, and other metabolic tissues. By affecting satiety signals, modulating the release of insulin and glucagon, and limiting hepatic glucose output, they transform digestive cues into systemic metabolic responses (Figure 3).

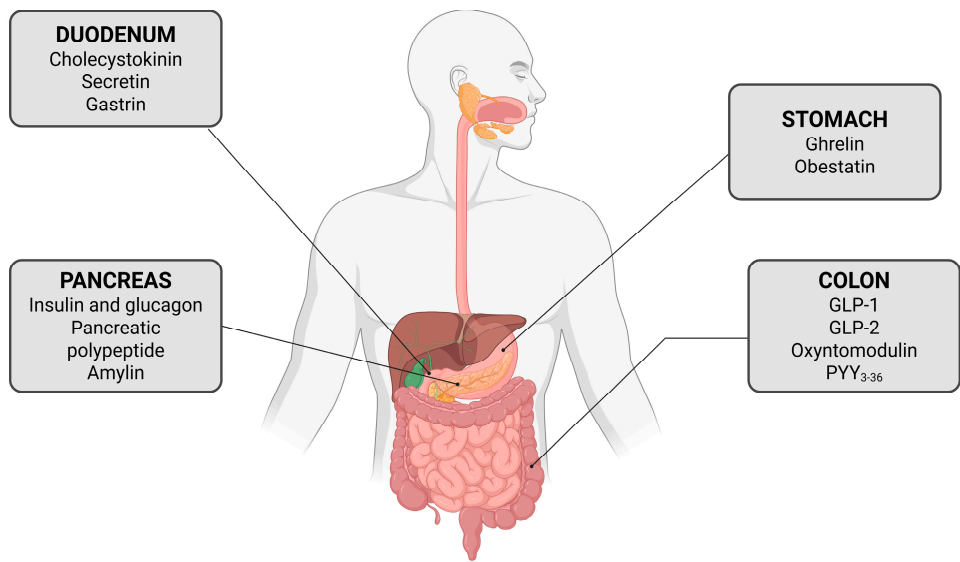


Figure 3. Anatomical distribution of key gastrointestinal peptides involved in metabolic regulation. Created with BioRender.com.

4. Therapeutic Implications and Combinatorial Rationale

4.1. From Single-Target to Network-Oriented Therapy

Unlike the previous idea that individual hormones function as isolated regulators, recent evidence indicates that metabolic regulation results from the combined activity of peptide networks, rather than single signalling points. Therefore, therapeutic strategies targeting a single receptor often address only a narrow component of the system, leaving broader bioenergetic dysregulation unresolved. This has led to a shift toward network-oriented pharmacology, where interventions aim to re-engage multiple physiological pathways simultaneously. Instead of focusing on enhancing a single receptor’s activity, modern peptide-based therapies aim to restore coordination within gut–brain–pancreas circuits. Peptide combinations or multi-receptor agonists mimic natural co-release patterns and re-establish coherence among metabolic signals that collectively regulate appetite, digestion and insulin secretion. In this framework, treatment success is measured by the restoration of system-level synchrony. Peptide hormones coordinate their actions through distinct yet convergent signalling pathways. Both GLP-1 and amylin are secreted in response to nutrient intake, but they utilise different receptor systems, exhibit unique

time courses, and target separate anatomical sites. GLP-1 acts via receptors on pancreatic β -cells and via vagal-hindbrain pathways, enhancing glucose-dependent insulin secretion, slowing gastric emptying, and increasing satiation. In contrast, amylin primarily acts through calcitonin receptor/RAMP complexes and targets the area postrema and other hindbrain nuclei [104,118]. Evidence indicates that GLP-1 and amylin function as co-secreted meal signals, regulating energy intake via distinct receptors and central circuits [151]. Additional gut-derived peptides further contribute to this regulatory diversity. PYY binds to Y2 receptors on vagal and hypothalamic neurons, reducing food intake and modulating gut motility [74,152,153]. CCK activates CCK₁ receptors on vagal afferents and within brainstem-forebrain circuits, resulting in potent meal-terminating effects [154]. The diversity in receptor localisation and signalling kinetics provides a rationale for combining peptides that target multiple sites along the gut-brain-pancreas axis (Figure 4).

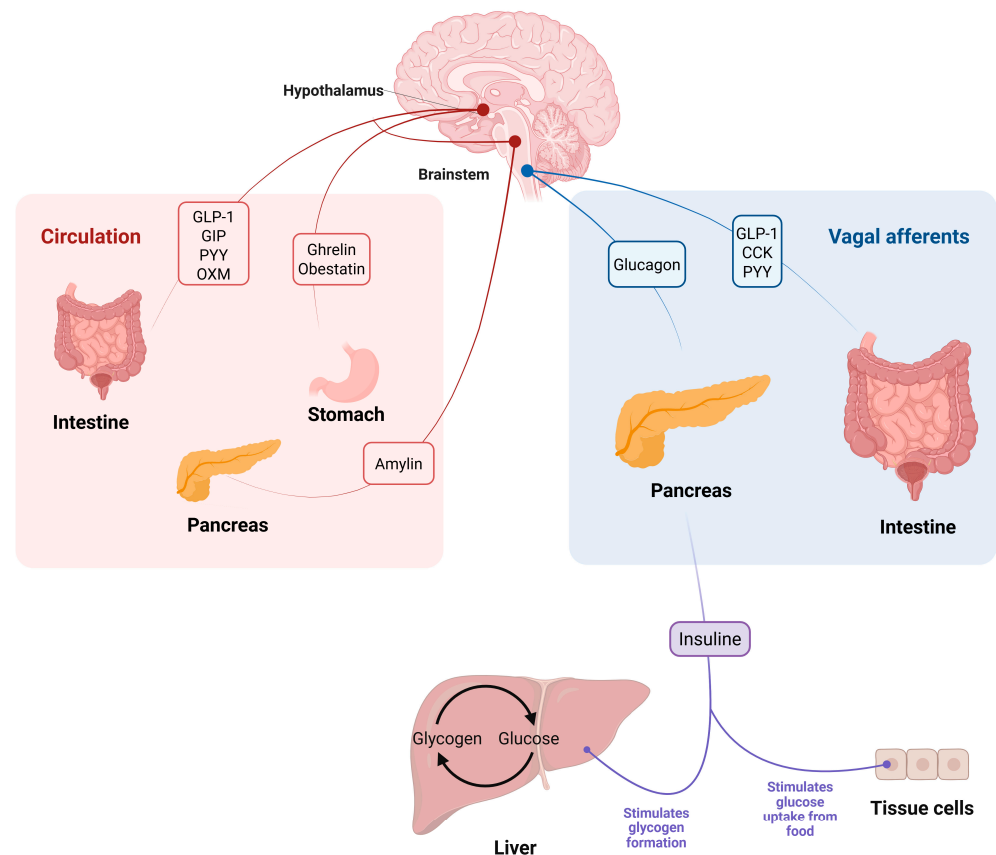


Figure 4. Integrated signalling across the gut–brain–pancreas axis. The schematic depicts humoral and neural communication between the gastrointestinal tract, pancreas and brain. Gut- and pancreas-derived peptides reach brainstem nuclei and hypothalamic centres via the circulation and vagal afferents, where signals are integrated to modulate pancreatic hormone secretion and the regulation of hepatic and peripheral glucose metabolism. Created with Biorender.com.

Preclinical research provides direct evidence supporting the concept of peptide co-activation beyond its role in appetite regulation. GLP-1 and its analogues exert pleiotropic metabolic effects across multiple tissues, extending their relevance to cellular energy regulation. Conversely, dysregulated peptide signalling, particularly involving amyloidogenic peptides such as aggregated amylin, has been consistently associated with metabolic and neurodegenerative pathology [155–157]. Experimental studies demonstrate that human amylin and A β share convergent toxicity pathways, including mitochondrial ROS overproduction, disruption of respiratory chain complexes, and impaired ATP generation [158,159]. Recent research integrates these findings, identifying mitochondrial oxidative stress as

a mechanistic link between type 2 diabetes, amylin aggregation, and neurodegenerative pathology [160–165].

4.2. Multi-Peptide and Dual/Triple Agonist Strategies

Recent translational advances in metabolic therapy focus on coordinated receptor activation. Dual and triple receptor agonists, such as GLP-1/GIP, GLP-1/glucagon, and GLP-1/GIP/glucagon, are engineered to mimic the physiological interplay of peptides following nutrient intake. Peptide engineering has enabled the development of single agents that target multiple pharmacologic receptors, particularly GPCRs involved in glucose homeostasis and energy balance. Several multireceptor agonists are currently in clinical development for type 2 diabetes mellitus (T2DM), obesity, and nonalcoholic steatohepatitis. Among these, the dual gastric inhibitory polypeptide receptor (GIPR) and GLP-1R agonist Tirzepatide exhibit greater activation of the GIP receptor compared to the GLP-1 receptor [166]. This molecule contains multiple structural optimisations, including a C20 fatty acid moiety for albumin binding and an alanine at position 2, substituted with non-canonical α -aminoisobutyric acid (Aib), which enhances helical stability and GIPR-biased signalling. These features confer long half-life, strong GIPR potency, and reduced gastrointestinal intolerance compared with selective GLP-1 agonists [167,168]. As an analogue balancing activity at both receptors, Tirzepatide offers improved glycemic control and weight reduction without increasing the risk of hypoglycemia, and it achieves superior HbA1c reduction compared to Semaglutide [169]. GIP co-activation appears to potentiate insulinotropic signalling while mitigating nausea and tachyphylaxis associated with GLP-1 monotherapy. Beyond the incretin family, experimental combinations extend to amylin, PYY, and glucagon analogues. The design of a dual agonist of GLP-1 and glucagon has also been explored [170–172]. Glucagon is a counter-regulatory hormone secreted at high levels during hypoglycemia and fasting. It promotes glycogenolysis and gluconeogenesis. It also stimulates hepatic fatty acid β -oxidation and ketogenesis, increases satiety, acutely reduces food intake, and increases energy expenditure [173–175]. Glucagon can be used therapeutically to promote satiety, increase energy expenditure, and support weight loss [176]. Another double agonist is the secretin/GLP-1 double agonist. Secretin regulates gastric pH and pancreatic bicarbonate secretion, and its effect on brown adipose tissue mediates thermogenesis [177]. The GLP1-secretin co-agonist (GUB06-046) can significantly reduce food intake and improve glucose tolerance in diabetic mice. Long-term administration of GUB06-046 to diabetic db/db mice improved glycemic control, retained β -cell quality, and did not affect the quality of the exocrine pancreas or pancreatic duct epithelium [178]. Combined activation of GLP-1 and CCK receptors may synergistically enhance appetite inhibition and glucose homeostasis. Studies have characterised acylated GLP-1/CCK hybrid peptides, such as [Lys¹²Pal]/exendin-4/CCK, which significantly stimulate insulin secretion, regulate glucose homeostasis, and reduce body weight [179]. Another fusion peptide, C2816, combines a stable GLP-1R agonist with a CCKR-selective agonist, retaining full activation of both receptors but with lower potency than single agents [180]. The previously reported (pGlu-Gln)-CCK-8/exendin-4 fusion peptide showed low receptor activity but effectively reduced triglyceride and cholesterol levels and improved β -cell area and insulin-stimulating ability. Compared to single administration, C2816 achieved greater weight reduction [181]. GLP-1 and PYY, both secreted from L cells in response to food, have a stronger inhibitory effect on food intake when combined than when used individually, reflecting their complementary roles. Nausea and vomiting are common side effects of obesity drugs, and PYY receptor activation is associated with these effects. Combining drugs may help reduce side effects. Studies show that GIPR agonists, when combined with PYY, can inhibit PYY-induced nausea, possibly by reducing conditioned taste avoidance with-

out affecting appetite suppression [182–184]. GIPR agonists also decrease PYY-mediated neuronal activity in the parabrachial nucleus, suggesting a mechanism by which GIP-based therapy may improve tolerance to weight-loss agents [182]. Retatrutide is a novel triple-agonist peptide that acts on GCGR, glucose-dependent insulin-stimulating GIPR, and GLP-1R. It significantly reduces body weight and improves blood glucose control compared to other incretin receptor-targeting agents [185]. GLP-1/GIP/Glucagon ternary therapy aims to enhance weight loss by combining the benefits of glucagon with those of GLP-1 and GIP. Combining GIP activity with GLP-1 and glucagon receptor agonists might enhance weight loss and glycemic control while also lowering the risk of diabetes from chronic glucagon receptor activation [186–188]. Future research should aim to explore these three in combination to achieve greater therapeutic benefit. Another ternary therapy targets GLP-1, OXM, and PYY. Studies show that postprandial release of these peptides increases after bariatric surgery, particularly Roux-en-Y gastric bypass (RYGB) [189,190]. Improved blood sugar control, diabetes remission, weight loss, and other metabolic benefits are observed even days after surgery. Acute continuous subcutaneous infusion of GLP-1, OXM, and PYY reduces food intake, improves glucose tolerance, and lowers glucose variability [191,192]. Triple activation of GLP-1, glucagon, and PYY receptors with this combination may surpass the metabolic effects of RYGB, suggesting a promising direction for future obesity drug research [193,194]. The GLP-1/GCG/CCK₂ triple agonist represents a promising therapeutic strategy for obesity and diabetes. Xenopus (X), a newly engineered peptide with selective agonist activity at GLP-1, glucagon, and CCK2 receptors, demonstrates markedly greater metabolic efficacy than existing dual-agonist approaches. In preclinical studies, Xenopus outperformed both ZP3022 (a GLP-1/CCK₂ dual agonist) and liraglutide, achieving greater weight loss, more pronounced reductions in hepatic steatosis, and superior improvements in metabolic parameters [195]. It also increased circulating insulin levels and produced more sustained improvements in glucose tolerance and overall glycemic control [196].

4.3. Peptide Stabilisation, Delivery, and Molecular Design

The translation of multi-peptide strategies from concept to clinic depends critically on advances in molecular engineering and delivery technology [197–200]. Native gut hormones are inherently unstable, with plasma half-lives of only a few minutes due to rapid enzymatic degradation and renal clearance [201]. Early efforts to improve therapeutic viability focused on amino acid substitutions that block key proteolytic sites, as seen in exenatide and other first-generation GLP-1 receptor agonists [202]. A breakthrough in diabetes treatment was the development of lipidated incretin analogues, modified peptides that enhance pharmacokinetic stability by attaching long-chain fatty acids to specific amino acid residues. These modifications, which typically involve C16, C18, or C20 lipid chains, enhance the peptide's ability to bind reversibly and with high affinity to serum albumin [203]. This process significantly reduces renal clearance and protects the peptide from enzymatic degradation. This principle is exemplified by liraglutide, which differs from native GLP-1 by substitution of Lys³⁴ with Arg³⁴ and by site-specific attachment of a C16 palmitoyl group to Lys²⁶ via a γ -glutamic acid spacer [204]. The Lys³⁴→Arg substitution prevents secondary acylation at position 34 and thus ensures homogeneous palmitoylation at Lys²⁶, a critical step for predictable pharmacokinetics and manufacturability [205]. Through these modifications, liraglutide achieves increased albumin binding, extending its half-life from just minutes to 13 h. Moreover, this significant enhancement enables once-daily dosing, marking a substantial improvement in diabetes management [206]. Second-generation GLP-1 analogues use fatty acid chemistry to enhance metabolic stability. Semaglutide includes a C18 fatty acid linked by a hydrophilic spacer to Lys²⁶, optimising albumin binding and maintaining receptor specificity. Moreover, Semaglutide incorporates

Aib at position 8, which confers resistance to dipeptidyl peptidase-4 (DPP-4) cleavage and stabilises the α -helix [207,208]. This design extends the peptide's half-life, enabling once-weekly injections [209,210]. The same strategy has been extended to dual agonists. Tirzepatide, which engages both GIP and GLP-1 receptors, contains a C20 fatty diacid moiety conferring robust albumin binding (~99% of circulating drug). This results in an elimination half-life of approximately 5 days, allowing sustained receptor engagement and flexible weekly dosing (Figure 5) [187].

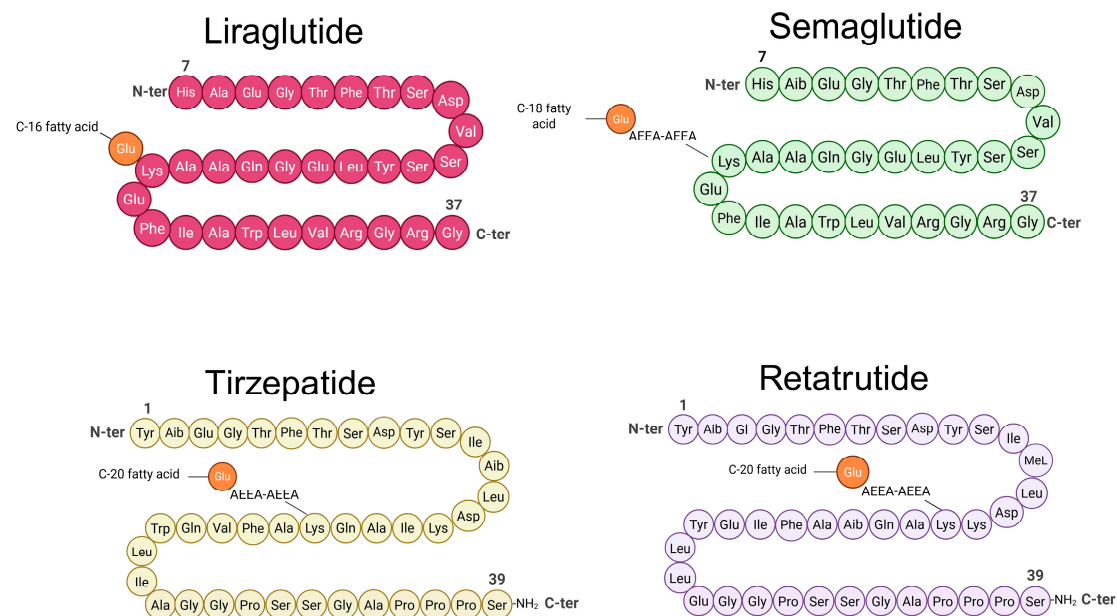


Figure 5. Sequence comparison of clinically relevant therapeutic peptides derived from GLP-1-based engineering, including the GLP-1 analogues liraglutide and semaglutide, and the multi-receptor agonists tirzepatide and retatrutide. Numerical values at the N- and C-termini of peptides indicate the specific positions of amino acid residues within the peptide sequence. Created with BioRender.com.

Similar strategies have been applied to amylin analogues, with molecules such as Cagrilintide and Pramlintide showing enhanced solubility and prolonged bioavailability [211,212]. Fusion technologies now enable conjugation of peptides to antibody Fc fragments or albumin scaffolds, greatly increasing circulatory persistence and tissue targeting. These constructs stabilise the molecule and allow precise control of receptor bias and agonist potency across multiple peptide domains. Dual- and triple-agonist molecules use these innovations to achieve balanced receptor engagement, which is essential for avoiding adverse metabolic effects. Delivery methods have also evolved from parenteral injection to oral, nasal, and transdermal platforms. One example is oral semaglutide, which is combined with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (salcaprozate sodium; SNAC), an absorption enhancer that improves semaglutide's absorption across the gastric mucosa via transcellular mechanisms. By 2021, subcutaneous semaglutide was also approved for obesity treatment [213]. Nanoparticle and hydrogel systems are being developed for targeted release to intestinal L-cells or pancreatic tissue, offering pharmacokinetic control and spatial specificity. Mechanistically, these delivery advances have bioenergetic implications. Sustained, rhythmic exposure to peptide agonists can restore physiological oscillations in nutrient sensing and mitochondrial function, thereby reducing metabolic noise caused by erratic pharmacological stimulation. Formulation science thus becomes a tool for re-entraining circadian and metabolic synchronisation across organs. To enhance the efficiency of these therapies, it can be useful to associate them with non-peptidic therapies, such as SGLT-2 inhibitors and thiazolidinediones. The first

one, in fact, by promoting renal glucose excretion, induces a controlled energy deficit that complements the appetite-suppressing and insulinotropic effects of GLP-1 analogues [214]. When used together, these agents coordinate the redistribution of energy fluxes, reducing substrate overload while preserving oxidative flexibility. The second one, also called “glitazones,” are PPAR- γ agonists. They are insulin sensitisers that act on intracellular metabolic pathways to enhance insulin action and increase insulin sensitivity in critical tissues [215]. Thiazolidinediones (TZDs) also increase adiponectin levels, decrease hepatic gluconeogenesis, and enhance insulin-dependent glucose uptake in muscle and adipose tissue. The addition of glucagon signalling reactivates hepatic β -oxidation and thermogenesis, counterbalancing the energy-conserving effects of prolonged GLP-1 stimulation [216].

4.4. Main Limitation of Therapeutic Peptides

Despite the promising efficacy of peptide-based multi-receptor therapies, important limitations and uncertainties persist regarding their long-term safety and adaptive responses. For liraglutide, gastrointestinal adverse events such as nausea, vomiting, diarrhoea, and constipation remain common [217]. Serious adverse events reported in post-marketing surveillance and pharmacovigilance databases, such as pancreatitis, underscore the need for ongoing monitoring, particularly given increased signals in spontaneous reporting systems for GLP-1 receptor agonists [218,219]. Semaglutide shares a similar adverse event profile, with gastrointestinal side effects predominating [220,221]. Additionally, rare reports of visual and neurologic adverse outcomes are emerging, indicating a need for further investigation beyond controlled clinical trials [222–224]. For tirzepatide, systematic safety assessments indicate generally acceptable tolerability comparable to GLP-1 receptor agonists but with specific concerns related to dose-dependent gastrointestinal symptoms, hypoglycemia at higher doses, and discontinuations due to adverse events [225,226]. Long-term safety data extending beyond standard follow-up intervals remain limited due to the relative novelty of widespread use. Retatrutide has demonstrated a safety profile in early clinical testing characterised primarily by transient gastrointestinal toxicity similar to other incretin-based therapies [227,228] (Table 3).

Table 3. Overview of therapeutic peptides, detailing clinical applications and limitations.

Peptide Drug	Endogenous Analogue	Receptor(s)	Key Clinical Evidence	Main Limitations
Liraglutide	GLP-1	GLP-1R	HbA1c reduction and moderate weight loss; CV risk reduction	Acute pancreatitis; GI adverse effects; Lower efficacy vs. newer agents [206,217,218]
Semaglutide	GLP-1	GLP-1R	Marked weight loss; Once-weekly dosing; CV benefit in outcome trials	GI intolerance in titration; Gallbladder disease risk; Rare ocular safety signals [209,220,222]
Tirzepatide	GIP/GLP-1	GIPR GLP-1R	Greater weight loss vs. GLP-1Ras; Superior glycemic control; Improved tolerability via GIP co-activation;	Limited long-term data; GI side effects; Adaptive neuroendocrine responses unclear [166–168,187,226]
Retatrutide	GCG/GIP/GLP-1	GCCR GIPR GLP-1R	Profound weight loss (early trials); Improved glycemia; Increased energy expenditure via GCCR	Long-term safety unknown; Theoretical GCCR-related risks [227,228]

However, chronic engagement of these peptides raises important questions regarding receptor desensitisation, altered neuronal responsiveness, and compensatory rewiring within gut–brain circuits. While available clinical trials have not demonstrated clinically

significant resistance to incretin-based therapies, long-term data extending beyond several years remain limited, particularly for newer dual- and triple-agonist molecules [229–231]. From a safety perspective, balanced receptor potency, gradual dose escalation, and preservation of physiological temporal signalling appear critical to minimising adverse effects while maintaining sustained metabolic efficacy. Ongoing long-term studies will be essential to determine whether multi-receptor agonism preserves network-level synchrony or induces adaptive mechanisms that ultimately constrain therapeutic benefit.

5. Gut–Brain–Pancreas Peptide Signalling and Mitochondrial Bioenergetics

Recent evidence highlights that peptides derived from the gut–brain–pancreas axis exert profound effects not only on systemic metabolic regulation but also directly on mitochondrial bioenergetics. Mitochondria, as central hubs of cellular energy production and redox balance, are responsive to these hormonal cues, which can act through direct cellular mechanisms and, indirectly, via central neuroendocrine circuits. The integration of these two pathways provides a comprehensive framework linking nutrient sensing to organelle function and systemic energy homeostasis. Peptides such as GLP-1 have been shown to directly enhance mitochondrial function in several cell types. In pancreatic β -cells, GLP-1 receptor agonists increase mitochondrial mass, membrane potential, oxygen consumption, and PGC-1 α expression, thereby improving ATP production and oxidative efficiency [232,233]. Similar effects have been observed in hepatocytes and vascular smooth muscle, where GLP-1 signalling stimulates mitochondrial Ca²⁺ mobilisation, enhances oxidative phosphorylation, and reduces oxidative stress [234,235]. Other emerging peptides also exert direct effects on mitochondria. Obestatin preserves β -cell viability under metabolic stress by maintaining mitochondrial integrity and reducing reactive oxygen species [96,236]. Amylin, when not aggregated, promotes peripheral lipid oxidation and may improve mitochondrial oxidative capacity, whereas amyloidogenic forms of amylin and related peptides induce mitochondrial dysfunction, ROS overproduction, and impaired ATP generation, linking peptide dysregulation to both β -cell failure and broader metabolic pathology [161,237,238]. Additional peptides such as oxyntomodulin, neurotensin, nesfatin-1, and GDF15 have been implicated in the modulation of mitochondrial function, often through AMPK or integrated stress-response signalling, although human data remain limited [135,139,145–148]. Beyond these direct effects, gut-derived peptides also modulate mitochondrial bioenergetics indirectly through central nervous system pathways. Hypothalamic circuits, particularly those integrating orexigenic and anorexigenic signals, translate circulating peptides into coordinated autonomic output that regulates substrate availability, nutrient partitioning, and mitochondrial workload in peripheral tissues. For example, activation of GLP-1 and amylin receptors in the hindbrain and hypothalamus modulates sympathetic and parasympathetic tone, thereby affecting hepatic glucose production, adipose tissue lipolysis, and skeletal muscle oxidative capacity [239,240]. Similarly, stress-responsive peptides such as GDF15 act primarily via the area postrema to reduce systemic metabolic load, indirectly alleviating mitochondrial stress in liver, muscle, and adipose tissue [147,241]. This centrally mediated regulation underscores that peptide-induced mitochondrial adaptations often result from network-level integration rather than isolated cellular effects, highlighting the importance of distinguishing direct receptor-mediated actions from neuroendocrine-mediated adaptations. Therapeutic exploitation of these mechanisms has been exemplified by multi-receptor agonists such as tirzepatide and retatrutide. Preclinical studies indicate that dual and triple agonists targeting GLP-1, GIP, and glucagon receptors not only improve glycemic control and body weight but also enhance mitochondrial oxidative capacity in skeletal muscle and liver, independently of weight loss, via coordinated cAMP-PKA-AMPK signalling [242,243].

Co-activation of peptides such as GLP-1 with amylin, CCK, or oxyntomodulin can further optimise mitochondrial substrate utilisation and energy expenditure by synchronising peripheral oxidative demands with central appetite and metabolic circuits [244]. These observations suggest that restoring coordinated peptide signalling through multi-receptor therapies may mitigate metabolic stress at the organelle level and enhance bioenergetic resilience. Despite the compelling evidence, several limitations must be considered. Most mechanistic insights derive from rodent or in vitro studies, and direct assessments of mitochondrial function in human tissues are scarce. Moreover, many observed mitochondrial benefits may be secondary to weight loss or caloric restriction rather than primary peptide effects. The bioenergetic impact of newly identified peptides, including GDF15, nesfatin-1, and oxyntomodulin, is incompletely characterised, and the temporal dynamics of acute versus chronic peptide exposure remain poorly understood. Addressing these gaps will require tissue-specific receptor manipulations, high-resolution mitochondrial phenotyping, and controlled human studies to disentangle direct from centrally mediated effects and to guide rational development of multi-peptide therapeutic strategies.

6. Conclusions and Future Perspectives

Energy homeostasis is regulated by the integrated actions of neural, endocrine, immune, and metabolic systems, which coordinate nutrient sensing with energy utilisation at both systemic and cellular levels. EECs function as chemosensory transducers that convert gut-derived signals into hormone release, thereby influencing both local and distant physiological targets [245]. Communication between the gut and the brain occurs via hormonal signalling and rapid neural pathways, including vagal sensory nerves that transmit gut-derived information to brainstem centres such as the nucleus tractus solitarius and area postrema, and subsequently to higher-order brain regions [246]. In addition to established roles in incretin signalling and satiety, certain gut-derived signals modulate cellular energy metabolism. In pancreatic β -cells, GLP-1 and exendin-4 have been demonstrated to increase mitochondrial mass and enhance mitochondrial function, as evidenced by improved membrane potential, elevated oxygen consumption, and increased PGC-1 α expression in INS-1 cells. These findings indicate a direct relationship between peptide signalling and mitochondrial efficiency [247]. Obestatin promotes survival of pancreatic β -cells and human islets, and upregulates genes associated with β -cell mass and function, suggesting a protective effect under metabolic stress conditions [96]. The cytokine GDF15, which is induced by cellular stress, acts via the GFRAL receptor in the hindbrain to suppress food intake, thereby illustrating how cellular stress responses can influence systemic energy balance [248,249]. Looking at the network as a whole has important clinical implications. While targeting individual pathways may suffice for specific objectives, employing drugs that interact with multiple receptors or combine peptides seeks to more accurately imitate the body's natural signalling processes. Clinical trials show that using tirzepatide, which targets two incretin receptors, leads to significant and lasting weight loss in adults with obesity [11]. Retatrutide, which targets three receptors, has also caused notable weight loss in a phase 2 trial [229]. Combining cagrilintide and semaglutide has produced meaningful weight loss in adults with overweight or obesity, supporting the use of multi-pathway peptide treatments in practice [250]. Several challenges and safety considerations remain. Prolonged administration of GLP-1 receptor agonists can induce receptor desensitisation in vitro; however, glucose regulation may remain intact in vivo, highlighting the need to distinguish between cellular and systemic effects [251]. In humans, GLP-1 delays gastric emptying, but this effect diminishes rapidly due to adaptive changes in vagal nerve activity, indicating physiological adaptation to sustained stimulation [252]. Future investigations should incorporate comprehensive assessments, including tissue- and pathway-specific

biomarkers, mitochondrial function assays, and long-term safety evaluations, to differentiate direct effects on energy metabolism from those mediated by central regulatory mechanisms. Future priorities include identifying additional gut-derived factors that consistently influence mitochondrial function or energy sensing in humans, developing strategies to selectively target specific pathways and tissues, including dosing regimens that account for physiological adaptation, and evaluating rational combinations with existing non-peptide therapies to align systemic energy expenditure with cellular bioenergetics. Recognising gut peptides as central components of the gut–brain axis provides a robust framework for the development of novel metabolic therapies.

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Abbreviations

The following abbreviations are used in this manuscript:

GLP-1 Ras	glucagon-like peptide-1 receptor agonists
EECs	intestinal enteroendocrine cells
GIP	gastric inhibitory peptide
PYY	peptide tyrosine tyrosine
CCK	cholecystokinin
POMC	proopiomelanocortin
AgRP	agouti-related neuropeptide
NTS	nucleus of the solitary tract
AMPK	AMP-activated protein kinase
mTOR	mechanistic target of rapamycin
PGC-1 α	peroxisome proliferator-activated receptor-gamma coactivator
ATP	adenosine triphosphate
HPA	hypothalamic–pituitary–adrenal
OXM	oxyntomodulin
GPCRs	G protein-coupled receptors
SGLT1	sodium-glucose co-transporter 1
ENS	enteric nervous system
CART	cocaine and amphetamine-regulated transcript
NPY	neuropeptide Y
PVN	paraventricular
VMH	ventromedial

LH	lateral hypothalamus
PKA	protein kinase A
GHS-R1a	ghrelin receptor
Y2R	presynaptic Y2 receptors
IAPP	islet amyloid polypeptide
CT	calcitonin
AMYRs	amylin receptors
CTR	calcitonin receptor
RAMPs	receptor activity-modifying proteins
BAT	brown adipose tissue
GDF15	growth differentiation factor 15
T2DM	type 2 diabetes mellitus
GIPR	gastric inhibitory polypeptide receptor
Aib	α -aminoisobutyric acid
RYGB	Roux-en-Y gastric bypass
SNAC	salcaprozate sodium
TZDs	thiazolidinediones

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