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The Enteric Neuronal Circuitry: A Key Ignored Player in Nutrient Sensing Along the Gut–Brain Axis

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ABSTRACT

The role of the gut-to-brain axis in the regulation of nutrient sensing has been studied extensively for decades. Research has mainly centered on vagal afferent and efferent neurotransmission along the gastrointestinal tract, followed by the integration of luminal information in the nodose ganglia and transmission to vagal integral sites in the brain. The physiological and cellular mechanisms of nutrient sensing by enterocytes and enteroendocrine cells have been well established; however, the roles of the enteric nervous system (ENS) remain elusive. Recent advances in targeting specific neuronal subpopulations and imaging techniques unravel the plausible roles of the ENS in nutrient sensing. In this review, we highlight physiological, cellular, and molecular insights that direct toward direct and indirect roles of the ENS in luminal nutrient sensing and vagal neurotransmission along the gut–brain axis and discuss functional maladaptations observed during metabolic insults, as observed during obesity and associated comorbidities, including type 2 diabetes.

1 | Introduction

The enteric nervous system (ENS), often referred to as the "second brain," is a vital component of the autonomic nervous system and plays pivotal roles in regulating gut motility, vasodilation, vasoconstriction, and epithelial secretions. The ENS is comprised of the myenteric (Auerbach) plexus, nestled between the longitudinal and circular smooth muscle layers, and the submucosal (Meissner) plexus [1], embedded in the submucosal layer of the small intestine that collectively maintain gut homeostasis [2]. The myenteric plexus consists of myenteric ganglia of varying sizes. The neurons of the myenteric plexus innervate the muscularis externa and neighboring myenteric neurons [3]. Intrinsic primary afferent neurons (IPANs) have cell bodies in the myenteric plexus [4]. Additionally, there are intestinofugal neurons (IFANs), a smaller population of myenteric neurons that project to the gallbladder, pancreas, and central nervous system (CNS) [3]. The submucosal plexus has two layers: an outer layer containing motor neurons that project to the smooth muscular layer and an inner layer that innervates the muscularis mucosae, defining the boundary between the mucosa and submucosa [5]. The submucosal plexus is a key regulator of intestinal secretion [6], with luminal distention activating its secretomotor reflex [7]. The myenteric and submucosal plexuses house the cell bodies of enteric neurons, while the axons and dendrons (as applicable) innervate the entire gut wall. Enteric neurons are typically identified and categorized based on morphology, location, chemistry, projections, and functions (Table 1). Historically, neurons

TABLE 1 | Types of enteric neurons.

Type	Location	Immunogenicity	Function
Ascending interneurons	MP	ChAT/Calretinin/TK	Send signals to excitatory motor neurons
Descending interneurons	Soma in MP with axon projections to SMP	ChAT/NOS/VIP/5-HT	Receive input from sensory neurons and relay signals to inhibitory motor neurons
IPANs	SMP and MP with projections going up to the mucosa	ChAT/Calb/TK/Nmu	Receive sensory input from other enteric neurons and relay signals across the ENS
Intestinofugal neurons	MP with projections to sympathetic ganglia	CCK/ENK	Form a portion of the afferent limbs for enteric inhibitory reflexes
Excitatory LM motor neurons	MP with projections to longitudinal muscle	ChAT/Calretinin/TK	Trigger muscle contractions in the longitudinal muscle layer
Inhibitory LM motor neurons	MP with projections to longitudinal muscle	NOS/VIP/GABA	Relaxing longitudinal muscle layer during peristaltic propulsion
Secretomotor neurons	Soma in SMP with projections to mucosa	ChAT/NPY/CCK/SOM CGRP/Dynorphine	Stimulate the release of various electrolytes, fluids, and mucus
Vasodilator neurons	SMP	ChAT/Calretinin Dynorophin	Regulate blood flow to intestinal mucosa by causing blood vessels to widen
Inhibitory CM motor neurons	MP with projections to the circular muscle	Nos/VIP/PACAP Dynorphin/ENK NPY/GABA	Relaxing circular muscle layer during peristaltic propulsion
Excitatory CM motor neurons	MP with projections to the circular muscle	ChAT/TK/ENK/GABA/NFP	Trigger muscle contractions in the circular muscle layer

have been classified as Dogiel type I or type II across a broad spectrum of species, with type III being the least understood type in humans [8]. Dogiel type I neurons are short, with one axon and many dendrites (up to 20), with broad endings that run through adjacent ganglia and occasionally into the muscle layer [8]. Dogiel type II neurons comprise about 10% of the myenteric plexus, with one axon and up to 16 dendrites [8] that project into the mucosa and other ganglia [9]. Dogiel type III neurons have not been studied in humans as much as in species such as guinea pigs and swine [8], but they have been described as multipolar with long dendrites and present in all areas of the small intestine [3]. Readers are directed to excellent reviews in this field and recent in-depth, comprehensive single-cell-based profiling studies for in-depth understanding of the specific functions of the different types of enteric neurons, based on location and immunoreactivity [3, 5, 7–14]. This review highlights the indirect and plausible direct pathways solicited by the ENS machinery and target receptors and neurotransmitters in luminal nutrient sensing, and the interactions with the gut–brain axis in the transmission of luminal information to the brain. Additionally, the causative roles of the ENS signaling in driving the propensity toward dysregulated nutrient sensing, as evidenced during obesity and type 2 diabetes (T2D), and the impact of obesity and T2D-driven metabolic dysregulation on the ENS machinery are discussed.

1.1 | Nutrient Sensing

1.1.1 | Indirect Nutrient Sensing by the ENS

The presence of nutrients within the gastrointestinal tract elicits functional changes in the ENS, contributing to enhanced motility, secretion, and circulation [15]. Nutrient-mediated mucosal secretion occurs through ENS pathways via mechanical and chemical stimulation of the mucosa. The nerve endings of enteric neurons do not extend into the lumen; instead, their synapses terminate at the basal epithelial membranes.

The indirect nutrient sensing pathways mediated by enteroendocrine cells (EECs) have been studied extensively for decades. EECs serve as pivotal intermediaries for neural signal propagation within the ENS, with nutrient receptors having been found predominantly on the cell surface [16]. Hormones released by these cells act on adjacent cells, nerve terminations, or organs [16]. Some of the hormones that commonly mediate food intake are CCK and glucagon-like peptide 1 (GLP-1), with GLP-1 known to directly impact glucose control [17, 18].

CCK is released from I cells, which are located in the proximal small intestine [19]. It is initially synthesized as a 115 amino acid pre-pro-CCK polypeptide and undergoes several

posttranslational cleavages before conversion into its biologically active form, CCK-8 [20]. CCK stimulates pancreatic amylase secretion, delays gastric emptying, and induces satiety by sensing duodenal lipids via neural networks. The specific mechanism for feeding control relies on the binding of CCK-8 to receptor CCK-A in the gastrointestinal tract [20].

GLP-1 is a proglucagon-derived peptide secreted by L cells [21], located in the intestinal mucosa [22], alpha cells of the pancreatic islets [23, 24] and neurons of the nucleus of the solitary tract [25–27]. In the intestine, GLP-1 is abundantly expressed by L cells in the distal sections and colon [28, 29] but is also sparsely expressed in the duodenum and proximal jejunum [30]. It acts as an incretin, triggering insulin release postprandially and inhibiting glucagon release [21, 30]. GLP-1, upon binding with GLP-1 receptor (GLP-1R) acts through $G\alpha_s$ to stimulate adenylate cyclase and increase cyclic AMP (cAMP) levels [31] The increase in intracellular cAMP recruits protein kinase A-dependent and exchange protein directly activated by cAMP (EPAC)-dependent processes to inhibit ATP-regulated potassium channels [32–35]. This subsequently opens L-type voltage-gated calcium channels [36–39], leading to increased calcium influx, thereby inducing insulin secretion from secretory vesicles.

GLP-1 also suppresses appetite and energy intake, acting as an "ileal break" by decreasing gastric emptying and intestinal motility [40–43]. Given its recently discovered roles in appetite regulation and food intake, interest has fueled the exploration of its therapeutic potential in ameliorating obesity. Additionally, GLP-1 release was shown to be dramatically decreased during morbid obesity [44, 45]. The postprandial surge in GLP-1 release was found to be virtually absent in morbidly obese subjects [46] and subjects with type 1 (T1D) and T2D [47]. Mechanisms underlying blunted GLP-1 release during obesity and diabetes remain elusive but may be related to insulin resistance [48] that accompanies weight gain and obesity. Potential roles of GLP-1 in appetite regulation and weight loss are highlighted by a robust increase in secretion in patients after bariatric surgery [49–52]. Although the surge in GLP-1 release post bariatric procedures, especially Roux-en-Y gastric bypass (RYGB) is thought to be a consequence of rapid nutrient delivery to the distal parts of the gut where the majority of L-cells are located, some preclinical studies show that rapid transit alone is not accountable for GLP-1 increase [53]. It is possible that intestinal physiology adapts to rapid nutrient entry by increasing L-cell numbers or the sensitivity of existing L-cells.

Given that the half-life of GLP-1 is approximately 1–2 min [54], involvement of endocrine and neural mechanisms to mediate effects of GLP-1 appears to be plausible. Immunohistochemical findings have uncovered the expression of GLP-1R on enteric neurons of the myenteric plexus [40], suggesting that the interaction of GLP-1 with enteric neurons may contribute to the expeditious impact. A sub-population of these neurons also co-express neuronal nitric oxide synthase (nNOS) or choline acetyltransferase (ChAT), which plays a significant role in motility [55]. This supports the notion that there is cross-talk between GLP-1 and nitric oxide (NO) [40]; furthermore, it corroborates the inhibitory effect of GLP-1 on excitatory cholinergic transmission in the mouse duodenal circular muscle [21]. This inhibitory effect seems to be mediated by the nitrergic pathway [55, 56]. There is evidence that the activation of cAMP-signaling due to the coupling of GLP-1R to the $G_{s\alpha}$ subunit causes an increase in NO production and subsequently inhibits excitatory mechanisms in the GI tract [40].

Notably, glucose has been demonstrated to elevate the secretion rate of sodium and chloride ions, while short-chain fatty acids (SCFAs) also exhibit the capability to augment chloride secretion. Glucose sensing in the gastrointestinal tract is facilitated by SGLT1, a sodium-glucose co-transporter, which has been detected on the apical surface of enterocytes [57]. Glucose sensing in the upper small intestine begins with the uptake of luminal glucose into enterocytes and/or EECs via SGLT1 [58]. Glucose then enters the basolateral membrane via the GLUT2 transporter. Glucose can directly and/or indirectly stimulate the release of CCK and GLP-1 via SGLT1. When glucose is co-transported with sodium via SGLT1 into EECs, it is metabolized into ATP and the co-transported sodium molecule triggers the release of calcium [59], mediating the release of CCK and GLP-1. Ileal glucose absorption is thought to stimulate the release of GLP-1 through SGLT1-independent mechanisms [60]. Fructose absorption in the upper small intestine operates through similar signaling pathways. Fructose entry into the enterocyte and then subsequent exit into the basolateral membrane is done via the GLUT5 transporter [61].

Sensing of fatty acids in the small intestine can be conducted through various pathways. Long-chain fatty acids (LCFAs) in the lumen are taken up by enterocytes by either CD36/FATP4 and/or simple diffusion [62]. Once inside the cell, they form triglycerides (TGs), which are then packaged into chylomicrons (CMs) and released into the bloodstream via lacteals. GPR40, a GPCR that senses LCFAs, modulates insulin secretion [63]. The CMs in the basolateral membrane can subsequently get hydrolyzed by nearby enterocytes, activate GPR40, and thus trigger the release of CCK and GLP-1 [64]. LCFAs can also be taken up by EECs and turn into LCFA-CoA via ACSL-3-dependent metabolism [65]. The metabolism of LCFA to LCFA-CoA activates PKC and subsequently releases CCK and/or GLP-1 [66]. LCFAs can also trigger CCK and GLP-1 release via GPR40/GPR120 [67, 68].

L-cells express interoceptors that precipitate responses to signals from glucose, amino acids, and fatty acids. The detection of free fatty acids by L-cells triggers the release of peptide YY (PYY) and GLP-1 from cellular vesicles. The Y1-R receptor binds both neuropeptide Y (NPY) and PYY and is expressed in the brain and peripheral organs, including nerve cell bodies of the submucosal and myenteric plexus [69]. Furthermore, Y1-R was found to be expressed by neurons that were immunoreactive for NPY, VIP, and NOS [69]. The co-localization of Y1-R and NOS in myenteric neurons indicates that NPY/PYY binding to Y1-R mitigates NO release from enteric neurons, which induces NANC relaxation of smooth muscle [69].

L-cells also release glucagon-like peptide-2 (GLP-2), which activates enteric neurons to increase glucose uptake through SGLT1 [70]. The effects of GLP-2 are mediated by its binding to the receptor (GLP-2R), which increases cAMP levels [71]. GLP-2 also

acts on VIP neurons, which subsequently increases chloride secretion [72]. The expression of the GLP-2 receptor on enteric neurons has been studied as well. Immunohistochemical findings indicated that GLP-2R is expressed by the myenteric and submucosal neurons in the mouse duodenum as well as several nerve varicosities that were abundant in the deep muscular plexus [41].

The presence of fatty acids affects the motility of the gastrointestinal tract via the release of CCK from I cells. I cells also express umami receptors, metabotropic glutamate receptor 1 (mGluR1) and mGluR4, which are activated by glutamate [73] and implicated in amino acid sensing [74]. In the small intestine, intestinal protein-sensing mechanisms can distinguish between protein metabolites such as amino acids and oligopeptides via distinct receptors [75]. One of the main GPCRs involved in protein sensing is the Ca^{2+}-sensing receptor (CaSR) [76], found on CCK-secreting I cells in the duodenum. Amino acids enter enterocytes and move to the basolateral membrane via amino acid transporters. The amino acids can then bind to CaSR on the EEC surface facing the basolateral membrane and trigger the release of GLP-1 and CCK [77]. Amino acids can also directly enter EEC via CaSR/T1R1/T1R3/GPRC6A to stimulate GLP-1 and CCK; however, the cellular mechanisms regulating amino acid uptake remain elusive [71, 78, 79]. The T1R1–T1R3 heterodimer has been implicated in amino acid sensing by responding to L-amino acids and stimulating CCK secretion [80]. GPRC6A is a receptor typically expressed on gastrin-producing G cells and somatostatin-producing D cells and has been found to respond to basic and neutral amino acids [81, 82]. Together with CaSR, they can sense various amino acids, including L-phenylalanine [83]. GPR92/93 are also expressed by G and D cells and elicit two different signaling pathways [84]. Oligopeptides enter enterocytes via PepT1 and get broken down to amino acids, then exit via an amino acid transporter into the basolateral membrane, stimulating CCK and GLP-1 release [85].

Nutrients influence the neurocircuitry of the ENS and can impact neighboring neurons and non-neuronal cells to modify their nutrient-sensing capabilities. The movement of ions in and out of cells results in the generation of either EPSPs or inhibitory post-synaptic potentials (IPSPs) [86, 87]. There are seven types of serotonin (5-HT) receptors present in the gastrointestinal tract, all of which are found in the myenteric plexus, while 5-HT_3, 5-HT_4, and 5-HT_7 are also present in the submucosal plexus [88]. Although speculation exists about a distinct 5-HT_{1P} receptor activated by 5-HT_1 and mediating slow EPSPs, insufficient evidence supports this claim [89]. Subgroups of I and L cells contain 5-HT, which, upon release, stimulates intrinsic sensory nerve endings in the mucosa, subsequently inducing smooth muscle contraction by binding to 5-HT receptors on enteric neurons and releasing acetylcholine (ACh) [90].

1.1.2 | Direct Nutrient Sensing in the Small Intestine and the Gut-to-Brain Axis

While indirect nutrient sensing has been studied extensively, the ability of enteric neurons to directly sense nutrients is still being examined. The expression of nutrient receptors by enteric neurons, akin to those on EECs, provides clues for possible direct sensing of nutrients. It has been found that enteric neurons express SGLT1, monocarboxylate transporters like MCT-2, GPR41, Pept2, and amino acid receptors [91–94]. It is known that intrinsic sensory neurons within the ENS directly discern stimuli without reliance on synaptic transmission, although the precise ionic mechanisms underpinning the transduction of mechanical and chemical stimuli remain incompletely elucidated [95].

The excitability of enteric neurons in response to glucose was identified by assessing their reactivity in the presence of glucose, focusing on ATP-sensitive K+ (K_{ATP}) channels. The K_{ATP} channel was found to consist of Kir6.2 and SUR1 subunits based on their immunoreactivity in a specific subset of enteric neurons [57]. These neurons co-stored ChAT, and some contained SP and calbindin immunoreactivities [57]. It is believed that submucosal SP, ChAT, and calbindin immunoreactive neurons, which also contain glutamate, serve as IPANs transmitting signals from the lumen to both the submucosal and myenteric plexus [57]. About 62% of neurons in the guinea pig myenteric plexus exhibited glucoresponsiveness by hyperpolarizing upon glucose removal and depolarizing upon K_{ATP} channel inhibition [57]. Furthermore, myenteric ChAT and calbindin immunoreactive neurons are primary afferent neurons [57]. The presence of K_{ATP} channel proteins in IPANs suggests their potential role in sensory transduction. Given the presence of K_{ATP} channels in the mucosa, it is hypothesized that glucose may stimulate IPANs by closing K_{ATP} channels on nerve terminals in the lamina propria [57].

Free fatty-acid receptors 2 and 3 (FFAR2 and FFAR3) sense SCFAs and couple via GPCRs through Gα signaling pathways [94, 96]. While both can inhibit cAMP production via $G\alpha_i$, FFAR2 can inhibit ghrelin secretion via $G\alpha_i$ and stimulate insulin secretion via $G\alpha_q$ [97, 98]. It has been generally known that FFAR2 is expressed by leukocytes and FFAR3 by EECs; however, immunohistochemical findings have indicated that FFAR3 alone is found on cell bodies in the submucosal and myenteric ganglia [94]. In the submucosal ganglia, some of those cells colocalize with VIP, which indicates that SCFAs are sensed by FFAR3 on secretomotor neurons [94].

Morarach et al. conducted a study aimed to delineate the neuronal composition of the murine ENS and further elucidate the distinct taxonomy of enteric neuron classes (ENCs) using single-cell RNA sequencing and immunohistochemical markers [99]. Their findings revealed a total of 12 distinct classes of ENCs, defined by their communication networks [99], Each of these classes was identified as excitatory motor neurons (ENC1-ENC4); interneurons (ENC5, ENC 7, ENC10); inhibitory motor neurons (ENC8, ENC9); and IPANs (ENC6, ENC12). ENC11 had a unique expression pattern and will need further investigation [99]. Ion channels showed class-specific distributions, which give insight into their unique electrophysiological properties. The ligands and receptors in ENC6, which displayed distinct IPAN characteristics, were positive for gene expressions of calcitonin gene-related peptide (CGRP) ligands and receptors, enkephalin receptors, galanin receptors, neuromedin U (Nmu) receptors, NO receptors, ACh ligands and receptors, GABA receptors, and glutamate, noradrenaline, and 5-HT receptors [99].

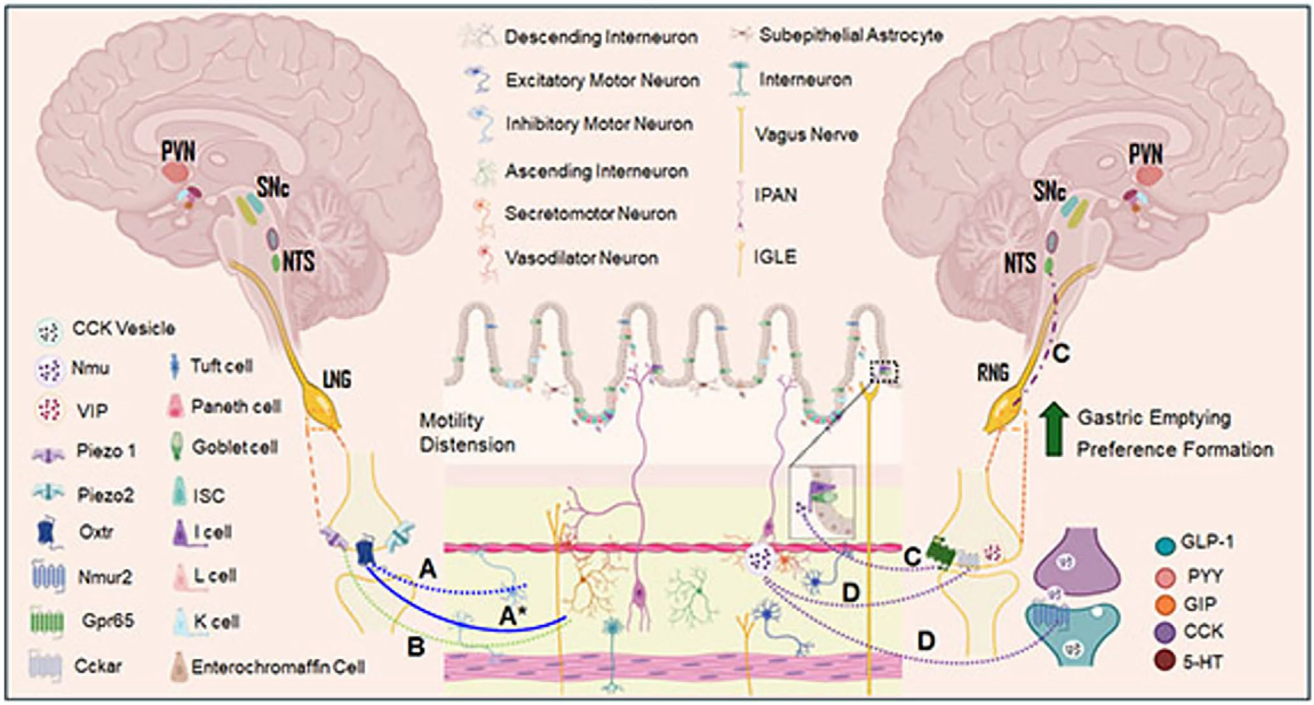

FIGURE 1 | Mechanosensory and chemosensory pathways connecting intestinal enteric neurons to the left (LNG) and right nodose ganglia (RNG) and brain. The afferent (A) and efferent (A*) oxytocin pathway connects the myenteric plexuses of the proximal small intestine and the oxytocin receptor on LNG vagal afferent neurons. (B) The mechanosensory pathway is induced by gastric distension and sensed by Piezo 1 and 2 channels on LNG vagal afferents projecting to the small intestine. Piezo 2 channels have also been identified on secretomotor neurons projecting into the intestinal mucosa, and these channels regulate 5-HT release by enterochromaffin cells. (C) CCK released by L-cells is sensed by RNG vagal afferent neurons that express Cckar and project to the NTS. Signals are integrated in the NTS before transmission to the SNc and the PVN and back to the nodose (efferent, C*). (D) NMU released by IPANs binds to the NMU receptor (Nmur2) on IFANs and CCK-positive neurons; the latter also interacts with RNG vagal afferents.

2 | Gut-to-Brain Axis

Current knowledge on the gut-to-brain axis is rooted in observations reporting signal transductions from the gastrointestinal tract to the vagus nerve and then the brain through vagal afferent innervations (Figure 1). The methodologies for tracking these afferent and efferent pathways have ranged from electrophysiology to retrograde and anterograde neuronal tracing of the neurocircuitry. While the sensory pathways of the gastrointestinal tract, vagus nerve, and CNS have all been studied as individual units, their mapping and interaction underlying regulation of feeding behavior remain elusive.

Findings have indicated a resemblance between the neurocircuitry mapping of the enteric and CNS regarding the perception of sweet tastes. Notably, the T1R2 and T1R3 sweet taste receptors, known for their role in detecting sugars within the oral cavity, have been identified to sense sugars within the gut [100], triggering a physiological response via alpha-gustducin signaling [100]. The post-ingestive mechanisms for sensing dietary fats, sugars, and amino acids involve the nodose ganglia that receive luminal inputs via the gastrointestinal vagal afferents (Figure 1). Several mechanosensory and chemosensory pathways connect intestinal enteric neurons to the nodose ganglia and brain, including the oxytocin pathway connecting the myenteric plexuses of the proximal small intestine and oxytocin receptor on the LNG (Figure 1A) and the mechanosensory pathway induced by gastric distension and sensed by Piezo 1 and 2 channels on LNG vagal afferents projecting to the small intestine (Figure 1B). CCK released by intestinal L-cells is sensed by cell bodies of the RNG that express Cckar and project to the nucleus tractus solaris (NTS) of the brain (Figure 1C). Additionally, NMU released by IPANs binds to the NMU receptor (Nmur2) on IFANs and CCK-positive neurons that interact with vagal afferent cell bodies in the RNG (Figure 1D). These circuits are not only responsible for the sensing of nutrients but also for the development and regulation of food preferences. Studies investigating the bilateral activation of the caudal NTS (cNTS) from stimuli such as fat and glucose when directly delivered into the gut support the notion that the fat-activated and sugar-activated neurons in the brain receive signals directly from the gut [101, 102]. The connection between nutrient-activated cNTS neurons and the nodose has been demonstrated utilizing trans-synaptic tracing. It is now known that cNTS neurons receive monosynaptic input from the nodose, specifically in the case of glucose [102].

It has been shown that the neural circuitry responsible for food intake is not ubiquitous bilaterally. The neural asymmetry described by de Arujo et al. illustrates two pathways for feeding behavior—mechanosensory and chemosensory. Cocaine- and amphetamine-regulated transcript (CART) deletion was performed on vagal afferents on the left and the right nodose ganglia (LNG^{CART} and RNG^{CART}, respectively). LNG^{CART} neurons were shown to have mechanosensory properties, innervating the myenteric layer of the duodenum. In vivo calcium imaging

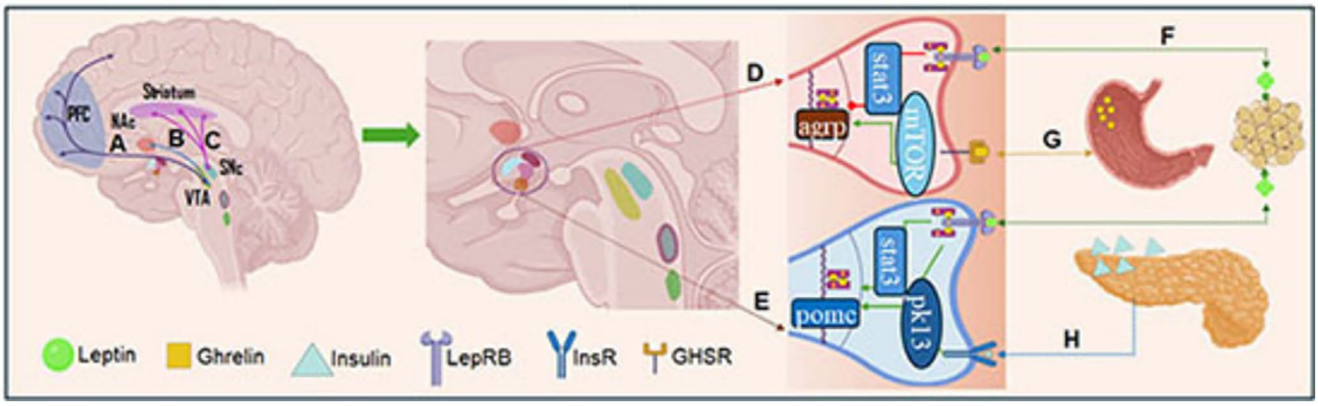

FIGURE 2 | Nutrient sensing and reward reinforcement pathways along the gut-to-brain axis. (A) Mesocortical pathway originates from VTA to PFC and is involved in decision making. (B) Mesolimbic pathway originates from VTA and NAc and is involved in the regulation of reward reinforcement and hedonic hunger. (C) Nigrostriatal pathway originates from SNc and projects to the striatum and is involved in the chemosensation and reward response to fat-sensing by RNG vagal afferents. (D) ARC to Lateral hypothalamus (LH) orexigenic pathway: NPY release and binding to secondary peripheral neurons in the VMH and PVN trigger downstream orexigenic effects and increase food intake. Once in the fed state, ghrelin activity is switched off by leptin-mediated signaling from POMC/CART neurons or by direct leptin binding to AgRP/NPY neurons. (E) ARC to LH anorexigenic pathway: Leptin signaling causes the release and subsequent binding of MSH-alpha from POMC/CART neurons to secondary peripheral neurons in the VMH and PVN. (F) Leptin signaling pathway: Leptin stimulates POMC neurons via STAT3 signaling/PK13 signaling cascade with insulin. Leptin also inhibits AgRP transcription in AgRP/NPY neurons via STAT3 signaling mechanisms. Phosphorylated STAT3 binds to the promoter regions of target neuronal populations and influences transcription to mediate anorexigenic effects. (G) Ghrelin signaling pathway: Ghrelin binds to GHSR on AgRP/NPY neurons and stimulates the transcription of AgRP through mTORC1-PS6K1 signaling. (H) Insulin signaling pathway: Circulating insulin that is released by beta-islet cells in the pancreas crosses the BBB and binds to InsR on POMC/CART neurons in the ARC and, along with leptin co-signaling via Pk13, triggers transcription of POMC and induces satiety.

indicated that LNG^{CART} neurons and a large fraction of the active dorsal motor nucleus (DMV) of the vagus nerve in the brainstem were activated in response to duodenal distension [103]. RNG^{CART} neurons were shown to innervate the villi and crypts and respond directly to fat [103]. These observations underscore the involvement of dopaminergic neurons in the SNc in response to fat [103], feeding off and responding to the chemosensory properties of RNG^{CART} neurons. Dopamine-releasing neurons are known to mediate reward reinforcement in the brain leading to seeking palatable food. The complex interplay of reward reinforcement and homeostatic satiety mechanisms (Figure 2) regulates calorie intake. The mesocortical and mesolimbic pathways regulate decision making and reward reinforcement, respectively (Figure 2A,B). The nigrostriatal pathway projecting into the striatum is involved in chemosensation and reward response to fat-sensing (Figure 2C). Orexigenic and anorexigenic pathways mediated by ghrelin and leptin (Figure 2D–G) regulate calorie intake and energy expenditure to match the caloric demands of the organism and integrate signals for storing excess calories as fat in the adipose tissue. Postprandial insulin release also interacts with orexigenic signaling and induces satiety (Figure 2H).

The core of hypothalamic metabolic control is the arcuate nucleus (ARC). Within the ARC lie two populations of neurons: agouti-related peptide (AgRP) neurons, which co-express NPY and are activated in an energy-deficient state, driven by ghrelin signaling to increase feeding behavior; and pro-opiomelanocortin neurons (POMC), which co-express CART and are activated in fed states to decrease feeding behavior, driven predominantly by leptin and insulin signaling [104]. CART-expressing vagal afferents could potentially coincide with the POMC/CART neuronal population in the ARC. This neuronal population is engrained in the mechanisms of the melanocortin system by producing α-MSH when activated. α-MSH binds to secondary neuronal populations in the paraventricular nucleus (PVN) and NTS to activate anorexigenic neurons and inhibit orexigenic neurons to control feeding behavior [105]. Interestingly, the neuronal population in the PVN co-expresses oxytocin. The LNG^{CART} vagal afferents implicated in sensing gastric distension also co-express oxytocin receptor as well as Piezo 1 and 2 channels. Piezo channels translate mechanical stress into calcium-dependent signals. Oxytocin inhibits feeding behavior by increasing the activity of brain regions that exert cognitive control while tandemly increasing the activity of structures implicated in reward and motivation [106–109]. While the overall mechanism of this neuronal class has not been fully elucidated, a potential mechanism of action could be related to oxytocin-mediated anorexigenic signaling involving the melanocortin system. However, further research is needed to fully understand the overlap between the two neuronal populations.

On the other hand, AgRP/NPY neurons are responsible for increasing food intake via mTORC1 signaling when ghrelin binds to the ghrelin receptor (GSHR-1). Once ghrelin binds to GSHR-1, NPY is produced and inhibits the anorexigenic secondary neurons of the PVN, while activating the secondary orexigenic neurons in the lateral hypothalamus (LH). AgRP/NPY neurons also enhance feeding behavior by the release of GABA molecules onto POMC/CART neurons to act as inhibitors of anorexigenic signaling [110]. However, leptin acts on this population of neurons as well via the same STAT3 signaling mechanisms as it does when binding to the leptin

receptors (LepRB) on POMC/CART neurons [104]. AgRP neurons have also been thought to play roles in both the homeostatic and hedonic feeding pathways. Feeding behavior is promoted through the homeostatic pathway connecting the ARC, ventromedial hypothalamus (VMH), and PVN, while circuits connecting the ventral tegmental area (VTA) and nucleus accumbens (NAc) regulate the hedonic feeding pathway [111, 112].

While vagal afferents are known to synapse with EECs, the interactions between them and enteric neurons are still unknown. As previously described, enteric neurons have displayed properties that would implicate them in direct nutrient sensing. However, the mechanisms underlying signal transduction have not been fully elucidated. In particular, the ability of enteric neurons to synapse with vagal afferents remains ambiguous. Considering the work of Morarach et al., it is established that two distinct ENCs, ENC 6 and ENC 7, manifest the expression of the Nmu ligand and its receptor, respectively [99]. Nmu, a neuropeptide implicated in physiological processes of appetite regulation, evidently denotes a substantial association with these ENCs [113]. Transcriptomic data reveal that ENC 7, postulated as an interneuron, expresses the Nmu receptor 2 (Nmur2). Nmur2 was previously thought to be mostly present in the CNS, with its greatest expression found in the hypothalamus, medulla, and spinal cord [114]. Nmu-Nmur2 signaling has previously been studied to regulate feeding behavior, with conflicting evidence on how deletion of Nmur2 affects food intake in mice [115]. However, it has been strongly postulated that Nmu-Nmur2 signaling could be involved in the development of food preferences [116]. At the transcriptome level, moderate levels of Nmu-Nmur2 mRNA were found to be expressed in areas of the brain involved with the reward system, such as the hypothalamus, substantia nigra (SNc), and striatum [117]. If Nmu-Nmur2 signaling is involved in dietary preferences, then one could question how that signaling may be related to RNG^{CART} neurons and their possible involvement in the development of preference. The classification of ENC 6 neurons as IPANs [99] offers further evidence of the potential role of these neurons in signal propagation by synapsing with other neurons in the ENS, as well as potentially synapsing with vagal afferents to transduce those signals to the NTS. Further studies must be conducted to elucidate this potential relationship and determine if there are two separate signaling pathways. While the functional purpose of the Nmu ligand expression on ENC 6 neurons and Nmur2 expression on ENC 7 neurons in the gut may still be ambiguous, it cannot be dismissed that, like T1R2 and T1R3, they could potentially mimic the neurocircuitry found in the CNS.

Two overarching, yet mutually exclusive, pathways activated by glucose and oleic acid have been identified in playing a crucial role in dictating feeding behavior. However, there are also instances where those pathways operate synergistically. It has been shown that when glucose and oleic acid were infused via an intragastric catheter, the number of activated dopamine-releasing neurons was higher than those activated by glucose or oleic acid infusions alone [118]. This finding not only highlights the relevance and significance of post-ingestive mechanisms but can also shed light on the reward effects of obesogenic food. Further research will need to be conducted to elucidate the dopaminergic response elicited by glucose and oleic acid in the gut lumen.

Bile acids (BAs), traditionally known for their roles in lipid digestion, have emerged as important signaling molecules regulating the ENS. Primary BAs are synthesized in the liver from a cholesterol precursor and are often conjugated with amino acids (glycine or taurine) to increase their water solubility before being stored and concentrated in the gallbladder. Gallbladder bile containing BAs, bilirubin, fatty acids, phospholipids, cholesterol, and proteins is emptied into the duodenum where it emulsifies dietary fats to facilitate absorption. BA profiles vary with diet and physiological status and are strongly influenced by the gut microbiome. While most BAs (> 95%) are reabsorbed by the ileum and returned to the liver via enterohepatic circulation, BAs that escape reabsorption enter the colon where they are transformed and deconjugated to secondary BA by intestinal bacteria with bile salt hydrolase activity.

BAs, both *en masse* and through select species via direct and indirect mechanisms, inform the CNS about the intestinal lumen environment, control gut hormone release, and regulate gut motility by slowing small intestine transit for nutrient absorption. These actions are facilitated by the widespread expression of BA nuclear receptors such as farnesoid X receptor (FXR) and membrane receptors such as Takeda G-protein coupled BA receptor, TGR5 (or G-protein coupled BA receptor; Gpbar1). The expression of these BA receptors in the brain [119, 120] and in different populations of myenteric, cholinergic, and nitrergic neurons in the small and large intestine [121] suggests a direct role for BAs in neurohumoral signaling. Gpbar1 is highly expressed on the cell membrane of enteric neurons in both mice and humans [122, 123]. TGR5 has been detected on IPANs regulating peristalsis via release of CGRP [124] and on the vagus nerve, impacting regulation of feeding through vagal afferent pathways [125]. Secondary BAs, such as lithocholic acid, influence intestinal transit times through interactions with TGR5 receptors on enteric neurons [122, 126]. TGR5 activation in the colon also inhibits basal and stimulated anion secretion by acting directly on epithelial cells and by inhibiting submucosal neurons [127]. BA activation of TGR5 in EECs leads to increased cAMP and intracellular calcium levels, which promotes secretion of PYY and GLP-1 [128, 129]. GLP-1 acts directly on GLP-1Rs on the beta cell to stimulate insulin release [130, 131] and on GLP-1R in the myenteric plexus that coordinate muscle contractions in the intestinal wall. This signaling, often referred to as the "ileal brake" reduces stomach motility through pathways involving the vagus nerve, leading to a relaxation of the proximal stomach and decreased antral contractions, thereby regulating nutrient absorption in the small intestine [132, 133].

The FXR is a nuclear BA receptor expressed in both the murine and the human ENS [134] that influences gut homeostasis, immune function, and intestinal barrier function. While much is known about FXR function in the brain, relatively little is known about its roles in the ENS. Like TGR5, FXR has been implicated in the release of GLP-1 from EECs [135, 136]. Evidence also supports that FXR can regulate enteric neurons indirectly through the release of FGF19 (humans)/ FGF15 (mice). In hyperglycemic mice, FGF19 increased the excitability of neurons

in the DMV in the brainstem through glutamatergic inputs from the area postrema and NTS [137]. FXR modulation also affects intestinal motility and can lead to abdominal pain hypersensitivity by influencing nerve growth factors, resulting in sensitization of TRPV1 channels in the dorsal root ganglia [138]. Other studies have shown that by inhibiting FXR signaling with tauro-chenodeoxycholic acid, an FXR agonist, the dorsal vagal complex can increase insulin sensitivity and lower glucose production in high-fat fed rats [139]. Further research targeting specific neuronal subpopulation/s is warranted to delineate the roles of FXR in ENS mediated signaling machinery and transmission to the brain.

3 | Long-Term Effects of Metabolic Maladaptations on ENS

Obesity and T2D are multifactorial global health concerns that overlap in a multitude of ways. The World Health Organization reported that worldwide obesity has doubled since 1990. In 2022, 43% of adults aged 18 years and older were overweight, and 16% were living with obesity. In the United States, obesity was prevalent in 42.4% of adults in 2017–2018. The International Diabetes Federation reported that in 2021, approximately 537 million adults were living with diabetes worldwide, a number expected to rise to 643 million by 2030 [140]. In the United States, the CDC's data revealed that more than 38 million people had diabetes, with T2D accounting for 90%–95% of the cases [141].

There has been a longstanding argument over which disease is the cause or the consequence of the other. Obesity can be linked to a milieu of genetic, environmental, or behavioral factors; however, the overall cause for this health outcome is hyperphagia. Hyperphagia is thought to be induced by either a hedonic feeding pathway or a homeostatic feeding pathway. The homeostatic pathway is responsible for maintaining energy homeostasis and is predominantly associated with the thalamus and hypothalamus. The hedonic pathway is connected to the reward system via the striatum, and it is what fuels motivation and reward for feeding behaviors [142]. While these two modalities may seem obvious, the underlying mechanisms remain unclear. Furthermore, these pathways tend to overlap, and chronic hyperglycemia and hyperlipidemia can cause perturbances in their intrinsic signaling capabilities. Obesity has been shown to alter nutrient sensing in the small intestine significantly, impairing satiety feedback mechanisms and disrupting signaling in the gut-to-brain axis. In individuals with obesity, the expression and function of nutrient sensors, such as SGLT1 and GPR40/GPR120, are dysregulated [143, 144]. The dysregulation of fatty acid sensing reduces GLP-1 and CCK-8 [145, 146], which can alter the gut–brain communication pathways, impairing satiety signals and leading to overeating. It has also been shown that heightened expression of nutrient transporters like SGLT1 and GLUT2 in the small intestine has been implicated in the exacerbation of hyperglycemia and insulin resistance [147].

One of the most effective treatments for individuals with obesity is RYGB. It has been shown to improve glycemic tolerance, increase satiety, as well as improve overall feeding behaviors [148, 149]. However, this is an incredibly invasive procedure, and individuals who undergo RYGB must meet a specific set of criteria to qualify for the procedure and may experience postoperative complications. While the overall health outcome of RYGB surgery is positive, the mechanisms underlying "reset" effect on the sensing of nutrients are still poorly understood. It has been thought that since RYGB surgery severs some of the vagal afferent fibers, thereby potentially remodeling the nerve terminals and causing downstream synaptic plasticity in the NTS [150–152]. Although this sounds promising, further work will need to be done to fully understand this mechanism.

The impaired secretion of GLP-1 in response to nutrient ingestion disrupts the incretin response, which is essential for enhancing postprandial insulin release and maintaining glucose homeostasis. Subjects with obesity were found to exhibit blunted sensitivity to nutrient-induced hormone release. When administered intraduodenal infusions of glucose and lipids, in contrast to their lean counterparts, individuals with obesity exhibited a diminished release of satiety hormones, including GLP-1 and PYY, and a blunted reduction in appetite [153]. These findings underscore the compromised nutrient sensing and satiety feedback mechanisms in individuals with obesity, further highlighting the challenges in managing appetite and energy balance. Furthermore, the attenuated nutrient response in individuals with obesity has been shown to induce irreversible physiological changes in the brain. In previous studies, it has been shown that bariatric weight loss was able to partially reverse obesity-associated impairments in the striatum. In a randomized crossover study, when compared to their lean counterparts, individuals with obesity showed a blunted striatal dopamine response to intragastric lipid infusions [154]. After diet-induced weight loss, the cohort of individuals with obesity showed an irreversible impacted post-ingestive response of dopamine in the striatum to intragastric lipid infusions. Notably, the striatum has been known to act as a caloric sensor in its role in feeding behavior, displaying a nutrient-specific response to lipid infusions versus glucose infusions in both cohorts [154]. When feeding behavior is delineated into hedonic and homeostatic pathways, one could infer that the striatum's nutrient-dependent nature could be involved in the homeostatic pathway. However, anything that can cause a feed-forward reaction and lead to acquired binge-eating behaviors, especially regarding obesogenic foods, is also implicated in hedonic feeding behaviors. These results could potentially explain why individuals with obesity may experience difficulties while trying to lose weight, as well as why they are highly susceptible to regaining the weight they have lost.

The secretion of GLP-1 and gastric inhibitory polypeptide (GIP) is significantly impaired in T2D as well. In healthy individuals, nutrients stimulate the release of these incretins, enhancing insulin secretion and promoting satiety. However, in subjects with T2D, the incretin effect is markedly reduced, as evidenced by blunted postprandial insulin release and subsequent poor glycemic control and impaired satiety signaling [155]. Insulin resistance is the hallmark nutrient-sensing maladaptation prevalent during T2D, extending to insulin-responsive glucose transporters expressed in the intestinal mucosa. Impaired expression and function of GLUT2, which is responsible for mediating facilitated diffusion of glucose into the apical membrane of enterocytes, can alter glucose sensing and transport, impacting postprandial

glucose levels and disrupting normal satiety signaling [156]. However, the degree of its implications in hyperglycemia has yet to be determined. It is now well known that the increased expression and activity of SGLT1 in the small intestine is a pathophysiological factor in hyperglycemia [147]. When SGLT1 was inhibited in humans, postprandial GIP decreased, and GLP-1 increased [157]. Studies have also targeted SGLT2, and this co-inhibition of SGLT1/2 improved glycemic control and resulted in decreased weight and increased GLP-1 levels in diabetic patients [158]. The differences in the release of satiety hormones between lean individuals and those with obesity could indicate that T2D may further exacerbate the already impaired nutrient sensing and satiety mechanisms in individuals with obesity, making it harder to control appetite and maintain glycemic homeostasis. GLP-1 has been a therapeutic target for individuals with T2D for its impact on the incretin response. Since GLP-1 by itself is not an ideal therapeutic agent because of its very short half-life, attributed to rapid degradation by dipeptidyl peptidase 4 (DPP-4), the development of DPP-4 inhibitors like sitagliptin, saxagliptin, linagliptin, and vildagliptin, to prolong the half-life of GLP-1 have met with a fair amount of success. However, these approaches were quickly met with shortcomings, including rapid renal clearance and potential immunogenicity. A successful strategy to inhibit renal clearance involves the conjugation of GLP-1R with agonists constituting hydrophobic long-chain FA moieties that exceed the size limit for glomerular filtration. Three long-acting agonists based on this approach received FDA approval for the treatment of obesity and T2D and include liraglutide, semaglutide, and tirzepatide. Liraglutide was the first daily injectable GLP-1 R agonist approved for use in patients with T2D [159–162]. Given the prevalence of obesity, several studies sought to evaluate the efficacy of GLP-1R agonists in obese subjects without T2D. Liraglutide and the other GLP-1R agonists have been shown to mediate significant weight loss, ranging from 1.0 ± 0.3 to 6.0 ± 1.8 kg [163–165]. Similarly, semaglutide, initially used as a medication for T2D, when administered at the higher dose of 2.4 mg/week, was found to induce weight loss in obese subjects [166–170]. Patients treated with semaglutide lower their body weight by approximately 15% [166]. The ability of GLP-1R agonists to increase satiety and decrease overall caloric intake has been reported to involve decreased reward value of palatable food [171]. However, preclinical studies have indicated a strong preference for sucrose concentrations in rats receiving semaglutide [171]. Rats receiving semaglutide increased total energy intake and body weight due to excessive sucrose consumption. One potential explanation for this finding could be that semaglutide may enhance the reward value of sucrose, as evidenced by altered dopamine signaling in the VTA [172, 173], amygdala [174], and NAc [175, 176] during acute GLP-1R agonism. The abundance of sucrose in the western diet cannot be dismissed while considering the clinical implications of GLP-1R agonism-based treatments. Fructose, when paired with glucose, forms the disaccharide sucrose and contributes to changes in the expression of gut transporters when consumed in excess [177]. These transporters include SGLT1, GLUT2, GLUT1, and GLUT5. Interestingly, GLP-2R expression increased in the proximal and distal small intestines of mice fed a high fructose diet, whereas GLP-1R expression remained unchanged [177]. Sellami et al. revealed that GLP-2R activation is necessary for rewiring gut glucose sensing in the presence of high fructose and is associated with adaptation of the small intestine by increasing surface area for absorption. Eventually, this leads to hyperglycemia that precedes the onset of obesity [177]. Nonetheless, overall, GLP-1 and GIP agonism is a promising therapeutic strategy with intestinal and central benefits on appetite regulation, food intake, and glycemic control.

Interestingly, although GLP-1 and GLP-2, ligands for GLP-1R and GLP-2R, respectively, are secreted in equimolar amounts from L-cells, they have opposing effects on postprandial intestinal lipid packaging. GLP-1 decreases postprandial intestinal CM production, as evidenced by a decrease in apoB48 and TG in the TG-rich lipoprotein fractions [178]. Conversely, GLP-2 promotes triolein uptake and increases the secretion of TG-rich, apoB48-containing CM particles via a CD36-dependent process [179]. The net effect of intravenous GLP-1/GLP-2 co-infusion was observed to be enhanced postprandial TG secretion [180]. While GLP-2 activates the GLP-2R that is located on EECs [181], myenteric enteric neurons [182], subepithelial myofibroblasts [183], and neurons connecting the nucleus of the solitary tract with the dorsomedial hypothalamic nucleus [184], notably, GLP-2R is not expressed by absorptive enterocytes. Therefore, the hyperlipidemic action of GLP-2 is mediated indirectly, presumably by signals transmitted from the enteric neurons to the absorptive enterocyte. Understanding lipid and nutrient sensing pathways operative along the intestinal mucosa, submucosa, and deeper myenteric layers warrants carefully designed mechanistic investigations.

In addition to influencing intestinal glucose sensing and subsequent physiological adaptation to increase absorption, dietary fructose was reported to stimulate the release of CCK, PYY, neurotensin, and 5-HT from I, L, N, and enterochromaffin cells, respectively, in rodents and humans [185, 186]. Furthermore, fructose stimulates GLP-1 and insulin release (but not GIP secretion) in healthy, nondiabetic rodents and humans [185, 187] and GIP secretion in streptozotocin-induced diabetic mice [187]. Long-term fructose consumption in rats was reported to induce leptin resistance prior to body weight, adiposity, and metabolic insults including hyperglycemia, hyperinsulinemia, and hyperleptinemia; fructose-induced leptin resistance accelerated high-fat-induced obesity [188]. Short-term fructose feeding was demonstrated to attenuate postprandial surges in insulin, GLP-1, and leptin [189–191]. Additionally, enhanced release of the hunger hormone ghrelin and suppressed release of the satiety signal $PYY_{3\text{-}36}$ was observed with short-term fructose feeding, along with downregulation of hypothalamic NPY mRNA [192]. Collectively, fructose impacts appetite and food intake regulation by influencing the release of hormones with roles in hunger and satiety regulation along the gut–brain axis.

Obesogenic foods contain ample amounts of sucrose, as well as other added sweeteners, and relatively high fat contents [193]. This combination induces weight gain and adiposity in pair-fed experiments independent of total energy consumption, indicating potential alterations in homeostatic feeding pathways [193]. On the other hand, dietary fructose paired with high dietary fiber had the opposite effect on satiety and post-prandial glucose levels [194]. These findings, akin to the aforementioned increase in reward signaling with high glucose–high oleic acid diets [118], implicate macronutrient distribution as a key factor in hyperphagia and T2D, and should be taken into consideration

upon implementation of pharmacological treatments. The lack of change in GLP-1R expression compared to GLP-2R in high-fructose feeding offers another potential target for obesity treatment. Further exploration of a potential GLP-1R agonist-cum-GLP-2R antagonist strategy for targeting both hedonic and homeostatic feeding pathways is warranted.

It is important to note that individuals with HFD and obesity seem to retain their sensitivity to protein sensing [195]. In fact, a high protein intake has been shown to have positive effects on metabolic outcomes [196–198]. A potential reason for this could be CaSR expressed in the small intestine. It has been shown to be resistant to functional desensitization due to its ability to undergo agonist-driven signaling. Not only that, but in vitro studies have shown that CaSR activation triggers the release of satiety hormones such as CCK and GLP-1 [85, 199, 200]. In vivo studies in mice have shown that oral administration of a CaSR agonist decreased food intake [201]. A high protein diet (HPD) has also been shown to preserve muscle mass during weight loss [202, 203] which is critical for maintaining a stable metabolism. An HPD activates the homeostatic feeding pathway via CCK-dependent mechanisms in the gut, which activate vagal afferent nerve fibers and subsequently activate neurons in the NTS [204]. It is hypothesized that an HPD also activates the hedonic feeding pathway, but that mechanism is poorly understood [205]. All these factors make protein nutrient sensing in the gut a potential therapeutic target for individuals with obesity. The exact nutrient sensing implications protein has on the gut-to-brain axis remain incompletely elucidated, however, and therefore must be further investigated.

Diabetic gastropathy further complicates nutrient sensing and satiety feedback by altering gastrointestinal motility. Delayed gastric emptying and changes in the intestinal transit time disrupt nutrient exposure to the mucosal surface, impairing the signaling pathways that regulate appetite and glucose homeostasis [206]. It was once thought that diabetic gastroparesis developed in individuals with T1D more frequently than in those with T2D; the increase in the prevalence of T2D has resulted in a direct increase in the prevalence of diabetic gastroparesis in those individuals as well [207]. Abnormalities in diabetic individuals that cause gastric motor dysfunction could be attributed to things such as autonomic neuropathy, enteric neuropathy, and even the use of incretin-based medications such as GLP-1 analogs [208]. In studies on the morphology of the vagus nerve in these individuals, demyelination was found, as well as a loss of nNOS expression in enteric neurons [209]. However, the neurons themselves remained intact.

Both obesity and T2D represent significant challenges to the homeostatic mechanisms of nutrient sensing in the small intestine. The dysregulation of nutrient sensing, impairment of satiety feedback, and disruption of the gut-to-brain axis underscore the complexity of gastrointestinal dysfunction in metabolic diseases and point toward potential therapeutic targets for intervention.

4 | Summary and Outlook

While substantial progress has been made in understanding the ENS and its functions, several areas warrant further investigation to elucidate its role in nutrient sensing. More research is needed to identify the specific enteric neurons, ionic channels, and receptors involved in direct nutrient sensing by the ENS, and how these mechanisms contribute to overall gut function and metabolism. This knowledge could lead to a deeper understanding of how the ENS maintains homeostasis and responds to dietary changes.

Further studies are required to explore how metabolic diseases such as obesity and T2D affect the nutrient sensing capabilities of the ENS, and how these changes contribute to disease progression. Investigating potential therapeutic targets within the ENS for treating metabolic disease could lead to new interventions to restore homeostatic nutrient sensing and gut function. This includes exploring the modulation of specific ENCs and their receptors.

Understanding how the ENS adapts to long-term changes in diet and metabolic state can reveal the extent of its plasticity and the potential for interventions that promote gut health and metabolic balance.

Author Contributions

Ester Nikolla, Ava Grandberry, Destiné Jamerson, Charles Robb Flynn, and Sinju Sundaresan wrote the manuscript. Sinju Sundaresan conceived the idea, prepared, and edited drafts. All authors approve the final version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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