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Review

Neuroendocrine gut–brain signaling in obesity

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The past decades have witnessed the rise and fall of several, largely unsuccessful, therapeutic attempts to bring the escalating obesity pandemic to a halt. Looking back to look ahead, the field has now put its highest hopes in translating insights from how the gastrointestinal (GI) tract communicates with the brain to calibrate behavior, physiology, and metabolism. A major focus of this review is to summarize the latest advances in comprehending the neuroendocrine aspects of this so-called 'gut–brain axis' and to explore novel concepts, cutting-edge technologies, and recent paradigm-shifting experiments. These exciting insights continue to refine our understanding of gut–brain crosstalk and are poised to promote the development of additional therapeutic avenues at the dawn of a new era of antiobesity therapeutics.

Highlights

The gut–brain axis regulates behavior, physiology, and metabolism to ensure dynamic control of energy homeostasis.

Single cell transcriptomics, optogenetics, and live imaging revealed a high degree of molecular and functional diversity of cell types comprising the gut–brain axis.

Central and peripheral gut peptides interact with vagal and hormonal signals allowing for cooperation, redundancy, as well as for independent signaling pathways.

Forebrain regions, notably the hypothalamus, intricately modulate brainstem neurocircuitries fine-tuning vagal feeding pathways.

History of high-fat diet consumption and obesity is associated with maladaptive changes in gut–brain communication in both mouse models and humans.

A gut feeling: how gastrointestinal feedback to the brain governs energy homeostasis

Maintaining an adequate intake of nutrients is considered the *sine qua non* for survival of the individual, as well as the species. Thus, immense evolutionary pressure was placed on the emergence of robust and highly precise feedback systems that reliably control nutrient intake and metabolic homeostasis. Major research efforts over the past 40 years have successfully uncovered many intricacies of this multiorgan crosstalk and its complicated signaling networks. Historically, the bidirectional communication between the GI tract and the brain (i.e., the 'gut–brain axis') has attracted particular interest in the field of energy homeostasis. The GI tract is situated in an anatomically ideal position for monitoring nutrient content and composition, acting as a direct chemosensory interface with ingested food. During the process of breaking down complex food matrices into single nutrient constituents, cells of the GI tract concomitantly convert this information into gut-derived humoral and neural signals and ultimately convey these to the brain.

Recent technological advances have reinvigorated the study of the gut–brain axis, providing us with exciting new insights, concepts, and therapeutic options, some of which have already made the leap from bench to bedside and into clinical practice. Here, we focus on the current understanding of the neuroendocrine aspects of gut–brain signaling and highlight emerging humoral and neural pathways. However, while the enteric nervous system and microbiota have significant roles in gut–brain signaling, we direct the reader to designated reviews [1–4] for comprehensive coverage of these aspects. Despite their importance, our focus here remains on the promising neuroendocrine-mediated gut–brain pathways for tackling ingestive and digestive disorders linked to the development of obesity.

Gut–brain sensory transduction

The GI tract has evolved distinctive structural features, notably a highly folded epithelial surface, enhancing contact area with digesting food (known as 'chyme'). This intricate structure comprises crypt and villus structures (i.e., finger-like protrusions formed by a constant stream of short-lived cells originating from crypt stem cells). Approximately 90% of these cells are absorptive enterocytes [5], with a rapid turnover rate of 3–5 days. Scattered in between are enteroendocrine

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cells: specialized cell types that survey incoming nutrients and convey this information to the brain via neural and humoral signals to jointly control behavior, physiology, and metabolism.

Even though enteroendocrine cells only make up ~1% of the intestinal epithelium, they constitute one of the largest endocrine organs by mass [6]. Cells of the enteric endocrine system are scattered throughout the gut, are functionally diverse, and comprise multiple subtypes, each expressing an individual set of transporters, G-protein-coupled receptors, including taste receptors, and peptide hormone effectors (Table 1) [6,7]. In contrast to other glands, enteroendocrine cells exhibit the same high turnover typical of the intestinal epithelium. This unique feature has spurred speculations as to whether it renders the pool of enteroendocrine cells more adaptable to environmental changes with respect to its cellular composition and function. If, and when, such plasticity proves to be beneficial (adaptive) versus detrimental (maladaptive), and how it is affected by dietary habits, such as chronic intake of obesogenic, high-calorie foods, remain largely unknown, although first investigations have begun addressing these important questions, by, for example, using single-cell RNA-sequencing technologies [8].

Approaches such as single-cell transcriptomics recently unraveled an unprecedented diversity of enteroendocrine cells that extends beyond the traditional classification system (Table 1) [7,9]. In addition to the canonical I/K/L-cell classes, these data identified additional, novel subtypes with previously elusive developmental trajectories and functions. For instance, I-cells producing cholecystokinin (*Cck*$^{+}$) exhibit characteristic gene expression signatures and prominent enrichment of certain

Table 1. Historic classification of the enteric endocrine system[a,b]

Cell type and localization	Gut peptides	Pre- and postprandial levels[c]	Function
X-cells, stomach	Ghrelin	400 (fasting)–80 pM	Stimulation of food intake [95], growth hormone secretion
K-cells, upper intestine	GIP	1–125 pM	Potentiation of glucose-stimulated insulin secretion (incretin effect), stimulation of fatty acid synthesis in adipose tissue, bone formation, inhibition of food intake
L-cells, lower intestine	GLP1, GLP2, PYY, glicentin	2–20 pM	Potentiation of glucose-stimulated insulin secretion (incretin effect), inhibition of food intake, delay of gastric emptying [96]
I-cells, upper intestine	CCK	1–10 pM	Acute suppression of food intake [7,38], increased activity of brainstem neurons in response to gastric distension, delay of gastric emptying [97], sugar preference via glutamate release from synapse-like neuropod structures [12]
Enterochromaffin cells	Serotonin (*Tph1*-dependent synthesis, 90% of body's stores)	Uptake and release via platelets prevent accurate determination	Intestinal peristalsis, secretion and blood flow regulation [26], nausea and distension pain; malaise-associated suppression of food intake [7], whole-body metabolic adaptations to starvation, such as increased hepatic glucose production and lipid mobilization from adipose stores [98]

[a]The historic classification system separates enteroendocrine cells into distinct subsets, each producing one (or several) of the various peptide hormones, which have pivotal functions in gut–brain communication.
[b]Abbreviations: CCK, cholecystokinin; GIP, glucose-dependent insulinotropic peptide/gastric-inhibitory peptide; GLP, glucagon-like peptides; PYY, peptide YY; Tph1, tryptophan hydroxylase 1.
[c]The pre- and postprandial concentrations provided are indications only and depend on various factors, including species, sampling site (i.e., hepatic portal vein versus systemic circulation), time point, type of meal, and assay specificity for the active form of the hormone.

chemoreceptors (i.e., *Abcc9* for sugar, *Casr* for amino acids, and *Ffar1/2/3* for fat), thus providing a window into cell type-specific nutrient-sensing mechanisms. Notably, the transcriptional profile of *Cck*$^+$ I-cells was largely unaffected by fasting, suggesting that at least acute changes in nutritional status do not significantly alter gene expression. Lastly, by using an intersectional genetic approach to selectively target specific subpopulations, it was shown that the chemogenetic activation of both I-cells (*Cck*$^+$) and enterochromaffin cells (*Tac1*$^+$/*Tph*$^+$) robustly suppressed eating in food-deprived mice. However, only activation of the former conferred a positive effect, as expressed by conditioned taste preference, which required CCK_AR signaling and intact vagal, but not spinal, innervation. Conversely, enterochromaffin cell activation was highly aversive mimicking malaise by triggering serotonergic signaling via spinal nerves. Overall, various enteroendocrine cell types appear to inhibit food intake in a similar manner, while generating opposite valence signals, that is, non-aversive, rewarding satiety versus aversive anorexia, possibly associated with nausea [7].

Intriguingly, >50% of *Cck*$^+$ I-cells form pseudopod-like basal processes, which are neuropod specializations that facilitate direct synaptic transmission with underlying mucosal nerves [10,11]. This signaling mechanism was recently implicated in sugar sensing, whereby *Cck*$^+$ I-cells distinguish intragastric sugar from noncaloric sweeteners, determining nutritive preference via glutamatergic transmission at the neuropod–vagus interface [12]. Using, for example, the latest iterations of wireless gut optogenetics, future studies should address the extent to which other enteroendocrine cell types form such neuropod-like structures [13].

Central action of gut peptides

The prevailing view suggests that endogenous gut peptides act primarily through local vagal afferents in a paracrine manner. When assessing their endocrine impact based on their presence in circulation, it becomes crucial to differentiate between total concentrations, reflecting the overall peptide release in response to a meal, and 'active' concentrations, indicating the potential systemic endocrine effect of the hormone, which typically remains low and increases are rather modest due to rapid degradation. Therefore, identifying situations that can elevate their concentrations (e.g., large meals), or other influencing factors, such as species, sampling site, time point, composition and type of meal, as well as assay specificity, becomes paramount for interpreting the potential effect of the active forms of circulating hormones and their specific effects in gut–brain communication (Table 1). Yet, it remains enigmatic as to why many forebrain and hindbrain regions are highly enriched in gut peptide receptors [14]. Notably, most regions enriched for gut peptide receptors are found in specific regions of the hypothalamus and brainstem (Table 2) exhibiting vascular specializations ('fenestrations'), which facilitate hormone entry [15–17]. Therefore, one might assume that structures such as the hypothalamic median eminence (ME) and the medullary area postrema (AP) are particularly sensitive and anatomically privileged, such that they can detect even subtle changes in endogenous hormone levels in the blood. Moreover, hormone accessibility to these structures is further enhanced through dynamic structural remodeling upon circadian and metabolic cues [18,19].

Intriguingly, not only their receptors, but also many of the gut peptides themselves are expressed in the brain. For example, CCK and glucagon-like peptide 1 (GLP1) are synthesized locally in discrete cell groups of the brainstem, where vagal and hormonal information converges with descending neuroendocrine signaling (Box 1). The additional layer of local gut peptide expression remains enigmatic, begging the question of whether these peripheral and central systems are either functionally intertwined or act independently from each other.

Control of food intake by vagal afferent neurons: toward finer-grained insights

Early studies using surgical severing of the vagus nerve (vagotomy) suggested that vagal afferent communication has a major role in the control of food intake [20,21]. Pioneering work has begun

Table 2. Brain cell types expressing gut peptide receptors and function

Gut peptide receptor, cell type, and localization	Abbreviation	Function
Glp1r^{+} neurons in the ARC	ARC^{Glp1r} ARC$^{Glp1r/Pomc}$	Major target of long-acting GLP1R agonists; subset co-expresses proopiomelanocortin (*Pomc),* suppress food intake upon chemogenetic activation [18,99,100]
Glp1r^{+} neurons in PVN	PVN^{Glp1r}	Suppress food intake upon chemogenetic activation; blocking exocytosis induces hyperphagic obesity [101]
Glp1r^{+} astrocytes	Astro^{Glp1r}	Promote mitochondrial bioenergetics in astrocytes; conditional deletion of Glp1r from astrocytes improves whole-body glucose metabolism via FGF21-dependent mechanism [102]
Glp1r^{+} neurons in NTS	NTS^{Glp1r}	Acute suppression of food intake [103,104], co-expressing proenkephalin (*Penk)* and natriuretic peptide C *(Nppc)*
Gipr^{+} neurons in inhibitory GABAergic neurons (brain-wide)	*Vgat*^{Gipr}	GIPR deletion from GABAergic neurons protects mice from diet-indued obesity and abrogates food intake suppression by long-acting GIPR agonists [105]
Gipr^{+} neurons in hypothalamic regions [ARC, PVN, and dorsomedial hypothalamic nucleus (DMH)]	ARC^{Gipr}, PVN^{Gipr}, DMH^{Gipr}	Acute suppression of food intake [16,17]
Gipr^{+} neurons in NTS	NTS^{Gipr}	Acute suppression of food intake; molecularly distinct from NTS^{Glp1r}, co-express prepronociceptin (*Pnoc)* and *Pomc,* provide long-range projections to parabrachial nucleus (PBN) and PVN [16,17]
Gipr^{+} neurons in the AP	AP^{Gipr}	Acute suppression of food intake, multi-modal, co-express various other metabolic receptors, including *Oxtr,* project locally [16,17]
Cckar^{+} neurons in PVN	PVN$^{Oxt+/Cckar+}$	Enriched in PVN [106], colocalize with oxytocin-expressing neurons [107]; implicated in food intake reduction in response to systemic CCK injection [38]

using *in vivo* calcium imaging, genetically guided mapping, optogenetics, and sequencing methods (and combinations thereof) to unravel molecular and functionally distinct vagal afferent neuron subtypes [22].

The vagus nerve surveys the peripheral milieu via its multimodal sensory afferent neurons. Gut-projecting vagal sensory neurons are pseudounipolar neurons the long axons of which 'wander' the body to form distinct sensory endings within the GI tract. Some vagal afferent fibers exhibit characteristic terminals of mechanical sensors [intramuscular arrays (IMAs) or intraganglionic laminar endings (IGLEs)] and, therefore, can relay food-induced mechanical cues to the brain, such as stomach stretch. By contrast, other fibers penetrate the lamina propria and consequently gain access to nutrient-induced signals released from enteroendocrine and neuropod cells (Figure 1; reviewed in [23,24]).

Recent technical developments have enabled the field to add substantial granularity to the classic dichotomy between mechano- and chemosensors. As such, a discrete set of *Gpr65*$^{+}$ vagal afferent neurons were found to control food intake by detecting the presence of luminal nutrients through mucosal endings [25]. Intriguingly, stimulation of a small IGLE subpopulation marked

Box 1. Gut peptide-producing neurons in the brainstem

Glucagon-like peptide-1 receptor-expressing nucleus tractus solitarius neurons (NTS^{Glp1} neurons)

A recent study revealed that NTS^{Glp1} neurons do not simply constitute a central extension of the gut GLP1 system relaying ascending vagal signaling; rather, this small group of cells was discovered to constitute its own and independent system. Specifically encoding larger meal satiation [108], NTS^{Glp1} neuron activation by optogenetic and chemogenetic means robustly suppresses eating [109], an effect that is dose dependent [59]. That non-aversive satiety persists even after NTS^{Glp1} neuronal stimulation has ceased [59] suggests involvement of a protracted, longer-lasting modulation of downstream circuits, such as enhanced glutamatergic AMPA receptor trafficking in the PVN of the hypothalamus [110] and reduced synaptic drive onto mesolimbic dopamine neurons [111]. Most importantly, however, NTS^{Glp1} neurons engage satiety mechanisms strictly separate from intestinal-vagal GLP1R signaling, as elegantly demonstrated by co-activation of peripheral and central GLP1 pathways, which resulted in additive food intake suppression. Consistent with this observation, NTS^{Glp1} neurons do not receive synaptic inputs from *Glp1r*$^+$ vagal sensory neurons, but from *Oxtr*$^+$ vagal afferents instead, which likely correspond to the highly anorexigenic mechanosensitive IGLE population described recently [7,108]. Intriguingly, NTS^{Glp1+} neurons are also robustly activated by descending oxytocinergic inputs and physiologically mediate oxytocin-induced food intake suppression [108]. In sum, this study [108] compellingly demonstrates the independent organization of brainstem versus peripheral GLP1 systems while reinforcing a major role of oxytocin signaling in gut–brain information processing.

Cholecystokinin-expressing NTS and AP neurons (NTS/AP^{Cck} neurons)

Similarly, CCK is produced not only by intestinal I-cells, but also by brainstem neurons, which widely project to various eating-related brain regions [112,113]. Somewhat unexpectedly, these cells are required to centrally mediate the anorexigenic and body weight-lowering effects of the peripherally administered GLP1R agonist exendin-4 [114], whereas the central GLP1 system is dispensable. Moreover, NTS/AP^{Cck} neuronal activity is also required for the development of conditioned taste aversion in response to exendin-4, a common adverse effect. Consistent with this notion, NTS/AP^{Cck} neurons express high levels of *Glp1r*, but are devoid of *Gipr* expression, which localizes to neighboring, putatively GABAergic interneurons. Strikingly, co-activating GIPR with GLP1R dampened the activity of a subset of NTS/AP^{Cck} neurons, such that it ameliorated GLP1R-associated nausea despite equal suppression of food intake. It remains to be determined whether indirect GIPR-modulation of NTS/AP^{Cck} neurons (or subpopulations thereof) constitutes a critical neuronal substrate conferring metabolic benefits and drug tolerance of dual agonists.

by oxytocin receptor (*Oxtr*$^+$) expression elicited the most robust suppression of food intake, surpassing that triggered by activation of a separate and much larger IGLE subpopulation marked by *Glp1r*$^+$. While molecularly largely distinct, *Oxtr*$^+$ and *Glp1r*$^+$ IGLEs both highly express *Cckar* mRNA (encoding the CCK_A receptor), supporting previous notions that vagal sensory neurons can be polymodal by integrating both mechanical and chemical signals [26], such as interactions between GLP1 and CCK signaling [27]. In addition to reducing food intake, activation of *Glp1r*$^+$ vagal neurons also improved glucose tolerance and increased glucose disposal into skeletal muscle during a hyperglycemic–euglycemic clamp [28].

Most recent advances in *in vivo* Ca^{2+} imaging of vagal sensory neurons revealed a relatively strict separation between gut–brain pathways detecting dietary sugar versus fat [29,30]. When artificially activated, these vagal neurons induce strong macronutrient-specific reinforcement, highlighting the previously described role of vagal afferent neurons in gut-induced reward [31]. Finally, nodose ganglia (containing the cell bodies of vagal afferent neurons) exhibit a profound left–right asymmetry in the types of signal that they detect: as such, it appears that the left nodose ganglion conveys distension-induced satiety, whereas the right nodose ganglion signals food reward and nutritional preference to the brain [31,32]. With regards to therapeutic application, this emerging granular view is likely to be both a blessing (novel targets) and a challenge (e.g., current vagal stimulation strategies need to take this neuronal diversity into account) [23].

Brainstem integration of vagal inputs and descending control of gastrointestinal physiology

The axons of vagal sensory neurons project from the nodose ganglia to the brainstem, where they synapse onto nucleus tractus solitarius (NTS) neurons. The NTS is an elongated nucleus that is organized in a columnar, topographic fashion, which reflects the sensory feedback that is received

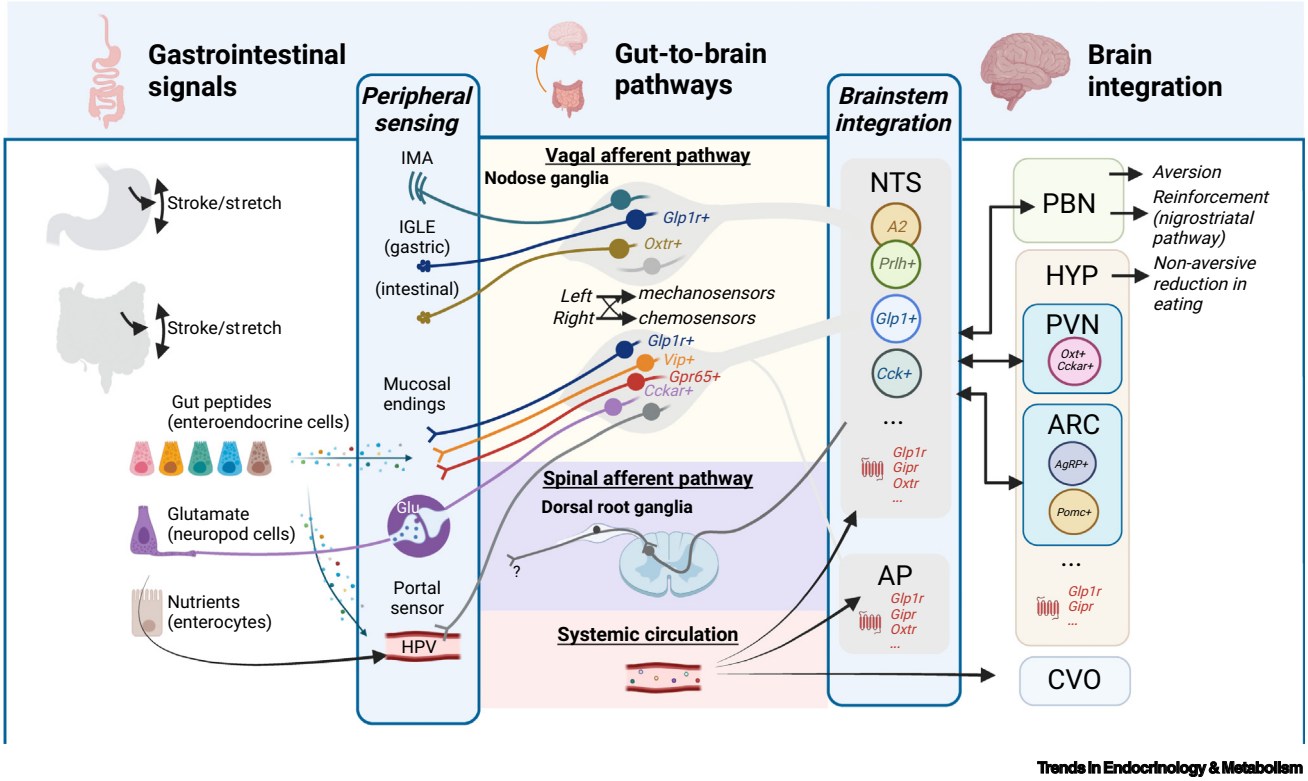

Figure 1. Wiring diagram of ascending gut-to-brain signals relevant for energy balance. Generation (left), gut–brain mediation (middle), and central integration (right) of gut–brain signals relevant for energy balance. The vagal and central neuronal populations and gut peptide receptors depicted are not an exhaustive list but instead match those described in the main text. Abbreviations: A2, catecholaminergic A2/C2 cell group; AP, Area postrema; ARC, arcuate nucleus of the hypothalamus; CVO, circumventricular organs; Glu, glutamate; HPV, hepatic portal vein; HYP, hypothalamus; IGLE, laminar endings; IMA, intramuscular arrays; NTS, nucleus tractus solitarii; PBN, parabrachial nucleus; PVH, paraventricular nucleus of the hypothalamus. Figure created using BioRender (biorender.com).

from proximal to distal portions of the viscera (viscerotopy). In close apposition resides the dorsal motor nucleus of the vagus (DMX), which contains cholinergic motor neurons that provide vagal efferent innervation to the viscera. The emerging diversity of DMX neurons [33] recently indicated that distinct vagal motor neurons orchestrate gastric function by engaging functionally opposed efferents [33]. Although much lower in number (approximately one ninth of sensory afferents) and less viscerotopically patterned, the efferent branch of the vagus nerve completes a bi-directional communication loop within the gut–brain axis: the vagovagal reflex [34]. This reflex directly relays GI feedback to digestive motor control to modulate critical aspects, such as the rate of gastric emptying, which is a pivotal determinant of satiation, meal size, and, thus, energy intake. Similar to recent studies in vagal afferents, future research is likely to highlight the complexity of descending vagal subcircuits and their respective relevance for the control of metabolic and digestive processes.

Brainstem-connected pathways tune vagal neurocircuits for food intake regulation

At the central level, interconnected networks of forebrain regions integrate higher-order processes (sensory, endocrine, social, emotional, stress related, and learning) and relay this information via descending projections to modulate brainstem circuits for episodic eating control. During this process, a vast range of neuropeptides and neurotransmitters infringe on the vagal brainstem circuitry and tune autonomic functions, including the vagovagal reflex. A major nexus within this pathway appears to be the bi-directional communication between the NTS/ DMX complex and various forebrain regions, including the hypothalamus.

Neurons in the paraventricular nucleus (PVN)expressing the neuropeptide oxytocin ($PVN^{Oxt\ neurons}$)

The $PVN^{Oxt\ neurons}$ provides particularly high numbers of descending inputs to the brainstem complex [35,36]. Besides their traditional roles in female reproductive physiology and sociability, PVN^{Oxt} neurons are now also recognized as important regulators of metabolic homeostasis and food intake [37]. For instance, mice undergoing adult-onset ablation of PVN^{Oxt} neurons [38] or the *Oxt* gene [39] developed extreme hyperphagic obesity in only 2 weeks, associated with disturbed gut–brain feedback. Oxytocin exerts its appetite suppressive effects in part by acting as an anorexigenic signaling molecule within NTS/DMX complex, which expresses high levels of *Oxtr* [40]. Brainstem oxytocin signaling robustly activates DMX/NTS neurons [41–44] and modulates visceral afferent transmission [45,46] and GI satiation signal processing [47–49], while integrating tonic humoral signals of energy sufficiency, such as the adipose hormone leptin [50,51].

The catecholaminergic A2/C2 cell group in the NTS ($NTS^{A2\ neurons}$)

The $NTS^{A2\ neurons}$ are bi-directionally connected with the hypothalamus and strongly implicated in food intake regulation. One distinct subset of NTS^{A2} neurons project to the arcuate nucleus of the hypothalamus (ARC), driving hunger in response to glucoprivation [52] and fasting [53]. Conversely, separate axonal projections targeting the PVN promote satiety instead, likely by integrating CCK signaling [54] and by synergizing with PVN^{Oxt} neurons [38]. Notably, and consistent with previous findings, the activity of this bi-directional pathway appears vulnerable to hormonal and dietary changes, as indicated by increased restraint through κ-opioid receptor signaling during pregnancy [55] or high-calorie feeding [38]. How exactly opioid signaling impinges onto this network remains to be determined mechanistically.

Caudal NTS neurons expressing the anorexigenic neuropeptide prolactin-releasing hormone (NTS^{Prlh} neurons)

The NTS^{Prlh} neurons have attracted significant interest because they functionally and anatomically intersect with catecholamine [56] and CCK signaling [57], and potently promote non-aversive satiety as well as body weight loss when activated artificially [58]. A recent milestone study revealed that NTS^{Prlh} neurons exhibit peculiar and highly distinct activity patterns during oral nutrient consumption versus intragastric infusions [59]. Specifically, intragastric infusion of nutrients induces a gradual and sustained activation of NTS^{Prlh} neurons that almost perfectly tracks cumulative calorie intake. Conversely, consuming the same amount of calories by mouth triggered a strong initial activation that rapidly declined thereafter and which depended on taste rather than caloric value. This suggest that both orosensory and visceral feedback signals converge on NTS^{Prlh} neurons, but that the isolated GI feedback is dispensable under natural eating conditions. Since activity patterns of individual NTS^{Prlh} neurons stringently track the frequency of licking events, the authors mimicked this natural dynamic by performing closed-loop optogenetics in which licking behavior instantaneously elicited laser stimulation. When NTS^{Prlh} neurons received optogenetic stimulation while licking, but not between licking, food intake was greatly suppressed, suggesting that NTS^{Prlh} neuronal activity provides an immediate feedback signal that paces consumption on a moment-to-moment basis. Thus, this study elegantly determined the temporal regulation of competing orosensory inputs versus GI feedback in a defined gut–brain neurocircuit, and expanded upon first attempts to understand the neurobiological basis of snacking behavior (‘salted nuts phenomenon’ [60]). However, it remains unclear how these peculiar, time-locked activity patterns of specific brainstem neurons are generated and what differentiates orosensory-dominated NTS^{Prlh} neurons from more traditional interoceptive neurons (e.g., NTS^{Glp1}). Since the caudal NTS is devoid of any significant monosynaptic innervation from primary gustatory regions, this top-down control likely involves yet-to-be-identified higher-order cortical brain regions.

Biphasic dopamine responses upon food consumption in humans

Intriguingly, previous results from human brain-imaging studies indicated that similar bi-phasic feedback patterns determine dopamine-regulated 'wanting' and duration of eating [61]. Using a combined functional magnetic resonance imaging (fMRI)/positron emission tomography (PET) approach, the authors showed that food intake elicits an immediate orosensory-mediated dopamine response in 'wanting'-associated brain areas, including the hippocampus as well as the anterior insular and cingulate cortices. Notably, this is followed by a delayed dopamine response in satiety-associated neurocircuits (i.e., the putamen) mediated by postingestive feedback from the GI tract and presumably transmitted via vagal nerve signaling and NMDA-dependent bursting of midbrain dopamine neurons [62]. In humans, it appears that a higher first peak of dopamine release indicates a stronger desire to eat, suppressing the second, postingestive dopamine rise. Thus, and strikingly similar to the cellular behavior of NTS^{Prlh} neurons, this bi-phasic pattern of dopaminergic brain activity might explain how high wanting and palatability can overwrite satiety-related GI signaling to prolong food intake.

In conclusion, we envisage that increasingly sophisticated technologies will facilitate the deconstruction of additional neural correlates of eating behavior in health and disease. Following in the footsteps of the pioneering studies described above, these approaches should start combine findings at different levels of resolution by focusing on how individual cell populations and distributed neuronal networks interact to integrate orosensory and GI feedback.

The gut–brain axis in obesity

Perturbations in the gut–brain axis are increasingly recognized in pathophysiological states linked to obesity. Deficiencies in this communication pathway, such as reduced neural responsiveness to appetite-suppressing gut hormones, are believed to contribute to the exacerbation of metabolic dysregulation in obesity [38,63]. Indeed, obesogenic diets are known to trigger major adverse changes in gut–brain communication, such as altered histology, metabolism, and function of the intestinal mucosa characterized by an increased proliferation of absorptive enterocytes that was associated with an upregulated lipid metabolism [8,64]. Moreover, gut inflammation, with accumulation of proinflammatory intestinal macrophages, is a hallmark of obesity in humans [65]. Interestingly, studies in mice fed a high-calorie diet showed that depletion of intestinal-specific macrophages improved fasting blood glucose levels, glucose tolerance, and insulin release [65]. Likewise, patients with metabolic disease exhibit alterations in circulating GLP1 and GIP [66,67], while eating disorders characterized by repeated binge-eating attacks are associated with reduced postprandial CCK release and delayed gastric emptying [68]. In agreement with this desensitization, chronic overeating has been shown to blunt stretch detection by vagal afferents [69], CCK-mediated food intake suppression, and neural activation of the NTS and PVN [38,56,70]. Notably, exposure to high-calorie diets also causes profound disruptions in oxytocinergic brainstem control over gastric emptying [71] and satiation [38], leading to the question of whether lifestyle or pharmacological interventions could be leveraged to heighten brainstem oxytocin signaling. Importantly, recent data in humans compellingly reinforce the notion that a history of obesity triggers long-lasting perturbations in postingestive GI feedback to the brain. While intragastric nutrient infusions elicited neuronal activity and dopamine release in the striatum of lean participants, patients with obesity exhibited a severely impaired response that was not restored by 10% diet-induced weight loss [72]. Therefore, several altered mechanisms at different levels have been proposed to underlie maladaptive gut–brain communication in obesity (Figure 2). These potential mechanisms involve: (i) reduced hormone release; (ii) early-onset inflammatory changes, microglial activation, and neuropeptide signaling in nodose ganglia [73,74]; (iii) dysfunctional integration of signals, such as fat or CCK, by distinct neurons of the hypothalamus and brainstem [38,54,75]; and (iv) microbial gut dysbiosis, intestinal hyperpermeability, and microbiome-induced disruption of gut-induced reward via the vagus nerve [76], among others.

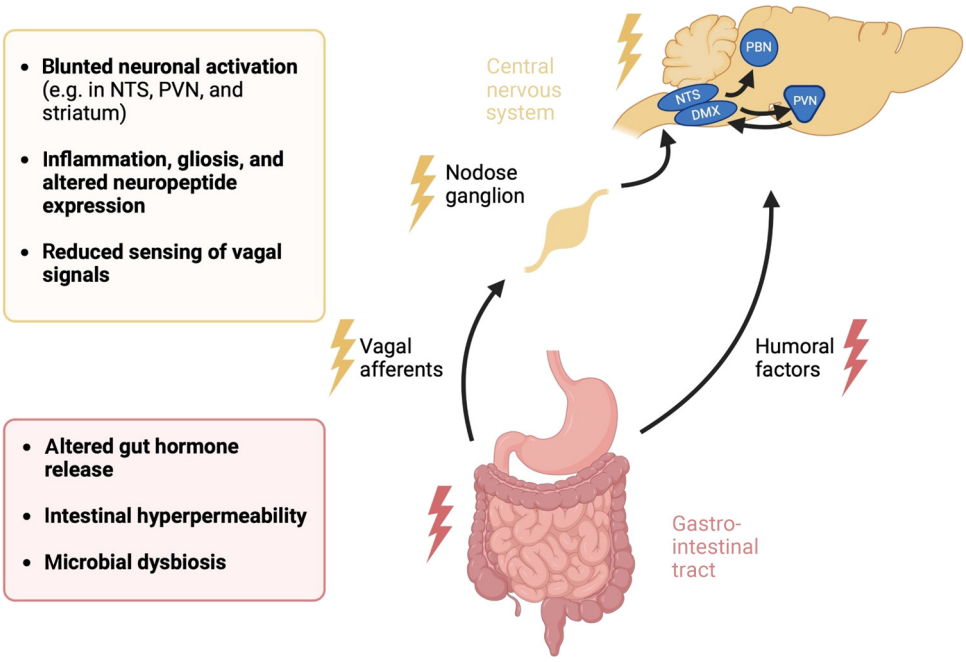

Figure 2. Obesity-associated perturbations along the gut–brain axis. Schematic depicting the neuroendocrine gut–brain axis, comprising neural (vagal) and humoral pathways targeting various brain regions, and a list of perturbations associated with obesity. Abbreviations: DMX, dorsal motor nucleus of the vagus; NTS, nucleus tractus solitarii; PBN, parabrachial nucleus; PVN, paraventricular nucleus of the hypothalamus. Figure created using BioRender (biorender.com).

Targeting the gut–brain axis: lifestyle and pharmacological interventions

Dietary strategies to enhance gut–brain feedback

Rather than eaten in isolation, foods are typically assembled as mixed meals combining components with complementary dietary properties (i.e., macronutrient profile, fiber, texture and flavor, water content, etc.). It was recently suggested that the order in which the various food components are consumed can have profound effects on gut–brain signaling. First randomized clinical trials support the notion that consuming protein and/or fiber before carbohydrates significantly enhances GLP1 secretion, delays gastric emptying, and curbs appetite, while improving postprandial glucose and lipid metabolism [77,78]. Moreover, an intriguing study in mice recently implicated gut–brain signaling in shaping behavioral choices by demonstrating that gut-derived signals can enhance motivation to exercise via spinal (but not vagal) afferent nerve signaling [79]. More studies are needed to underscore the emerging utility of lifestyle interventions as simple as physical exercise, meal-sequencing strategies or preloading with, for example, whey protein shakes [80], for behavioral nonpharmacological modulation of the gut–brain axis.

With respect to the influence of macronutrients on gut–brain signaling, several lines of evidence suggest a particularly detrimental role of increasing dietary fat, specifically of certain saturated lipid species, such as palmitic acid [81]. As such, intragastric infusions of fat, but not of carbohydrates, have been shown to disturb GI feedback and promote overconsumption independently of palatability [30,82]. Conversely, other studies reported that certain sugars negatively impact the integrity of the GI barrier [83] and exert strong appetitive effects via gut–brain vagal pathways [84]. Future work needs to elucidate exactly which dietary factors, either individually or in combination, are able to perturb gut–brain communication and whether these changes are implicated in

body-weight gain. Putative mechanisms entail altered sensing of specific sugars and lipid species by enteroendocrine and neuropod cells [7,12], enzymatic conversion of dietary factors into direct signaling molecules (e.g., endocannabinoids and oleoylethanolamide [85,86]), impaired barrier integrity and proinflammatory signaling [83], and diet-induced changes in the intestinal microbiota (i.e., gut dysbiosis) [2,3].

Pharmacological therapies

The translational success story of gut–brain research enables clinicians to choose from a broad armamentarium of safe and efficacious antiobesity drugs. Based on various gut peptides, either in the form of individual analogs or unimolecular poly-agonist [87], these next-generation pharmacotherapies have ushered in a new era for treating metabolic diseases. Even though these drugs reliably achieve body-weight reductions of up to 20–25% [88,89], discontinuation of treatment inevitably results in weight regain. This fact suggest that a history of obesity can permanently shift the set (or 'settling') point of body weight upward, which cannot be overcome by merely hijacking gut–brain signaling using pharmacological means. However, the putative mechanisms, semantics, and even the mere existence of such homeostatic regulatory thresholds remain intensely debated in the field of obesity [90,91]. Nevertheless, and as one of many potential explanations [92], we here outline the hypothesis that maladaptive changes along the gut–brain axis upon chronic exposure to obesogenic high-calorie diets contribute to regaining lost weight once pharmacological and/or behavioral interventions ceases. Importantly, we argue that insights into the underlying pathophysiological mechanisms might be leveraged to overcome this undesired rebound effect. Intensified efforts are underway to elucidate: (i) the cellular and molecular mechanisms underlying diet-induced dysfunctions along the gut–brain axis; (ii) processes that promote hedonic overeating by biasing orosensory-and-gut reinforcement over GI satiety feedback; and (iii) the potential for novel pharmacological and/or lifestyle interventions to reverse these changes, thereby achieving sustained obesity remission.

Concluding remarks and future perspectives

The past few years have witnessed the approvals and market launches of various antiobesity drugs that enable patients to safely lose a meaningful amount of excess body weight. Although the modes of action between pharmacological and endogenous gut peptide signaling differ [93,94], gut–brain signaling remains at the mechanistic core of obesity management and the advent of these drugs has accelerated basic gut–brain research even further. The field is now quickly overcoming previous technological barriers, using techniques such as singe-cell transcriptomics, wire-less optogenetics, or live recordings of discrete populations along the gut–brain axis (see Outstanding questions). The near future is expected to provide a window into how these signaling pathways intersect and converge, and specifically how neurocircuits integrate GI feedback with dynamic orosensory cues and cognitive processes, such as impulse control. This exploration will occur at different spatiotemporal scales, offering a more comprehensive understanding of the neural mechanisms underlying eating behavior. As scientists continue to unravel these fascinating aspects of basic biology, it will be vital to also shed light on pathophysiological mechanisms driving long-lasting maladaptations in gut–brain signaling due to a history of obesity.

Outstanding questions

What is the exact interplay between GI feedback and higher-order inputs (i.e., orosensory, motivational, and emotional)?

To what extent is weight regain ('yo-yo diet') following behavioral and pharmacological interventions driven by dysfunctions in gut–brain signaling?

Can we harness vagus nerve signaling (i.e., pacemakers) in combination with gut peptide formulations to treat metabolic diseases?

Is perturbed gut–brain signaling involved in the pathogenesis of other disorders, including neurodegenerative diseases, such as Parkinson's disease?

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Declaration of interests

Authors declare no competing (financial, personal, or professional) interests.

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