

Review

The Possible Involvement of Glucagon-like Peptide-2 in the Regulation of Food Intake through the Gut–Brain Axis

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Abstract: Food intake regulation is a complex mechanism involving the interaction between central and peripheral structures. Among the latter, the gastrointestinal tract represents one of the main sources of both nervous and hormonal signals, which reach the central nervous system that integrates them and sends the resulting information downstream to effector organs involved in energy homeostasis. Gut hormones released by nutrient-sensing enteroendocrine cells can send signals to central structures involved in the regulation of food intake through more than one mechanism. One of these is through the modulation of gastric motor phenomena known to be a source of peripheral satiety signals. In the present review, our attention will be focused on the ability of the glucagon-like peptide 2 (GLP-2) hormone to modulate gastrointestinal motor activity and discuss how its effects could be related to peripheral satiety signals generated in the stomach and involved in the regulation of food intake through the gut–brain axis. A better understanding of the possible role of GLP-2 in regulating food intake through the gut–brain axis could represent a starting point for the development of new strategies to treat some pathological conditions, such as obesity.

Keywords: glucagon-like peptide-2 (GLP-2); gastric motility; food intake; peripheral satiety signals; gut–brain axis



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1. Introduction

The regulation of the hunger-satiety cycle is a complex mechanism of interplay among signals originating from both central and peripheral structures that are mainly integrated at the hypothalamic level [1]. In particular, in the arcuate nucleus, two neuronal populations that exert antagonistic functions in the control of food intake and energy balance have been described: one co-expressing Neuropeptide Y (NPY) and Agouti-related protein (AgRP), and the other co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). These neuronal populations express several types of receptors whose activation might cause orexigenic or anorexigenic effects [2,3]. Peptides synthesized by such neuronal populations have been considered essential biomarkers of metabolic disorders occurring in obese subjects, while disruption of these neurons is considered one of the causes of obesity [4]. The arcuate hypothalamic nucleus is recognized as the main integrative center of signals coming from other hypothalamic areas involved in feeding behavior or from extra hypothalamic nuclei [5], such as the nucleus tractus solitarius (NTS), as well as from the periphery. Hypothalamic integration of information from the pancreas, adipose tissue, and gastrointestinal tract plays a key role in the neuroendocrine control of food intake, translating this into a feeding behavior [3,6–9].

The gastrointestinal tract represents also a source of both nervous and hormonal signals which play important roles in the peripheral regulation of the hunger-satiety cycle [9–12]. Several hormones released by nutrient-sensing enteroendocrine cells can send anorexigenic signals to central structures involved in the regulation of food intake

by engaging more than one mechanism [9,13]. Many peptide hormones, entering the systemic circulation, can directly reach the hypothalamic arcuate nucleus, likely through an incomplete blood–brain barrier [14]. Therefore, they may exert their effects through the direct activation of POMC/CART neurons and/or inactivation of NPY/AgRP ones, on which the presence of specific receptors has been identified [3,15]. Furthermore, as better described below, the hormones of intestinal origin can send signals to the central structures involved in the regulation of food intake through the activation of the gut–brain axis. Finally, the observation that some of the intestinal hormones that influence the hunger-satiety cycle by acting at a central level also influence the gastric motor responses responsible for peripheral satiety signals is an interesting feature since peripheral effects may represent additional mechanisms to the central ones in regulating food intake. While this double mechanism has been recognized for some gut-derived anorexigenic hormones (e.g., GLP-1, CCK, and PYY), it has not been completely clarified for GLP-2, which has demonstrated the ability to induce gastrointestinal motor changes in addition to its central anorexigenic effects [16].

In the present review, our attention will be focused on the ability of GLP-2 to modulate gastrointestinal motor responses and discuss how its effects could be related to peripheral satiety signals originating from the stomach and involving the central structures regulating food intake through the gut–brain axis. A better understanding of the possible role of GLP-2 in influencing food intake through the gut–brain axis could provide insights into the development of new therapeutic approaches in the treatment of some pathological conditions, such as obesity. In fact, some forms of obesity, characterized by dysregulation of the hunger-satiety cycle, are imputable to alterations of peripheral signaling that promote hyperphagia and weight gain [17] and are susceptible to bariatric therapy as a result [18].

2. Mechanisms through Which Gut-Derived Hormones May Activate the Gut–Brain Axis to Generate Satiety Signals

In addition to their direct action on receptors in the central nervous system (CNS) via the classic bloodstream way, gut-derived hormones can indirectly send anorexigenic signals to the hypothalamic nuclei, activating vagal afferent fibers from the gastrointestinal tract [18]. The latter mechanism implies the presence of specific receptors on the terminal afferent vagal fibers located in the gut mucosa which have been described for many different regulatory peptides [19]. These signals reach the hypothalamus through the interposition of the NTS [14]. A further mechanism involving the gut–brain axis is represented by the ability of peptide hormones of intestinal origin to exert their anorexigenic effects through the modulation of those gastric motor phenomena known to be a source of peripheral signals involved in the control of food intake at a central level [18,20]. Both gastric accommodation and gastric emptying play an important role in the regulation of organ distension [21]. Gastric wall distension, by causing stretch and tension, stimulates the mechanosensitive receptors which, in turn, activate the vagal afferent nerve fibers. These latter induce satiety signals to the hypothalamic regions involved in the regulation of food intake, through the interposition of the NTS [9,22].

Delayed gastric emptying, which plays a critical role in regulating short-term food intake, has been reported to be associated with increasing sensation of satiety and stopping food consumption in humans [23] due to gastric wall distension. This information fits well with the observation that obese subjects present with faster gastric emptying [24,25]. Moreover, gastric emptying determines the rate of arrival of nutrients in the small intestine which, in turn, regulates satiety. As gastric emptying occurs, chyme enters the small intestine where the presence of nutrients is mainly detected by specialized receptors expressed on the apical side of open-type enteroendocrine cells which respond by releasing hormones [26–28]. Some anorexigenic hormones reach the stomach to slow gastric emptying, inducing gastric distension and thus contributing to a satiety sensation [29]. Furthermore, some hormones, in response to the arrival of nutrients, mainly lipids and proteins, reach the ileal portion and inhibit its motor responses. This generates a feedback

response at the stomach level to induce delayed gastric emptying, a mechanism that is known as the physiological ileal brake reflex [18]. The latter is the result of the activation of enteroendocrine cells and mucosal afferent nerves and is regulated by hormones released from either the proximal gut portion, such as GLP-1 and CCK, or the distal one, as PYY [8].

An illustration summarizing the main mechanisms through which gut hormones may regulate food intake to induce anorexigenic effects is reported in Figure 1.

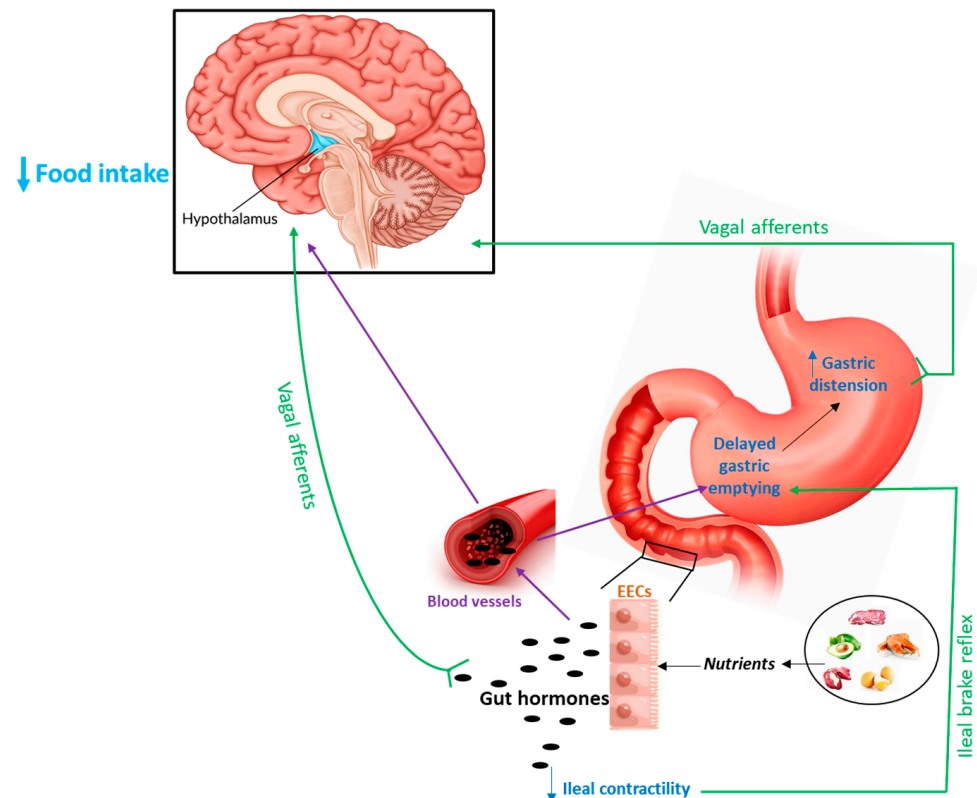


Figure 1. Schematic representation of the main mechanisms through which gut hormones may influence hypothalamic structures to induce anorexigenic effects. Purple lines (bloodstream); green lines (nervous fibers); and EECs (enteroendocrine cells).

Therefore, the action of intestinal anorexigenic hormones in regulating food intake can be exerted directly at the central level or indirectly at the peripheral level through changes in gastric motor responses which contribute to the sense of satiety. In this view, GLP-2 has been reported to exert some central anorexigenic effects and also to influence gastrointestinal motor responses which could be associated with peripheral satiety signals generated by the stomach and involved in the regulation of food intake, as discussed below.

3. Glucagon-Like Peptide 2

Glucagon-like peptide 2 and glucagon-like peptide 1 (GLP-1) derive from proglucagon, which is a 158 amino acid precursor protein predominantly expressed in the pancreas, gut, and distinct neuronal populations of the hindbrain [30]. In the brain and the intestine, proglucagon is cleaved by the action of the prohormone convertase 1/3 (PC1/3) into GLP-1, GLP-2, glicentin, glicentin-related polypeptide (GRPP), and oxyntomodulin (OXM) [30–32]. A schematic overview of tissue-specific proglucagon processing in the gut, brain, and pancreas is reported in Figure 2.

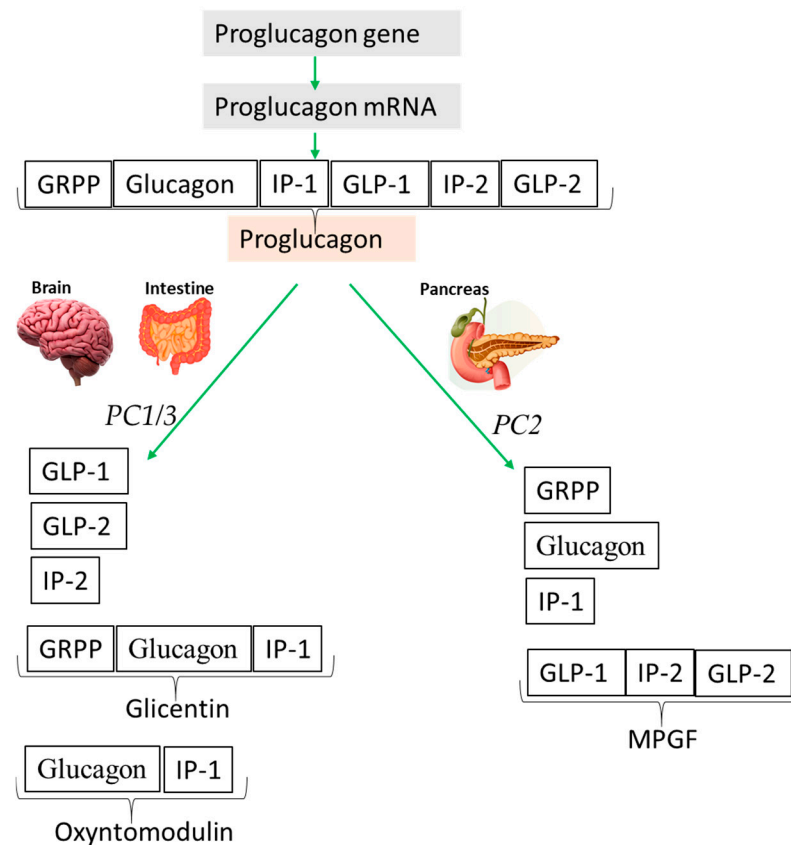


Figure 2. Schematic representation of tissue-specific proglucagon processing in the intestine, brain, and pancreas. The proglucagon gene is transcribed to generate proglucagon messenger RNA (mRNA), which is subsequently translated to the precursor protein, proglucagon.

In the brain and enteroendocrine intestinal L-cells, proglucagon is processed by prohormone convertase 1/3 (PC1/3) to generate glucagon-like peptides-1 (GLP-1) and -2 (GLP-2), intervening peptide-2 (IP-2), glicentin, and oxyntomodulin.

In pancreatic alpha-cells, proglucagon is processed into glicentin-related pancreatic polypeptide (GRPP), glucagon, intervening peptide 1 (IP1), and major proglucagon fragment (MPGF) by the processing enzyme prohormone convertase 2 (PC2).

GLP-2 is a 33 amino acid peptide mainly expressed in the gut, together with GLP-1, by enteroendocrine L-type cells of the distal small intestine and colonic mucosa [30,33–35]. In this regard, the classical definition of L cells as a homogeneous population has recently been revised [36] as important differences between them have been reported along the length of the intestine and also between different species. Furthermore, some subpopulations of L-cells express other peptides in addition to glucagon-like ones [27]. Enteroendocrine L-type cells are activated in response to luminal nutrient content [37], mostly fat and glucose [38,39]. However, there are also several regulating mechanisms underlying L cell secretion, such as circulating hormones (e.g., CCK and some adipokines), paracrine/neuronal substances, as well as gut microbiota with its metabolites [14,27]. The same diet nutrients may cause changes in the gut microbiota composition which in turn influences gut anorexigenic hormone release, thus influencing food intake [40].

GLP-2 has been reported to colocalize with GLP-1 in the same mammalian secretory granule [41] from which it is co-secreted in a 1:1 ratio [42] and the molecular mechanisms that link hormone exocytosis to the circulating patterns of glucagon-like peptides are only recently beginning to be fully understood [27]. Despite the distal localization of L-cells, GLP-1 and GLP-2 plasma levels (as well as other L-cell-derived hormones) rapidly rise following ingestion [43], suggesting the existence of a proximal gut signal also regulating hormone release from the L cells of the distal small intestine [43]. Circulating GLP-2 and

GLP-1 are quickly degraded by dipeptidyl peptidase IV (DPP-IV) [44,45], resulting in half-lives of ~7 and 1–2 min, respectively [30,46–48]. Due to their short circulating half-life, the native glucagon-like peptides have only limited pharmacological potential [49], so DPP-IV-resistant analogs as well as DPP-IV inhibitors have been considered for possible therapeutic strategies [50,51]. In this view, GLP-2 analogs have demonstrated their efficacy in the management of short small bowel syndrome (SBS) [52–54].

In addition to intestinal L-cells, GLP-2 is also secreted by brainstem neurons that innervate the paraventricular nucleus (PVN) and dorsomedial hypothalamus (DMH) [55]. Moreover, the presence of GLP-2 immunoreactive fibers has also been revealed in the arcuate nucleus (ARC) and PVN [56], hypothalamic areas involved in the regulation of food intake and energy balance, thus suggesting a role for GLP-2 as a neurotransmitter in these areas.

The expression of the specific G protein-coupled GLP-2 receptor (GLP-2R) is predominant in the gastrointestinal tract and CNS of humans and rodents. Its presence has been widely described in the DMH and ARC and particularly in a rodent subpopulation of POMC-expressing neurons [3,29,57] that are known to be implicated in the regulation of energy balance by integrating long-term adiposity and short-term satiety endocrine signals. The GLP-2R expression has also been reported in extra-hypothalamic areas such as the NTS [58]. The presence of the GLP-2R in other brain areas involved in the regulation of energy balance, including the brainstem (dorsal motor nucleus of vagus nerve [DMV]) and hippocampus (parabrachial neurons), suggests the role of GLP-2 in metabolic regulation [29,57,59–61]. Interestingly, GLP-2Rs have been localized on cell bodies of vagal afferents of the nodose ganglion in the rat [62]. GLP-2R signaling in the CNS has been reported to be involved in the regulation of several physiological processes, including feeding behavior and gastrointestinal functions (see below).

A schematic representation of the GLP-2R activation following nutrient stimulation of GLP-2 release from L cells is reported in Figure 3.

Effects of GLP-2 in the Regulation of Food Intake

Among its multiple functions, GLP-2 has also been reported to influence food intake by exerting anorexigenic effects. Mice lacking GLP-2R in POMC neurons showed hyperphagia, supporting a central action of GLP-2 in satiety regulation [60]. Appetite suppression has been observed in mice following activation of the hypothalamic GLP-2R by intracerebroventricular administration of GLP-2 [60] or of a degradation-resistant GLP-2 analog [63]. This hormone effect has been proposed to occur, at least in part, through the activation of the melanocortin receptor-4 (MC4-R) signaling pathway [60]: blockade of MC4R abolished the inhibitory effects on food intake of GLP-2 injection into the NTS in fasted rats has been reported [64]. These observations further support the central inhibitory effects of the hormone on food intake in rodents. Of note, in rodents, the inhibitory effects of GLP-2 on food intake were abolished by the loss of the GLP-1R [65], whereas these effects were increased following the loss of GLP-1R signaling [58]. These results indicate the existence of an interplay between the two hormones in the regulation of food intake. Moreover, inhibition of food intake due to GLP-2 injection in the DMH of fasted rats also occurs through the involvement of a specific GLP-2 signaling pathway: the effects of locally delivered GLP-2 can be blocked by Exendin(9–39), a specific GLP-1 receptor antagonist, but not the MC4-R antagonist SHU9119, revealing that GLP-2 inhibition of food intake in DMH could be blocked functionally by Exendin(9–39) [66].

Despite all the reported observations, conflicting results have been found in animals and humans regarding the actual ability of GLP-2 to modulate feeding, and the mechanisms activated by the hormone are still a matter of debate. No influence on appetite or post-prandial feeling of satiety has been shown following peripheral administration of GLP-2 in lean, healthy individuals [67,68], whereas inhibition of feeding either by central [56,58] or peripheral [69–71] injection of the hormone has been observed in animals. GLP-2 has been also proposed as a neurotransmitter in controlling feeding behavior [69] and may mediate

preproglucagonergic neuron-induced synaptic transmission linking the hypothalamus and the brain stem [55].

Although it has been reported that GLP-2 controls energy homeostasis [57], at least in part through the regulation of food intake [72], the involvement of GLP-2 in the hunger-satiety cycle remains subject to debate, and more investigations are certainly required in humans, at variance with the well-established central anorexigenic effects of GLP-1 [73]. Interestingly, the observation that GLP-2 inhibits ghrelin secretion in humans [74] may support the involvement of GLP-2 in the short-term regulation of the hunger-satiety cycle. The effects of GLP-2 on gastrointestinal motility may also indicate its ability to generate peripheral satiety signals from the stomach, which could agree with its central anorexigenic action as detailed in Section 5.

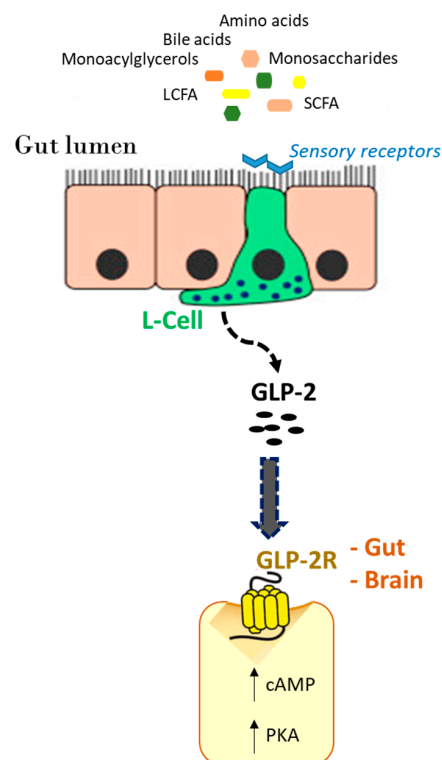


Figure 3. A schematic representation of the activation of the GLP-2R in the gut and brain following the release of GLP-2 from L cells stimulated by nutrients entering the intestinal lumen, which are detected and sensed by receptors on the apical border. SCFA (short-chain fatty acids); LCFA (long-chain fatty acids); cAMP (cyclic adenosine monophosphate); and PKA (protein kinase A).

4. The GLP-2 Effects in the Gastrointestinal Tract

4.1. GLP-2 and Metabolism

Most of the peripheral regulatory functions of GLP-2 are exerted in the digestive apparatus, where GLP-2R expression has been described [34,61,75,76]. Initially, GLP-2 was identified as an intestinotrophic hormone able to promote the growth and repair of the mouse small intestine [77]. The same effect was later observed in short-bowel jejunostomy patients [78], contributing to the subsequent development of GLP-2 analogs to treat SBS [54]. In the gastrointestinal tract of both humans and animals, GLP-2 signaling modulates the secretion of different enzymes involved in the digestion and uptake of nutrients [46,79–81] to control metabolism and promote a positive energy balance [72]. In particular, GLP-2 signaling facilitates the absorption of fatty acids [82], amino acids [83], and glucose [84]. For the latter, peripheral administration of GLP-2 has also been shown to increase the expression of glucose transporters in the mouse small intestine [85]. Moreover, positive effects on glucose metabolism by the hormone have also been observed in obese mice [79].

GLP-2 signaling increases dietary lipid absorption, promotes chylomicron release in rodents [82], is implicated in regulating hepatic insulin sensitivity in mice [29], and plays a lipogenic role in the mouse and hamster liver [86]. A particular feature of GLP-2 concerns its ability to regulate lipid handling in the intestine: studies in humans and rodents showed that exogenous GLP-2 not only enhances dietary fat absorption during the postprandial state but also releases intestinally stored lipids during the post-absorptive state through both local and central mechanisms (see [28]). In both these effects of GLP-2, VIP and nitric oxide (NO) have been suggested to be involved [87,88] and, more specifically, an up-regulation of neuronal NOS (nNOS) expression has been observed [89]. Among the multiple GLP-2R signaling pathways [28,35] NO and VIP have been reported to be recruited in many actions of the hormone in the gastrointestinal tract. In this view, GLP-2 has also been reported to increase intestinal blood flow in both healthy humans [90,91] and in patients with SBS [92] by involving NO and VIP. The observation that the hormone-induced enhancement of intestinal blood flow was attenuated in rodents [93] and humans [91] by co-infusion with nitric oxide synthase (NOS) inhibitors proved that this effect was, at least in part, NO-dependent and agrees with the presence of GLP-2R on enteric neurons expressing endothelial NOS [75]. On the other hand, it has been shown that such neurons also express VIP [75] which, as NO, is known for regulating mucosal blood flow. Both these vasoactive neurotransmitters are reported to be important mediators in the increase in blood flow by GLP-2 (see [28]). Furthermore, it has been hypothesized that the increased mesenteric blood flow, following enhanced NO production, might contribute to the increased chylomicron secretion by GLP-2 even if the exact mechanisms through which GLP-2 modulates intestinal lipid handling are still not fully elucidated [28].

4.2. GLP-2 and Anti-Inflammatory Activity

GLP-2 signaling has also been reported to promote anti-inflammatory functions through the activation of the GLP-2R in human islets [94]. The hormone injection decreased mucosal inflammatory cytokine production in an animal model of enterocolitis [95] while hepatic anti-inflammatory action of GLP-2 was shown in multidrug resistance 2 knockout mice [96] and in obese mice [97]. In the latter, chronic administration reduced inflammation also in the brain [98]. In this view, endogenous GLP-2 has been suggested to exert beneficial effects against some metabolic disorders in both humans and animals [28,72,86,99,100]. The anti-inflammatory effects occurred, at least in part, via VIP release from enteric neurons in a rat animal model of inflammatory bowel disease [101–103]. Moreover, GLP-2 was reported to increase the proportion of neurons expressing VIP in cells derived from primary cultures of submucosal enteric neurons [104] similar to what was reported in the colon submucosal plexus of a rat model of colitis [102].

In addition to VIP, some of the GLP-2 protective effects have been reported to be mediated by NO. Of note, other than in promoting intestinal growth [105], the NO pathway appears to be involved in the effects of the hormone in preventing cisplatin-induced damage in the gastrointestinal tract of mice: the GLP-2 analog ([Gly(2)]GLP-2) was reported to counteract the morphological and functional damages induced by cisplatin treatment and protect nNOS neurons in mice gastric fundus [106] and distal colon [107]. GLP-2 also attenuates chemotherapy-induced mucositis, reduces epithelial permeability, improves intestinal barrier function, and decreases meal-stimulated gastric acid secretion as well as gastrointestinal motility [108], making the hormone a suitable agent for the treatment not only of SBS but also inflammatory bowel diseases and chemotherapy-induced mucositis [28].

4.3. GLP-2 and the Microbiota

Among its different functions, intestinal microbiota has been reported to play a role in the regulation of food intake since some of its metabolites can increase enteroendocrine L cell anorexigenic hormone secretion [27,40]. Alterations in gut microbiota composition have been shown to promote significant changes in satiety signals, acting both locally and via the gut-microbiota–brain axis, likely promoting hyperphagia and thus obesity [40].

Therefore, targeting the gut microbiota might represent a strategy to counteract overweight, in addition to other highlighted beneficial effects, such as improving the activity and efficacy of anticancer drugs [109]. In this view, the protective effects of some bacteria have been reported towards cisplatin in mice experimental models [110]. It has been recently observed that a diet enriched in prebiotics also prevented cisplatin-induced changes in mucus secretion in mice, likely protecting the microbiota [111].

Interestingly, gut dysbiosis may also alter gut barrier function, the so-called ‘leaky gut’, which by translocation of pathogens into circulation may represent a contributing cause of obesity-associated systemic inflammation [16,112]. It has recently been reported that chronic enteropathy-related dysbiosis in dogs may contribute to reduced plasma GLP-2 concentrations, suggesting that the association between GLP-2 secretion and microbiome indices may direct future research on the treatment of enteropathies [113]. Thus, the protection of the intestinal barrier integrity exerted by GLP-2 and by substances that counteract dysbiosis could represent an interesting strategy to attenuate inflammation in obesity and its associated comorbidities.

The major functions of GLP-2 on the gastrointestinal tract in both humans and animals are summarized in Table 1, which also includes the effects of the hormone on gastrointestinal motor responses discussed in the following paragraphs.

Table 1. Effects of GLP-2 signaling on the gastrointestinal tract.

Effects of GLP-2 Signaling	Route of Administration	Species	References
Increased small intestinal weight and jejunal crypt-villus height	Subcutaneous	Mouse	[77]
Increased villus height and crypt depth	Subcutaneous	Human	[78]
Increased jejunal amino acid absorption	Isolated preparations	Mouse	[83]
Increased glucose uptake	Intravenous	Piglet	[84]
Increased expression of glucose transporters	Peripheral administration	Mouse	[85]
Increased fatty acids absorption	Intraperitoneal	Mouse and hamster	[82]
Increased plasma levels of free fatty acids and triglyceride	Intravenous	Human	[80]
Increased plasma levels of chylomicron and triglyceride	Subcutaneous	Human	[91]
Mobilization of intestinally stored lipids	Intraduodenal	Mouse and hamster	[87]
Mobilization of intestinally stored lipids	Intraperitoneal	Rat	[114]
Decreased mucosal inflammatory cytokine production	Subcutaneous	Rat	[95]
Reduction in pro-inflammatory cytokines and crypt cell apoptosis	Subcutaneous	Rat	[101]
Increased intestinal blood flow	Intravenous	Human	[90]
Increased intestinal blood flow	Subcutaneous	Human	[91]
Increased intestinal blood flow	Subcutaneous	Human	[92]
Increased intestinal blood flow	Intravenous	Piglet	[84]
Increased intestinal blood flow	Jugular vein	Rat	[93]
Prevention of cisplatin-induced morphological changes in the gastric fundal strips	Intraperitoneal	Mouse	[106]
Prevention of cisplatin-induced morphological changes in isolated distal colon	Intraperitoneal	Mice	[107]
Reduced antral motility	Intravenous	Pig	[115]
Gastric emptying inhibition	Intracerebroventricular	Mouse	[60]
Gastric emptying inhibition	Central	Human	[116]
Decreased gastric emptying rate	Peripheral	Mouse	[69]
Gastric smooth muscle relaxation	Isolated whole organ	Mouse	[117]
Gastric smooth muscle relaxation of fundal strips	<i>In vitro</i>	Mouse	[117]
Increased amplitude of the neurally induced relaxation of gastric fundal strips	<i>In vitro</i>	Mouse	[118,119]
Counteracted cisplatin-induced increase in the amplitude of contractions in the gastric fundal strips	Intraperitoneal	Mouse	[106]
Inhibition of duodenal contractions	Isolated whole preparation or segment	Mouse	[76]
Depression contractility of ileal segments	<i>In vitro</i>	Mouse	[120]
Inhibition of contractility in isolated colonic segments	<i>In vitro</i>	Mouse	[121]

5. Effects of GLP-2 in the Modulation of Gastrointestinal Motility as a Possible Source of Peripheral Satiety Signals Generated by the Stomach through the Gut–Brain Axis

Several centrally acting hormones can, through efferent innervation, lead to changes in the gastric motor functions known to be involved in the regulation of food intake, such as motility, tone, or emptying [21,122]. Gastric emptying rates can be slowed by the hypothalamus which, through the brainstem nuclei (such as the NTS and the dorsal motor nucleus of the vagus), stimulates vagal efferent fibers that activate intramural gastric nitrergic neurons to decrease gastric motility [18,123]. On the other hand, many hormones that act centrally to influence the hunger-satiety cycle have also been reported to modulate gastric functions and particularly motor responses, even in isolated preparations [19,124–126]. These motor responses, in turn, may generate peripheral signals that reach the central structures involved in the regulation of food intake. Therefore, the hunger-satiety cycle may be influenced by a hormone-driven bidirectional gut–brain axis.

Although many studies support both central and peripheral roles for GLP-2 in the regulation of gastric motility, contrasting results have been reported in humans and animals. In pigs and mice, reduced antral motility following intravenous infusion of GLP-2 [115] and suppressed gastric emptying by intracerebroventricular activation of GLP-2R signaling [60] were reported. These hormonal effects were coupled with loss of appetite and occurred, at least in part, through the activation of the MC4-R signaling pathway [60,66]. Interestingly, mice lacking GLP-2R in POMC neurons showed accelerated rates of gastric emptying besides hyperphagia, thus supporting a central role for GLP-2 in either slowing gastric emptying or satiety regulation [60]. Therefore, activation of central GLP-2R appears to play an important role in both the reduction in food intake and gastric emptying rate in rodents. A decreased gastric emptying rate in mice has been reported [69] following peripheral administration of the degradation-resistant analog of GLP-2, [Gly2]GLP2 [35]. The localization of GLP-2Rs on cell bodies of vagal afferents of the nodose ganglion in the rat [62] suggests that GLP-2 from the gut may signal to the hypothalamic nuclei involved in the regulation of food intake, not only directly by crossing the blood–brain barrier, but also through the activation of vagal afferent pathways.

Contrasting results on the ability of GLP-2 to affect gastric emptying have been reported in humans: while peripheral administration of GLP-2 resulted in no effect [67], GLP-2 infusions caused a dose-dependent increase in antral emptying time, although less powerfully than GLP-1 [116]. These discrepant results have been ascribable to the different methodological approaches [33] or to the rapid degradation of peripherally administered native GLP-2 [67–69] by the ubiquitous enzyme DPP-IV [127].

GLP-2 and Enteric Nervous System

An important role in the control of gastric motility is played by intrinsic motor neurons, which supply the smooth muscle and whose nervous fibers release a variety of either excitatory or inhibitory neurotransmitters [128,129]. Among them, acetylcholine is known to be one of the major excitatory neurotransmitters released from cholinergic fibers, whereas NO and VIP are considered the main inhibitory neurotransmitters released by non-adrenergic, non-cholinergic (NANC) fibers supplying the smooth muscle and causing gastric relaxation [130,131]. Gastric smooth muscle motor responses are indeed the result of a balance between excitatory and inhibitory nervous activity that may be modulated by hormonal influences.

The first experimental evidence that GLP-2 can induce gastric relaxation *in vitro* acting on the mouse stomach was provided by Amato and collaborators [117]. Particularly, by recording intraluminal pressure from isolated preparations, they observed that GLP-2 decreased fundus tone, an effect that could actually be regarded as an additional peripheral mechanism contributing to the central anorexigenic actions of the hormone reported in rodents [57]. Notably, inhibition of fundus tone increases murine gastric capacity which may underline the short-term inhibition of food intake by GLP-2 [132]. Furthermore, the decrease in the proximal gastric tone caused by GLP-2 could also delay the flow through

the pylorus, thus prolonging the gastric emptying time, as suggested by Amato and collaborators [117].

The peripheral effects of GLP-2, through which it modulates rodent gastric fundus motility, are likely due to a neuromodulatory action of GLP-2 on the enteric nervous system. In agreement, GLP-2R protein and mRNA expression was described, other than in enteroendocrine, subepithelial cells and myofibroblasts, in myenteric neurons of humans, rodents, and pigs [75,133,134]. In human preparations, GLP-2R immunoreactivity was detected in the cell bodies of the myenteric neuron but not in the nerve fibers supplying circular and longitudinal muscle layers [134]. In rodents, GLP-2 has been reported to cause gastric fundus relaxation by increasing the release of the two major NANC inhibitory neurotransmitters, VIP and NO. A prejunctional neuronal release of VIP by GLP-2 has been reported to occur in either isolated whole stomachs or gastric circular muscle strips, as proved by the reduced relaxant effects of the hormone following VIP receptor desensitization in mice [117]. Subsequent experiments carried out in the longitudinal strips from mouse gastric fundus showed that the hormone exerted a neuromodulatory action by influencing the component of the neurally induced relaxant responses [119] ascribable to VIP release [131,135].

In addition to VIP, GLP-2 has been reported to facilitate smooth muscle relaxation through NO as many other hormones do [118,136–139]. In fact, the hormone involvement in the circuits that regulate gastric emptying through myenteric inhibitory neurons that release NO has been demonstrated in humans and animals [122,140]. Moreover, in animals, the ability of NO to control the gastric pyloric sphincter, where nitrergic nerves are very numerous [141], has been reported [142], thus supporting its role also in regulating the transit of chyme from the stomach into the duodenum. GLP-2 was found to depress the amplitude of the contractile responses in longitudinal strips from the mouse gastric fundus and to enhance the amplitude of that component of the neurally induced relaxant response [118] ascribable to NO release from NANC inhibitory neurons [143]. Thus, GLP-2 induces proximal stomach relaxation also by modulating the nitrergic neurotransmission, likely through the up-regulation of NO production [143]. Immunohistochemical experiments revealed an increased nNOS immunoreactivity in the nerve structures after GLP-2 exposure of gastric specimens [118]; co-localization of GLP-2Rs with the two constitutive NOS isoforms (eNOS and nNOS) in myenteric and submucosal neurons of the stomach [75]; and colocalization of GLP-2 with NOS or VIP in the myenteric plexus of different mammalian species [144], including human gastric fundus [145].

The above-reported effects of GLP-2 in the stomach may agree with its involvement in the generation of peripheral satiety signals involved in the short-term regulation of food intake. The decrease in the gastric fundal tone by GLP-2, which causes an increased stomach capacity, and the slow gastric emptying rate may be regarded as peripheral mechanisms addressed to suppress food intake. Furthermore, the same decrease in proximal gastric tone caused by GLP-2 would also prolong gastric emptying time.

However, the possible relationship between peripheral effects of GLP-2 on gut motility and the regulation of food intake is not limited to the ability of the hormone to influence motor responses of the stomach since GLP-2 has been proven to exert inhibitory effects on the motility of the small intestine too.

In this view, GLP-2 has been reported to induce changes in intestinal motor responses acting either centrally or peripherally, through a dual mechanism involving the inhibition of the excitatory component and/or an enhancement of the inhibitory one. GLP-2 administration *in vivo* has been shown to inhibit intestinal transit in mice [146], likely by exerting a neuromodulatory role to increase inhibitory inputs on excitatory enteric neurons. This mechanism fits well with the detection of GLP-2R expression on either excitatory or inhibitory myenteric and submucosal neurons of the mouse duodenum, in which the hormone depressed contractile responses by decreasing the cholinergic neurotransmission and by increasing NO production in isolated preparations [76].

More recently, it has been demonstrated that GLP-2 also depresses ileal contractility in isolated preparations from mice [120], thereby filling a gap in the literature on the effects of the hormone in this isolated intestinal segment where its production occurs and in which GLP-2Rs are also highly expressed [147]. The depressant effects of GLP-2 on ileal contractility likely occur through a dual opposite modulatory effect on inhibitory nitrenergic and excitatory cholinergic neurotransmission, as supported by immunohistochemical results showing a significant increase in nNOS-positive fibers in the ileal muscle wall and a significant decrease in ChAT-positive myenteric neurons in GLP-2-exposed preparations [120].

A simplified scheme summarizing the neuromodulatory action of GLP-2 on enteric neurons is reported in Figure 4.

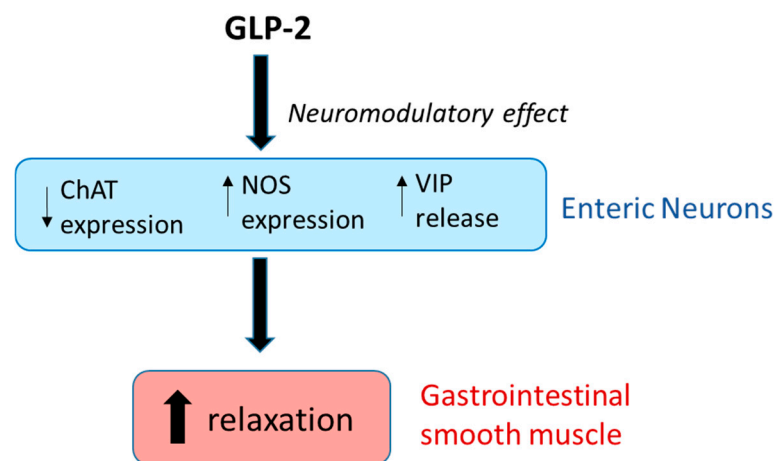


Figure 4. Schematic illustration summarizing the main modulatory actions of GLP-2 on the enteric neurotransmission. GLP-2 decreases the number of choline acetyl transferase (ChAT)-positive myenteric neurons, reducing the excitatory cholinergic input to the smooth muscle. The indirect pro-relaxant effects of GLP-2 are also exerted through a modulatory action on NANC inhibitory neurotransmission. GLP-2 modulates the nitrenergic neurotransmission by up-regulating nitric oxide synthase (NOS) expression, thereby increasing NO production/release. GLP-2 also enhances VIP release from myenteric neurons.

The general physiological significance of the depressant effects of the hormone on intestinal motility could be directed at prolonging the transit time and thus promoting nutrient absorption processes. The same is true for the depressant action of GLP-2 on ileal contractility that extends the permanence of the contents in the more proximal intestinal portions. This function agrees with the reported role of the hormone in the small intestine [34] and the successful introduction of a GLP-2 analog in the treatment of patients affected by SBS [54]. However, GLP-2 favoring nutrient absorption would even appear in contrast with its anorexigenic effects, which should have an impact on body weight loss. On the other hand, the inhibitory effects of GLP-2 on intestinal contractility by increasing the contact time of nutrients with enteroendocrine cells may increase anorexigenic hormone release, as occurs in the ileal brake reflex [148,149], also generating a positive feedback loop on its own release. Moreover, as reported in the introduction section, the activation of the ileal brake reflex leads to delayed gastric emptying. Therefore, even if many aspects still need to be clarified, the inhibitory effects exerted by GLP-2 on small intestine contractility could indeed represent an additional peripheral satiety signal in rodents. The effects of GLP-2 on gastrointestinal motor responses, some of which may agree with its role in the generation of peripheral satiety signals, are reported in Table 1.

6. Concluding Remarks

The increasing incidence of obesity has led to a growing interest in the gastrointestinal tract as a potential target for both pharmacological and nutritional approaches to weight management [150]. In this context, the role of gut-derived hormones in the gut–brain axis is a topical issue in the regulation of food intake.

While the role of some gut-derived hormones to inhibit food intake not only centrally but also peripherally by inducing changes in the gastrointestinal motor responses has been recognized in humans, this relation for GLP-2 has not been fully elucidated yet. Nevertheless, among its several effects, GLP-2 has been reported to exert central anorexigenic actions in animal preclinical studies and to affect those gastrointestinal motor responses whose changes are strictly related to the generation of peripheral satiety signals through the gut–brain axis. These peripheral effects may represent an additional mechanism engaged by the hormone, contributing to its central actions, in the short-term regulation of food intake in rodents. Therefore, a better understanding of this mechanism could point towards a possible use of GLP-2 analogs as an additional strategy for the management of body weight gain. In this view, GLP-2R has been recently proposed as a target for the treatment of obesity [16]. Moreover, it has been hypothesized that an altered intestinal microbiota, which is primarily affected by diet composition, may contribute to the onset of obesity through the gut-microbiota–brain axis [151]. Intestinal microbiota metabolites have been reported to have a role in inducing the release of GLP-2 as well as other anorexigenic hormones by intestinal enteroendocrine cells [27,40]. Although microbiome manipulation for the treatment of obesity needs to be further explored in humans, diet, prebiotics, probiotics, and symbiotics may have a beneficial impact on several metabolic pathway disorders involved in the onset of obesity [152].

Among the new proposed therapeutic approaches, stimulation of the endogenous secretion of glucagon-like peptides from enteroendocrine L-cells has been suggested [27] given the successful introduction of GLP-1-based drugs in the treatment of obesity. From this perspective, a possible future scenario in the approach to the treatment of obesity could be to exploit the different systems present in enteroendocrine cells that are affected by substances that modify the release of hormones. A better understanding of the mechanisms by which GLP-2 may influence food intake may therefore be important for its therapeutic implications beyond its clinical use for the treatment of SBS. However, limitations in its therapeutic applications should be considered, mainly due to its short half-life and possible side effects also related to the pharmacological activation of the GLP-2R [16].

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Abbreviations

AgRP	Agouti-related protein
CART	cocaine- and amphetamine-regulated transcript
CCK	cholecystokinin
ChAT	choline acetyl transferase
CNS	central nervous system

GLP-1	glucagon-like peptide-1
GLP-2	glucagon-like peptide-2
GLP-2R	glucagon-like peptide-2 receptor
NANC	non-adrenergic, non-cholinergic
NO	nitric oxide
nNOS	neuronal nitric oxide synthase
NPY	neuropeptide Y
NTS	nucleus tractus solitarius
POMC	pro-opiomelanocortin
PYY	peptide tyrosine tyrosine
SBS	short bowel syndrome
VIP	vasoactive intestinal peptide

References

1. Abdalla, M.M. Central and peripheral control of food intake. *Endocr. Regul.* **2017**, *51*, 52–70. [[CrossRef](#)] [[PubMed](#)]
2. Jais, A.; Brüning, J.C. Arcuate Nucleus-Dependent Regulation of Metabolism-Pathways to Obesity and Diabetes Mellitus. *Endocr. Rev.* **2022**, *43*, 314–328. [[CrossRef](#)] [[PubMed](#)]
3. Yang, D.; Hou, X.; Yang, G.; Li, M.; Zhang, J.; Han, M.; Zhang, Y.; Liu, Y. Effects of the POMC System on Glucose Homeostasis and Potential Therapeutic Targets for Obesity and Diabetes. *Diabetes Metab. Syndr. Obes.* **2022**, *15*, 2939–2950. [[CrossRef](#)]
4. Vohra, M.S.; Benchoula, K.; Serpell, C.J.; Hwa, W.E. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. *Eur. J. Pharmacol.* **2022**, *915*, 174611. [[CrossRef](#)] [[PubMed](#)]
5. Duca, F.A.; Covasa, M. Current and emerging concepts on the role of peripheral signals in the control of food intake and development of obesity. *Br. J. Nutr.* **2012**, *108*, 778–793. [[CrossRef](#)] [[PubMed](#)]
6. Klockars, A.; Levine, A.S.; Olszewski, P.K. Hypothalamic Integration of the Endocrine Signaling Related to Food Intake. *Curr. Top. Behav. Neurosci.* **2019**, *43*, 239–269.
7. Hong, S.H.; Choi, K.M. Gut hormones and appetite regulation. *Curr. Opin. Endocrinol. Diabetes Obes.* **2024**, *31*, 115–121. [[CrossRef](#)]
8. Cifuentes, L.; Acosta, A. Homeostatic regulation of food intake. *Clin. Res. Hepatol. Gastroenterol.* **2022**, *46*, 101794. [[CrossRef](#)]
9. Tack, J.; Verbeure, W.; Mori, H.; Schol, J.; Van den Houste, K.; Huang, I.H.; Balsiger, L.; Broeders, B.; Colomier, E.; Scarpellini, E.; et al. The gastrointestinal tract in hunger and satiety signalling. *United Eur. Gastroenterol. J.* **2021**, *9*, 727–734. [[CrossRef](#)]
10. Browning, K.N.; Carson, K.E. Central Neurocircuits Regulating Food Intake in Response to Gut Inputs-Preclinical Evidence. *Nutrients* **2021**, *13*, 908. [[CrossRef](#)]
11. Stengel, A.; Taché, Y. Interaction between gastric and upper small intestinal hormones in the regulation of hunger and satiety: Ghrelin and cholecystokinin take the central stage. *Curr. Protein Pept. Sci.* **2011**, *12*, 293–304. [[CrossRef](#)] [[PubMed](#)]
12. Cummings, D.E.; Overduin, J. Gastrointestinal regulation of food intake. *J. Clin. Investig.* **2007**, *117*, 13–23. [[CrossRef](#)] [[PubMed](#)]
13. Roh, E.; Choi, K.M. Hormonal Gut-Brain Signaling for the Treatment of Obesity. *Int. J. Mol. Sci.* **2023**, *24*, 3384. [[CrossRef](#)] [[PubMed](#)]
14. Li, S.; Liu, M.; Cao, S.; Liu, B.; Li, D.; Wang, Z.; Sun, H.; Cui, Y.; Shi, Y. The Mechanism of the Gut-Brain Axis in Regulating Food Intake. *Nutrients* **2023**, *15*, 3728. [[CrossRef](#)] [[PubMed](#)]
15. Hillebrand, J.J.; de Wied, D.; Adan, R.A. Neuropeptides, food intake and body weight regulation: A hypothalamic focus. *Peptides* **2002**, *23*, 2283–2306. [[CrossRef](#)]
16. Pálsson, T.G.; Gilliam-Vigh, H.; Jensen, B.A.H.; Jeppesen, P.B.; Lund, A.B.; Knop, F.K.; Nielsen, C.K. Targeting the GLP-2 receptor in the management of obesity. *Peptides* **2024**, *177*, 171210. [[CrossRef](#)]
17. Hajishafiee, M.; Bitarafan, V.; Feinle-Bisset, C. Gastrointestinal Sensing of Meal-Related Signals in Humans, and Dysregulations in Eating-Related Disorders. *Nutrients* **2019**, *11*, 1298. [[CrossRef](#)]
18. Camilleri, M. Peripheral mechanisms in appetite regulation. *Gastroenterology* **2015**, *148*, 1219–1233. [[CrossRef](#)] [[PubMed](#)]
19. Steinert, R.E.; Feinle-Bisset, C.; Asarian, L.; Horowitz, M.; Beglinger, C.; Geary, N. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. *Physiol. Rev.* **2017**, *97*, 411–463, Erratum in *Physiol. Rev.* **2017**, *97*, 1229. [[CrossRef](#)]
20. Blanco, A.M.; Calo, J.; Soengas, J.L. The gut-brain axis in vertebrates: Implications for food intake regulation. *J. Exp. Biol.* **2021**, *224*, 231571. [[CrossRef](#)]
21. Janssen, P.; Vanden Berghe, P.; Verschueren, S.; Lehmann, A.; Depoortere, I.; Tack, J. Review article: The role of gastric motility in the control of food intake. *Aliment. Pharmacol. Ther.* **2011**, *33*, 880–894. [[CrossRef](#)] [[PubMed](#)]
22. Phillips, R.J.; Powley, T.L. Tension and stretch receptors in gastrointestinal smooth muscle: Re-evaluating vagal mechanoreceptor electrophysiology. *Brain Res. Brain Res. Rev.* **2000**, *34*, 1–26. [[CrossRef](#)] [[PubMed](#)]
23. Halawi, H.; Camilleri, M.; Acosta, A.; Vazquez-Roque, M.; Oduyebo, I.; Burton, D.; Busciglio, I.; Zinsmeister, A.R. Relationship of gastric emptying or accommodation with satiation, satiety, and postprandial symptoms in health. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2017**, *313*, G442–G447. [[CrossRef](#)] [[PubMed](#)]
24. Cifuentes, L.; Camilleri, M.; Acosta, A. Gastric Sensory and Motor Functions and Energy Intake in Health and Obesity-Therapeutic Implications. *Nutrients* **2021**, *13*, 1158. [[CrossRef](#)]

25. Gonzalez-Izundegui, D.; Campos, A.; Calderon, G.; Ricardo-Silgado, M.L.; Cifuentes, L.; Decker, P.A.; Vargas, E.J.; Tran, L.; Burton, D.; Abu Dayyeh, B.; et al. Association of gastric emptying with postprandial appetite and satiety sensations in obesity. *Obesity* **2021**, *29*, 1497–1507. [[CrossRef](#)] [[PubMed](#)]
26. Spreckley, E.; Murphy, K.G. The L-Cell in Nutritional Sensing and the Regulation of Appetite. *Front. Nutr.* **2015**, *2*, 23. [[CrossRef](#)]
27. Brubaker, P.L. The Molecular Determinants of Glucagon-like Peptide Secretion by the Intestinal L cell. *Endocrinology* **2022**, *163*, 159. [[CrossRef](#)]
28. Mukherjee, K.; Xiao, C. GLP-2 regulation of intestinal lipid handling. *Front. Physiol.* **2024**, *15*, 1358625. [[CrossRef](#)]
29. Shi, X.; Zhou, F.; Li, X.; Chang, B.; Li, D.; Wang, Y.; Tong, Q.; Xu, Y.; Fukuda, M.; Zhao, J.J.; et al. Central GLP-2 enhances hepatic insulin sensitivity via activating PI3K signaling in POMC neurons. *Cell Metab.* **2013**, *18*, 86–98. [[CrossRef](#)]
30. Müller, T.D.; Finan, B.; Bloom, S.R.; D'Alessio, D.; Drucker, D.J.; Flatt, P.R.; Fritsche, A.; Gribble, F.; Grill, H.J.; Habener, J.F.; et al. Glucagon-like peptide 1 (GLP-1). *Mol. Metab.* **2019**, *30*, 72–130.
31. Muller, T.D.; Finan, B.; Clemmensen, C.; DiMarchi, R.D.; Tschop, M.H. The New Biology and Pharmacology of Glucagon. *Physiol. Rev.* **2017**, *9*, 721–766. [[CrossRef](#)] [[PubMed](#)]
32. Zeigerer, A.; Sekar, R.; Kleinert, M.; Nason, S.; Habegger, K.M.; Muller, T.D. Glucagon's Metabolic Action in Health and Disease. *Compr. Physiol.* **2021**, *11*, 1759–1783. [[PubMed](#)]
33. Janssen, P.; Rotondo, A.; Mulé, F.; Tack, J. Review article: A comparison of glucagon-like peptides 1 and 2. *Aliment. Pharmacol. Ther.* **2013**, *37*, 18–36. [[CrossRef](#)]
34. Drucker, D.J.; Yusta, B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu. Rev. Physiol.* **2014**, *76*, 561–583. [[CrossRef](#)] [[PubMed](#)]
35. Rowland, K.J.; Brubaker, P.L. The “cryptic” mechanism of action of glucagon-like peptide-2. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2011**, *301*, G1–G8. [[CrossRef](#)]
36. Kuhre, R.E.; Deacon, C.F.; Holst, J.J.; Petersen, N. What Is an L-Cell and How Do We Study the Secretory Mechanisms of the L-Cell? *Front. Endocrinol.* **2021**, *12*, 694284. [[CrossRef](#)]
37. Steinert, R.E.; Frey, F.; Topfer, A.; Drewe, J.; Beglinger, C. Effects of Carbohydrate Sugars and Artificial Sweeteners on Appetite and the Secretion of Gastrointestinal Satiety Peptides. *Br. J. Nutr.* **2011**, *105*, 1320–1328. [[CrossRef](#)]
38. Roberge, J.N.; Brubaker, P.L. Secretion of proglucagon-derived peptides in response to intestinal luminal nutrients. *Endocrinology* **1991**, *128*, 3169–3174. [[CrossRef](#)]
39. Brubaker, P.L.; Anini, Y. Direct and indirect mechanisms regulating secretion of glucagon-like peptide-1 and glucagon-like peptide-2. *Can. J. Physiol. Pharmacol.* **2003**, *81*, 1005–1012. [[CrossRef](#)]
40. Hamamah, S.; Amin, A.; Al-Kassir, A.L.; Chuang, J.; Covasa, M. Dietary Fat Modulation of Gut Microbiota and Impact on Regulatory Pathways Controlling Food Intake. *Nutrients* **2023**, *15*, 3365. [[CrossRef](#)]
41. Nishimura, K.; Hiramatsu, K.; Monir, M.M.; Takemoto, C.; Watanabe, T. Ultrastructural study on colocalization of glucagon-like peptide (GLP)-1 with GLP-2 in chicken intestinal L-cells. *J. Vet. Med. Sci.* **2013**, *75*, 1335–1339. [[CrossRef](#)] [[PubMed](#)]
42. Abdalqadir, N.; Adeli, K. GLP-1 and GLP-2 Orchestrate Intestine Integrity, Gut Microbiota, and Immune System Crosstalk. *Microorganisms* **2022**, *10*, 2061. [[CrossRef](#)] [[PubMed](#)]
43. Rocca, A.S.; Brubaker, P.L. Role of the vagus nerve in mediating proximal nutrient-induced glucagon-like peptide-1 secretion. *Endocrinology* **1999**, *140*, 1687–1694. [[CrossRef](#)]
44. Xiao, Q.; Boushey, R.P.; Drucker, D.J.; Brubaker, P.L. Secretion of the intestinotropic hormone glucagon-like peptide 2 is differentially regulated by nutrients in humans. *Gastroenterology* **1999**, *117*, 99–105. [[CrossRef](#)]
45. Moller, D.E. New drug targets for type 2 diabetes and the metabolic syndrome. *Nature* **2001**, *414*, 821–827. [[CrossRef](#)]
46. Brubaker, P.L. Glucagon-like Peptide-2 and the Regulation of Intestinal Growth and Function. *Compr. Physiol.* **2018**, *8*, 1185–1210.
47. Drucker, D.J.; Shi, Q.; Crivici, A.; Sumner-Smith, M.; Tavares, W.; Hill, M.; DeForest, L.; Cooper, S.; Brubaker, P.L. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. *Nat. Biotechnol.* **1997**, *15*, 673–677. [[CrossRef](#)] [[PubMed](#)]
48. Hartmann, B.; Harr, M.B.; Jeppesen, P.B.; Wojdemann, M.; Deacon, C.F.; Mortensen, P.B.; Holst, J.J. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 2884–2888. [[CrossRef](#)] [[PubMed](#)]
49. Tan, Q.; Akindehin, S.E.; Orsso, C.E.; Waldner, R.C.; DiMarchi, R.D.; Müller, T.D.; Haqq, A.M. Recent Advances in Incretin-Based Pharmacotherapies for the Treatment of Obesity and Diabetes. *Front. Endocrinol.* **2022**, *13*, 838410. [[CrossRef](#)]
50. Deacon, C.F. Physiology and Pharmacology of DPP-4 in Glucose Homeostasis and the Treatment of Type 2 Diabetes. *Front. Endocrinol.* **2019**, *10*, 80, Erratum in *Front. Endocrinol.* **2019**, *10*, 275.
51. Lafferty, R.A.; O'Harte, F.P.M.; Irwin, N.; Gault, V.A.; Flatt, P.R. Proglucagon-Derived Peptides as Therapeutics. *Front. Endocrinol.* **2021**, *12*, 689678. [[CrossRef](#)]
52. Austin, K.; Markovic, M.A.; Brubaker, P.L. Current and potential therapeutic targets of glucagon-like peptide-2. *Curr. Opin. Pharmacol.* **2016**, *31*, 13–18. [[CrossRef](#)]
53. Pizzoferrato, M.; Puca, P.; Ennas, S.; Cammarota, G.; Guidi, L. Glucagon-like peptide-2 analogues for Crohn's disease patients with short bowel syndrome and intestinal failure. *World J. Gastroenterol.* **2022**, *28*, 6258–6270. [[CrossRef](#)]
54. Sabra, H.K.; Remeih, G.S.; Kereet, I.M.; Hamad, M.; Ahmed, Y.A.; Jahangir, K.; Bakr, M.A.; Alagelli, F.A.; Sherif, H.; Elsaid, M. Efficacy and safety of glucagon-like peptide 2 in patients with short bowel syndrome: A systematic review and network meta-analysis. *J. Gastrointest. Surg.* **2024**, *28*, 1194–1205. [[CrossRef](#)]

55. Vrang, N.; Hansen, M.; Larsen, P.J.; Tang-Christensen, M. Characterization of brainstem preproglucagon projections to the paraventricular and dorsomedial hypothalamic nuclei. *Brain Res.* **2007**, *1149*, 118–126. [[CrossRef](#)]
56. Tang-Christensen, M.; Larsen, P.J.; Thulesen, J.; Rømer, J.; Vrang, N. The proglucagon-derived peptide, glucagon-like peptide-2, is a neurotransmitter involved in the regulation of food intake. *Nat. Med.* **2000**, *6*, 802–807. [[CrossRef](#)]
57. Guan, X. The CNS glucagon-like peptide-2 receptor in the control of energy balance and glucose homeostasis. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2014**, *307*, R585–R596. [[CrossRef](#)]
58. Lovshin, J.; Estall, J.; Yusta, B.; Brown, T.J.; Drucker, D.J. Glucagon-like peptide (GLP)-2 action in the murine central nervous system is enhanced by elimination of GLP-1 receptor signaling. *J. Biol. Chem.* **2001**, *276*, 21489–21499. [[CrossRef](#)]
59. Estall, J.L.; Drucker, D.J. Glucagon-like Peptide-2. *Annu. Rev. Nutr.* **2006**, *26*, 391–411. [[CrossRef](#)]
60. Guan, X.; Shi, X.; Li, X.; Chang, B.; Wang, Y.; Li, D.; Chan, L. GLP-2 receptor in POMC neurons suppresses feeding behavior and gastric motility. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *303*, E853–E864. [[CrossRef](#)]
61. Yusta, B.; Huang, L.; Munroe, D.; Wolff, G.; Fantaste, R.; Sharma, S.; Demchyshyn, L.; Asa, S.L.; Drucker, D.J. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. *Gastroenterology* **2000**, *119*, 744–755. [[CrossRef](#)]
62. Nelson, D.W.; Sharp, J.W.; Brownfield, M.S.; Raybould, H.E.; Ney, D.M. Localization and activation of glucagon-like peptide-2 receptors on vagal afferents in the rat. *Endocrinology* **2007**, *148*, 1954–1962. [[CrossRef](#)] [[PubMed](#)]
63. Dalvi, P.S.; Belsham, D.D. Glucagon-like peptide-2 directly regulates hypothalamic neurons expressing neuropeptides linked to appetite control in vivo and in vitro. *Endocrinology* **2012**, *153*, 2385–2397. [[CrossRef](#)] [[PubMed](#)]
64. Sun, H.; Meng, K.; Hou, L.; Shang, L.; Yan, J. Melanocortin receptor-4 mediates the anorectic effect induced by the nucleus tractus solitarius injection of glucagon-like Peptide-2 in fasted rats. *Eur. J. Pharmacol.* **2021**, *901*, 174072. [[CrossRef](#)] [[PubMed](#)]
65. Tang-Christensen, M.; Vrang, N.; Larsen, P.J. Glucagon-like peptide containing pathways in the regulation of feeding behaviour. *Int. J. Obes. Relat. Metab. Disord.* **2001**, *25*, S42–S47. [[CrossRef](#)]
66. Sun, H.; Meng, K.; Hou, L.; Shang, L.; Yan, J. GLP-2 decreases food intake in the dorsomedial hypothalamic nucleus (DMH) through Exendin (9–39) in male Sprague-Dawley (SD) rats. *Physiol. Behav.* **2021**, *229*, 113253. [[CrossRef](#)]
67. Schmidt, P.T.; Näslund, E.; Grybäck, P.; Jacobsson, H.; Hartmann, B.; Holst, J.J.; Hellström, P.M. Peripheral administration of GLP-2 to humans has no effect on gastric emptying or satiety. *Regul. Pept.* **2003**, *116*, 21–25. [[CrossRef](#)]
68. Sørensen, L.B.; Flint, A.; Raben, A.; Hartmann, B.; Holst, J.J.; Astrup, A. No effect of physiological concentrations of glucagon-like peptide-2 on appetite and energy intake in normal weight subjects. *Int. J. Obes. Relat. Metab. Disord.* **2003**, *27*, 450–456. [[CrossRef](#)]
69. Baldassano, S.; Bellanca, A.L.; Serio, R.; Mulè, F. Food intake in lean and obese mice after peripheral administration of glucagon-like peptide 2. *J. Endocrinol.* **2012**, *213*, 277–284. [[CrossRef](#)]
70. Scott, R.B.; Kirk, D.; MacNaughton, W.K.; Meddings, J.B. GLP-2 augments the adaptive response to massive intestinal resection in rat. *Am. J. Physiol.* **1998**, *275*, G911–G921.
71. Tsai, C.H.; Hill, M.; Asa, S.L.; Brubaker, P.L.; Drucker, D.J. Intestinal growth-promoting properties of glucagon-like peptide-2 in mice. *Am. J. Physiol.* **1997**, *273*, E77–E84. [[CrossRef](#)] [[PubMed](#)]
72. Baldassano, S.; Amato, A.; Mulè, F. Influence of glucagon-like peptide 2 on energy homeostasis. *Peptides* **2016**, *86*, 1–5. [[CrossRef](#)] [[PubMed](#)]
73. Gutzwiller, J.P.; Göke, B.; Drewe, J.; Hildebrand, P.; Ketterer, S.; Handschin, D.; Winterhalder, R.; Conen, D.; Beglinger, C. Glucagon-like peptide-1: A potent regulator of food intake in humans. *Gut* **1999**, *44*, 81–86. [[CrossRef](#)]
74. Banasch, M.; Bulut, K.; Hagemann, D.; Schrader, H.; Holst, J.J.; Schmidt, W.E.; Meier, J.J. Glucagon-like peptide 2 inhibits ghrelin secretion in humans. *Regul. Pept.* **2006**, *137*, 173–178. [[CrossRef](#)] [[PubMed](#)]
75. Guan, X.; Karpen, H.E.; Stephens, J.; Bukowski, J.T.; Niu, S.; Zhang, G.; Stoll, B.; Finegold, M.J.; Holst, J.J.; Hadsell, D.; et al. GLP-2 receptor localizes to enteric neurons and endocrine cells expressing vasoactive peptides and mediates increased blood flow. *Gastroenterology* **2006**, *130*, 150–164, Erratum in *Gastroenterology* **2006**, *130*, 1019–1021. [[CrossRef](#)]
76. Cinci, L.; Faussonne-Pellegrini, M.S.; Rotondo, A.; Mulè, F.; Vannucchi, M.G. GLP-2 receptor expression in excitatory and inhibitory enteric neurons and its role in mouse duodenum contractility. *Neurogastroenterol. Motil.* **2011**, *23*, 383–392. [[CrossRef](#)]
77. Drucker, D.J.; Erlich, P.; Asa, S.L.; Brubaker, P.L. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 7911–7916. [[CrossRef](#)]
78. Jeppesen, P.B.; Hartmann, B.; Thulesen, J.; Graff, J.; Lohmann, J.; Hansen, B.S.; Tofteng, F.; Poulsen, S.S.; Madsen, J.L.; Holst, J.J.; et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology* **2001**, *120*, 806–815. [[CrossRef](#)]
79. Baldassano, S.; Amato, A.; Caldara, G.F.; Mulè, F. Glucagon-like peptide-2 treatment improves glucose dysmetabolism in mice fed a high-fat diet. *Endocrine* **2016**, *54*, 648–656. [[CrossRef](#)]
80. Meier, J.J.; Nauck, M.A.; Pott, A.; Heinze, K.; Goetze, O.; Bulut, K.; Schmidt, W.E.; Gallwitz, B.; Holst, J.J. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. *Gastroenterology* **2006**, *130*, 44–54. [[CrossRef](#)]
81. Thulesen, J. Glucagon-like peptide 2 (GLP-2), an intestinotrophic mediator. *Curr. Protein Pept. Sci.* **2004**, *5*, 51–65. [[PubMed](#)]
82. Hsieh, J.; Longuet, C.; Maida, A.; Bahrami, J.; Xu, E.; Baker, C.L.; Brubaker, P.L.; Drucker, D.J.; Adeli, K. Glucagon-like peptide-2 increases intestinal lipid absorption and chylomicron production via CD36. *Gastroenterology* **2009**, *137*, 997–1005. [[CrossRef](#)] [[PubMed](#)]

83. Lee, J.; Koehler, J.; Yusta, B.; Bahrami, J.; Matthews, D.; Rafii, M.; Pencharz, P.B.; Drucker, D.J. Enteroendocrine-derived glucagon-like peptide-2 controls intestinal amino acid transport. *Mol. Metab.* **2017**, *6*, 245–255. [[CrossRef](#)] [[PubMed](#)]
84. Guan, X.; Stoll, B.; Lu, X.; Tappenden, K.A.; Holst, J.J.; Hartmann, B.; Burrin, D.G. GLP-2-mediated up-regulation of intestinal blood flow and glucose uptake is nitric oxide-dependent in TPN-fed piglets 1. *Gastroenterology* **2003**, *125*, 136–147. [[CrossRef](#)]
85. Moran, A.W.; Al-Rammahi, M.A.; Batchelor, D.J.; Bravo, D.M.; Shirazi-Beechey, S.P. Glucagon-Like Peptide-2 and the Enteric Nervous System Are Components of Cell-Cell Communication Pathway Regulating Intestinal Na⁺/Glucose Co-transport. *Front. Nutr.* **2018**, *5*, 101. [[CrossRef](#)]
86. Taher, J.; Baker, C.; Alvares, D.; Ijaz, L.; Hussain, M.; Adeli, K. GLP-2 Dysregulates Hepatic Lipoprotein Metabolism, Inducing Fatty Liver and VLDL Overproduction in Male Hamsters and Mice. *Endocrinology* **2018**, *159*, 3340–3350. [[CrossRef](#)]
87. Hsieh, J.; Trajcevski, K.E.; Farr, S.L.; Baker, C.L.; Lake, E.J.; Taher, J.; Iqbal, J.; Hussain, M.M.; Adeli, K. Glucagon-Like Peptide 2 (GLP-2) Stimulates Postprandial Chylomicron Production and Postabsorptive Release of Intestinal Triglyceride Storage Pools via Induction of Nitric Oxide Signaling in Male Hamsters and Mice. *Endocrinology* **2015**, *156*, 3538–3547. [[CrossRef](#)]
88. Shew, T.; Wolins, N.E.; Cifarelli, V. VEGFR-3 Signaling Regulates Triglyceride Retention and Absorption in the Intestine. *Front. Physiol.* **2018**, *9*, 1783. [[CrossRef](#)]
89. Grande, E.M.; Raka, F.; Hoffman, S.; Adeli, K. GLP-2 Regulation of Dietary Fat Absorption and Intestinal Chylomicron Production via Neuronal Nitric Oxide Synthase (nNOS) Signaling. *Diabetes* **2022**, *71*, 1388–1399. [[CrossRef](#)]
90. Bremholm, L.; Hornum, M.; Henriksen, B.M.; Larsen, S.; Holst, J.J. Glucagon-like peptide-2 increases mesenteric blood flow in humans. *Scand. J. Gastroenterol.* **2009**, *44*, 314–319. [[CrossRef](#)]
91. Xiao, C.; Stahel, P.; Morgantini, C.; Nahmias, A.; Dash, S.; Lewis, G.F. Glucagon-like peptide-2 mobilizes lipids from the intestine by a systemic nitric oxide-independent mechanism. *Diabetes Obes. Metab.* **2019**, *21*, 2535–2541. [[CrossRef](#)] [[PubMed](#)]
92. Bremholm, L.; Hornum, M.; Andersen, U.B.; Hartmann, B.; Holst, J.J.; Jeppesen, P.B. The effect of Glucagon-Like Peptide-2 on mesenteric blood flow and cardiac parameters in end-jejunosomy short bowel patients. *Regul. Pept.* **2011**, *168*, 32–38. [[CrossRef](#)] [[PubMed](#)]
93. Deniz, M.; Bozkurt, A.; Kurtel, H. Mediators of glucagon-like peptide 2-induced blood flow: Responses in different vascular sites. *Regul. Pept.* **2007**, *142*, 7–15. [[CrossRef](#)] [[PubMed](#)]
94. Qi, K.K.; Wu, J.; Deng, B.; Li, Y.M.; Xu, Z.W. PEGylated porcine glucagon-like peptide-2 improved the intestinal digestive function and prevented inflammation of weaning piglets challenged with LPS. *Animal* **2015**, *9*, 1481–1489. [[CrossRef](#)] [[PubMed](#)]
95. Nakame, K.; Kaji, T.; Mukai, M.; Shinyama, S.; Matsufuji, H. The protective and anti-inflammatory effects of glucagon-like peptide-2 in an experimental rat model of necrotizing enterocolitis. *Peptides* **2016**, *75*, 1–7. [[CrossRef](#)]
96. Fuchs, C.D.; Claudel, T.; Mlitz, V.; Riva, A.; Menz, M.; Brusilovskaya, K.; Haller, F.; Baumgartner, M.; Königshofer, P.; Unger, L.W.; et al. GLP-2 Improves Hepatic Inflammation and Fibrosis in Mdr2^{-/-} Mice Via Activation of NR4a1/Nur77 in Hepatic Stellate Cells and Intestinal FXR Signaling. *Cell Mol. Gastroenterol. Hepatol.* **2023**, *16*, 847–856. [[CrossRef](#)]
97. Cani, P.D.; Possemiers, S.; Van de Wiele, T.; Guiot, Y.; Everard, A.; Rottier, O.; Geurts, L.; Naslain, D.; Neyrinck, A.; Lambert, D.M.; et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* **2009**, *58*, 1091–1103. [[CrossRef](#)]
98. Nuzzo, D.; Baldassano, S.; Amato, A.; Picone, P.; Galizzi, G.; Caldara, G.F.; Di Carlo, M.; Mulè, F. Glucagon-like peptide-2 reduces the obesity-associated inflammation in the brain. *Neurobiol. Dis.* **2019**, *121*, 296–304. [[CrossRef](#)]
99. Fischer, K.D.; Dhanvantari, S.; Drucker, D.J.; Brubaker, P.L. Intestinal growth is associated with elevated levels of glucagon-like peptide 2 in diabetic rats. *Am. J. Physiol.* **1997**, *273*, E815–E820. [[CrossRef](#)]
100. Baldassano, S.; Rappa, F.; Amato, A.; Cappello, F.; Mulè, F. GLP-2 as Beneficial Factor in the Glucose Homeostasis in Mice Fed a High Fat Diet. *J. Cell Physiol.* **2015**, *230*, 3029–3036. [[CrossRef](#)]
101. Sigalet, D.L.; Wallace, L.E.; Holst, J.J.; Martin, G.R.; Kaji, T.; Tanaka, H.; Sharkey, K.A. Enteric neural pathways mediate the anti-inflammatory actions of glucagon-like peptide 2. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2007**, *293*, G211–G221. [[CrossRef](#)] [[PubMed](#)]
102. Sigalet, D.L.; Wallace, L.; De Heuvel, E.; Sharkey, K.A. The effects of glucagon-like peptide 2 on enteric neurons in intestinal inflammation. *Neurogastroenterol. Motil.* **2010**, *22*, 1318–e350. [[CrossRef](#)] [[PubMed](#)]
103. Talbot, J.; Hahn, P.; Kroehling, L.; Nguyen, H.; Li, D.; Littman, D.R. Feeding-dependent VIP neuron-ILC3 circuit regulates the intestinal barrier. *Nature* **2020**, *579*, 575–580. [[CrossRef](#)]
104. de Heuvel, E.; Wallace, L.; Sharkey, K.A.; Sigalet, D.L. Glucagon-like peptide 2 induces vasoactive intestinal polypeptide expression in enteric neurons via phosphatidylinositol 3-kinase- γ signaling. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *303*, E994–E1005. [[CrossRef](#)]
105. Dubé, P.E.; Brubaker, P.L. Frontiers in glucagon-like peptide-2: Multiple actions, multiple mediators. *Am. J. Physiol. Endocrinol. Metab.* **2007**, *293*, E460–E465. [[CrossRef](#)]
106. Pini, A.; Garella, R.; Idrizaj, E.; Calosi, L.; Baccari, M.C.; Vannucchi, M.G. Glucagon-like peptide 2 counteracts the mucosal damage and the neuropathy induced by chronic treatment with cisplatin in the mouse gastric fundus. *Neurogastroenterol. Motil.* **2016**, *28*, 206–216. [[CrossRef](#)] [[PubMed](#)]
107. Nardini, P.; Pini, A.; Bessard, A.; Duchalais, E.; Niccolai, E.; Neunlist, M.; Vannucchi, M.G. GLP-2 Prevents Neuronal and Glial Changes in the Distal Colon of Mice Chronically Treated with Cisplatin. *Int. J. Mol. Sci.* **2020**, *21*, 8875. [[CrossRef](#)] [[PubMed](#)]

108. Drucker, D.J. Biological actions and therapeutic potential of the glucagon-like peptides. *Gastroenterology* **2002**, *122*, 531–544. [[CrossRef](#)]
109. Gori, S.; Inno, A.; Belluomini, L.; Bocus, P.; Bisoffi, Z.; Russo, A.; Arcaro, G. Gut microbiota and cancer: How gut microbiota modulates activity, efficacy and toxicity of antitumoral therapy. *Crit. Rev. Oncol. Hematol.* **2019**, *143*, 139–147. [[CrossRef](#)]
110. Ikeda, Y.; Suga, N.; Matsuda, S. Efficacy of Life Protection Probably from Newly Isolated Bacteria against Cisplatin-Induced Lethal Toxicity. *Microorganisms* **2023**, *11*, 2246. [[CrossRef](#)]
111. Biagioni, C.; Traini, C.; Fausone-Pellegrini, M.S.; Idrizaj, E.; Baccari, M.C.; Vannucchi, M.G. Prebiotics counteract the morphological and functional changes secondary to chronic cisplatin exposition in the proximal colon of mice. *J. Cell Mol. Med.* **2024**, *28*, 18161. [[CrossRef](#)] [[PubMed](#)]
112. Horowitz, A.; Chanez-Paredes, S.D.; Haest, X.; Turner, J.R. Paracellular permeability and tight junction regulation in gut health and disease. *Nat. Rev. Gastroenterol. Hepatol.* **2023**, *20*, 417–432. [[CrossRef](#)]
113. Voudren, C.D.; Mayhue, E.J.; Riehm, M.D.; Jugan, M.C. Evaluation of the relationship between plasma glucagon-like peptide-2 and gastrointestinal dysbiosis in canine chronic enteropathies. *PLoS ONE* **2024**, *19*, 0305711. [[CrossRef](#)]
114. Stahel, P.; Xiao, C.; Davis, X.; Tso, P.; Lewis, G.F. Glucose and GLP-2 (Glucagon-Like Peptide-2) Mobilize Intestinal Triglyceride by Distinct Mechanisms. *Arterioscler. Thromb. Vasc. Biol.* **2019**, *39*, 1565–1573. [[CrossRef](#)]
115. Wøjdemann, M.; Wettergren, A.; Hartmann, B.; Holst, J.J. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. *Scand. J. Gastroenterol.* **1998**, *33*, 828–832.
116. Nagell, C.F.; Wettergren, A.; Pedersen, J.F.; Mortensen, D.; Holst, J.J. Glucagon-like peptide-2 inhibits antral emptying in man, but is not as potent as glucagon-like peptide-1. *Scand. J. Gastroenterol.* **2004**, *39*, 353–358. [[CrossRef](#)] [[PubMed](#)]
117. Amato, A.; Baldassano, S.; Serio, R.; Mulè, F. Glucagon-like peptide-2 relaxes mouse stomach through vasoactive intestinal peptide release. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2009**, *296*, G678–G684. [[CrossRef](#)] [[PubMed](#)]
118. Garella, R.; Idrizaj, E.; Traini, C.; Squecco, R.; Vannucchi, M.G.; Baccari, M.C. Glucagon-like peptide-2 modulates the nitrgic neurotransmission in strips from the mouse gastric fundus. *World J. Gastroenterol.* **2017**, *23*, 7211–7220. [[CrossRef](#)]
119. Traini, C.; Idrizaj, E.; Garella, R.; Squecco, R.; Vannucchi, M.G.; Baccari, M.C. Glucagon-like peptide-2 interferes with the neurally-induced relaxant responses in the mouse gastric strips through VIP release. *Neuropeptides* **2020**, *81*, 102031. [[CrossRef](#)]
120. Idrizaj, E.; Biagioni, C.; Traini, C.; Vannucchi, M.G.; Baccari, M.C. Glucagon-like Peptide-2 Depresses Ileal Contractility in Preparations from Mice through Opposite Modulatory Effects on Nitrgic and Cholinergic Neurotransmission. *Int. J. Mol. Sci.* **2024**, *25*, 1855. [[CrossRef](#)]
121. Amato, A.; Cinci, L.; Rotondo, A.; Serio, R.; Fausone-Pellegrini, M.S.; Vannucchi, M.G.; Mulè, F. Peripheral motor action of glucagon-like peptide-1 through enteric neuronal receptors. *Neurogastroenterol. Motil.* **2010**, *22*, 664–e203. [[CrossRef](#)] [[PubMed](#)]
122. Goyal, R.K.; Guo, Y.; Mashimo, H. Advances in the physiology of gastric emptying. *Neurogastroenterol. Motil.* **2019**, *31*, e13546. [[CrossRef](#)] [[PubMed](#)]
123. Mori, H.; Verbeure, W.; Schol, J.; Carbone, F.; Tack, J. Gastrointestinal hormones and regulation of gastric emptying. *Curr. Opin. Endocrinol. Diabetes Obes.* **2022**, *29*, 191–199. [[CrossRef](#)]
124. Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R.M.; Tanaka, H.; Williams, S.C.; Richardson, J.A.; Kozlowski, G.P.; Wilson, S.; et al. Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell* **1998**, *92*, 697. [[CrossRef](#)] [[PubMed](#)]
125. Baccari, M.C.; Bani, D.; Calamai, F. Evidence for a modulatory role of orexin A on the nitrgic neurotransmission in the mouse gastric fundus. *Regul. Pept.* **2009**, *154*, 54–59. [[CrossRef](#)]
126. Idrizaj, E.; Garella, R.; Squecco, R.; Baccari, M.C. Can adiponectin have an additional effect on the regulation of food intake by inducing gastric motor changes? *World J. Gastroenterol.* **2020**, *26*, 2472–2478. [[CrossRef](#)]
127. Hansen, L.; Hare, K.J.; Hartmann, B.; Deacon, C.F.; Ugleholdt, R.K.; Plamboeck, A.; Holst, J.J. Metabolism of glucagon-like peptide-2 in pigs: Role of dipeptidyl peptidase IV. *Regul. Pept.* **2007**, *138*, 126–132. [[CrossRef](#)]
128. Furness, J.B. The enteric nervous system and neurogastroenterology. *Nat. Rev. Gastroenterol. Hepatol.* **2012**, *9*, 286–294. [[CrossRef](#)]
129. Furness, J.B.; Callaghan, B.P.; Rivera, L.R.; Cho, H.J. The enteric nervous system and gastrointestinal innervation: Integrated local and central control. *Adv. Exp. Med. Biol.* **2014**, *817*, 39–71.
130. Sanders, K.M.; Ward, S.M. Nitric oxide and its role as a non-adrenergic, non-cholinergic inhibitory neurotransmitter in the gastrointestinal tract. *Br. J. Pharmacol.* **2019**, *176*, 212–227. [[CrossRef](#)]
131. Lefebvre, R.A. Non-adrenergic non-cholinergic neurotransmission in the proximal stomach. *Gen. Pharmacol.* **1993**, *24*, 257–266. [[CrossRef](#)] [[PubMed](#)]
132. Baccari, M.C.; Vannucchi, M.G.; Idrizaj, E. Glucagon-Like Peptide-2 in the Control of Gastrointestinal Motility: Physiological Implications. *Curr. Protein Pept. Sci.* **2022**, *23*, 61–69. [[CrossRef](#)] [[PubMed](#)]
133. Amato, A.; Rotondo, A.; Cinci, L.; Baldassano, S.; Vannucchi, M.G.; Mulè, F. Role of cholinergic neurons in the motor effects of glucagon-like peptide-2 in mouse colon. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2010**, *299*, G1038–G1044. [[CrossRef](#)]
134. Halim, M.A.; Degerblad, M.; Sundbom, M.; Karlbom, U.; Holst, J.J.; Webb, D.L.; Hellström, P.M. Glucagon-Like Peptide-1 Inhibits Prandial Gastrointestinal Motility Through Myenteric Neuronal Mechanisms in Humans. *J. Clin. Endocrinol. Metab.* **2018**, *103*, 575–585. [[CrossRef](#)]
135. Grider, J.R.; Cable, M.B.; Said, S.I.; Makhlof, G.M. Vasoactive intestinal peptide as a neural mediator of gastric relaxation. *Am. J. Physiol.* **1985**, *248*, G73–G78. [[CrossRef](#)] [[PubMed](#)]

136. Verbeure, W.; van Goor, H.; Mori, H.; van Beek, A.P.; Tack, J.; van Dijk, P.R. The Role of Gasotransmitters in Gut Peptide Actions. *Front. Pharmacol.* **2021**, *12*, 720703. [[CrossRef](#)]
137. Idrizaj, E.; Garella, R.; Francini, F.; Squecco, R.; Baccari, M.C. Relaxin influences ileal muscular activity through a dual signaling pathway in mice. *World J. Gastroenterol.* **2018**, *24*, 882–893. [[CrossRef](#)]
138. Idrizaj, E.; Garella, R.; Castellini, G.; Francini, F.; Ricca, V.; Baccari, M.C.; Squecco, R. Adiponectin Decreases Gastric Smooth Muscle Cell Excitability in Mice. *Front. Physiol.* **2019**, *10*, 1000. [[CrossRef](#)]
139. Squecco, R.; Garella, R.; Idrizaj, E.; Nistri, S.; Francini, F.; Baccari, M.C. Relaxin Affects Smooth Muscle Biophysical Properties and Mechanical Activity of the Female Mouse Colon. *Endocrinology* **2015**, *156*, 4398–4410. [[CrossRef](#)]
140. Konturek, J.W.; Thor, P.; Domschke, W. Effects of nitric oxide on antral motility and gastric emptying in humans. *Eur. J. Gastroenterol. Hepatol.* **1995**, *7*, 97–102.
141. Soediono, P.; Burnstock, G. Contribution of ATP and nitric oxide to NANC inhibitory transmission in rat pyloric sphincter. *Br. J. Pharmacol.* **1994**, *113*, 681–686. [[CrossRef](#)] [[PubMed](#)]
142. Bayguinov, O.; Sanders, K.M. Role of nitric oxide as an inhibitory neurotransmitter in the canine pyloric sphincter. *Am. J. Physiol.* **1993**, *264*, G975–G983. [[CrossRef](#)] [[PubMed](#)]
143. Rand, M.J. Nitroergic transmission: Nitric oxide as a mediator of non-adrenergic, non-cholinergic neuro-effector transmission. *Clin. Exp. Pharmacol. Physiol.* **1992**, *19*, 147–169. [[CrossRef](#)] [[PubMed](#)]
144. Van Geldre, L.A.; Lefebvre, R.A. Interaction of NO and VIP in gastrointestinal smooth muscle relaxation. *Curr. Pharm. Des.* **2004**, *10*, 2483–2497. [[CrossRef](#)]
145. Tonini, M.; De Giorgio, R.; De Ponti, F.; Sternini, C.; Spelta, V.; Dionigi, P.; Barbara, G.; Stanghellini, V.; Corinaldesi, R. Role of nitric oxide- and vasoactive intestinal polypeptide-containing neurones in human gastric fundus strip relaxations. *Br. J. Pharmacol.* **2000**, *129*, 12–20. [[CrossRef](#)]
146. McDonagh, S.C.; Lee, J.; Izzo, A.; Brubaker, P.L. Role of glial cell-line derived neurotropic factor family receptor alpha2 in the actions of the glucagon-like peptides on the murine intestine. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2007**, *293*, G461–G468. [[CrossRef](#)]
147. Koopmann, M.C.; Nelson, D.W.; Murali, S.G.; Liu, X.; Brownfield, M.S.; Holst, J.J.; Ney, D.M. Exogenous glucagon-like peptide-2 (GLP-2) augments GLP-2 receptor mRNA and maintains proglucagon mRNA levels in resected rats. *JPEN J. Parenter. Enteral Nutr.* **2008**, *32*, 254–265. [[CrossRef](#)]
148. Jarvie, B.C.; Knight, Z.A. Breaking down a gut-to-brain circuit that prevents malabsorption. *Cell* **2022**, *185*, 2393–2395. [[CrossRef](#)]
149. Wilbrink, J.; Masclee, G.; Klaassen, T.; van Avesaat, M.; Keszthelyi, D.; Masclee, A. Review on the Regional Effects of Gastrointestinal Luminal Stimulation on Appetite and Energy Intake: (Pre)clinical Observations. *Nutrients* **2021**, *13*, 1601. [[CrossRef](#)]
150. Petersen, N.; Greiner, T.U.; Torz, L.; Bookout, A.; Gerstenberg, M.K.; Castorena, C.M.; Kuhre, R.E. Targeting the Gut in Obesity: Signals from the Inner Surface. *Metabolites* **2022**, *12*, 39. [[CrossRef](#)]
151. Pizarroso, N.A.; Fuciños, P.; Gonçalves, C.; Pastrana, L.; Amado, I.R. A Review on the Role of Food-Derived Bioactive Molecules and the Microbiota-Gut-Brain Axis in Satiety Regulation. *Nutrients* **2021**, *13*, 632. [[CrossRef](#)] [[PubMed](#)]
152. Portincasa, P.; Khalil, M.; Graziani, A.; Frühbeck, G.; Baffy, G.; Garruti, G.; Di Ciaula, A.; Bonfrate, L. Gut microbes in metabolic disturbances. Promising role for therapeutic manipulations? *Eur. J. Intern. Med.* **2024**, *119*, 13–30. [[CrossRef](#)] [[PubMed](#)]

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