Review Article

Physiological Role of Intestinotropic Glucagon Like Peptides in Health and Disease

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ABSTRACT

Gastrointestinal hormones are the set of hormones which are secreted from the enteroendocrine cells of gastrointestinal tract. They coordinate functions like nutrient assimilation, food intake and signal transduction of various physiological processes. The remarkable enteroendocrine cells include enterochromaffin (EC) cells, enterochromaffin like (ECL) cells, G cells, D cells, M/Mo cells, S cells, K cells, I cells, N cells and L cells. Out of them, L cells in the ileum and colon secrete GLP-1, GLP-2, oxyntomodulin, peptide YY from glucagon coding gene (GCG) or proglucagon gene. GLP-1 is reported to perform functions like glycemia, glucose dependent insulin secretion, gastric emptying, regulation of food intake, β cell proliferation whereas GLP-2 is reported for variety of functions like regulation of mucosal growth in small and large intestine, enterocyte glucose transport nutrient absorption, inhibition of gastric emptying as well as gastric acid secretion, stimulation of intestinal blood flow, relaxation of intestinal smooth muscle. These intestinotropic glucagon like peptides channelize several homeostatic mechanisms and involve in the target specific actions all the way. The above mentioned functions of intestinotropic glucagon like peptides might be due torapid release by means of neural reflex and delayed release driven by the presence of food in the gut.

Key words: Gastrointestinal hormones, L cells, GLP-1, GLP-2, Intestinotropic glucagon like peptides.

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INTRODUCTION

Gastrointestinal system intended for digestion is an efficient system that works on the overall homeostasis of the functional systems in the body. Proteins, carbohydrates, fats, minerals and vitamins act as major nutrients required for the healthy existence. The gastrointestinal system is under the control of hormones as well as neurons with respect to the functions that it performs. The collective set of hormones that are secreted from the cells of the gastrointestinal tract (gut) are called gastrointestinal hormones or gut hormones. The enteroendocrine cells produce a wide variety of gut hormones which coordinate functions like nutrient assimilation, food intake, intestinal function and others by means of signalling pathways including G-protein coupled receptor as well as ion channel mechanisms.[1] The gut hormones are peptides that are synthesized from gene transcription and protein translation into preprohormones. The processing of preprohormones results in the formation of prohormones which undergo post-translational processing in specific hormone secreting cell to yield peptide hormones. The post-translational maturation of these secretory peptides involve various enzymatic modifications. Irrespective of peptide processing, the peptides can be quantified using processing independent analysis.[2] The G-protein coupled receptors that are expressed in the cell membranes of different target cells behave as the molecular targets of each bioactive peptide.[3]

There are various types of enteroendocrine cells that secrete various essential peptides like enterochromaffin (EC) cells that secrete substance P, motilin and encephalin; enterochromaffin like (ECL) cells that are in the proximity of parietal cells secrete histamine; G cells of the stomach that secrete gastrin; D cells present in stomach, intestine and pancreas secrete somatostatin; M/ Mo cells

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present in the gut associated or mucosa associated lymphoid tissues of small intestine secrete motilin; S cells of duodenum and jejunum secrete secretin; K cells of the duodenum that secrete glucose-dependent insulinotropic hormone or gastric inhibitory polypeptide (GIP); I cells in the duodenum and jejunum secrete cholecystokinin (CCK); N cells in the jejunum secrete neurotensin; enteroglucagon/ L cells in the ileum colon along with neuronal cells secrete glucagon-like peptide-1 (GLP-1), glucagon like peptide-2 (GLP-2), oxyntomodulin, peptide YY (PYY).[4]

The enteroglucagon or L cells specific to the ileum and colon secrete peptide hormones from glucagon coding gene (GCG) or proglucagon gene. The cell-type specific GCG expression controls endogenous peptide production which maintain glucose homeostasis in the blood, intestinal cell proliferation and satiety (feel to feed). The GCG expression is controlled by protein kinase A and EPAC signalling pathways as a response to three modulations namely cAMP elevation, insulin controlled specific cell-types and Wnt signalling effectors.[5] The proglucagon gene is expressed in the pancreatic alpha cells, intestinal L cells as well as brain neuronal cells and is represented on the second chromosome with six exons and five introns. This gene undergoes transcription to mRNA and gets translated into a proglucagon composed of 178 amino acids. The proglucagon undergoes post-translational modification by the help of proconvertases (PCs) that are organ specific and result in the generation of active peptides.[6] Though PC 2 in the pancreas release glicentin related pancreatic polypeptide (GRPP), glucagon, intervening peptide 1 (IP-1) and major proglucagon fragment with GLP-1, IP-2 and GLP-2; PC 1/3 is also responsible for the release of GLP-1. However, the PCs 1 and 3 release glicentin, oxyntomodulin, GLP-1, IP-2 and GLP-2 in intestinal L cells and brain neuronal cells respectively.

GLUCAGON-LIKE-PEPTIDE-1 (GLP-1)

The posttranslational processing of proglucagon in the β-cells of pancreas, L-cells of ileum and colon along with the brain neuronal cells synthesize GLP-1. L-cells exist in direct contact with the nutrients in the intestinal lumen[7] and their close proximity with the neurons and microvasculature allows the neuronal and hormonal signalling of secretion. GLP-1 follows two phase release profile where in first phase the proximal gut results in a rapid rise due to neural reflex and in second phase the release is driven by the arrival of food in the distal gut.[8] The profound effects of GLP-1 includes regulation of glycemia, stimulation of glucose-dependent insulin secretion, expression of proinsulin gene, proliferation of β-cell and anti-apoptosis, inhibition of glucagon release, gastric emptying and regulation of food intake. GLP-1 is released in two amide forms that are tissue specific namely, GLP-1 (7-36 amide) which is 80% circulating and is predominant in pancreas and then GLP-1 (7-37 amide) predominant in ileum and hypothalamus. The rapid degradation of GLP-1 by ubiquitous dipeptidyl peptidase IV (DPP IV) assigns an extreme short half-life of ~ 2min. Development of GLP-1 analogues like exenatide and DPP-4 resistant GLP-1 analogues like lixisenatide regulate the biogenic function of GLP-1.[9] The secretion of GLP-1 is regulated by signalling pathways mediated by acetylcholine (stimulation), gastrin releasing peptide (stimulation), calcitonin-gene related peptide (stimulation), fatty acids (direct stimulation).[10] The secretion of GLP-1 is also regulated by somatostatin (inhibition).[11] The GLP-1 receptors (GLP-1Rs) are expressed in stomach, pancreas, heart, lungs, kidney and hypothalamus.[12]

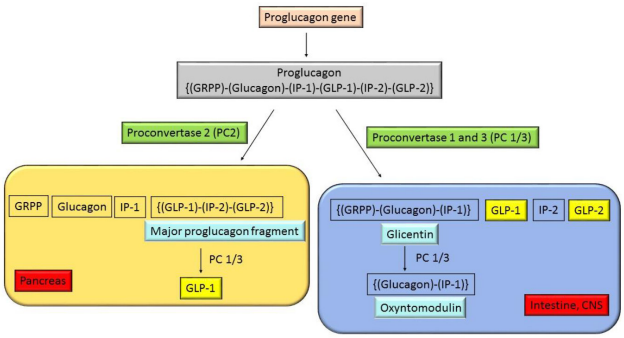
Actions of GLP-1

Gastrointestinal system

The incretin effect of GLP-1 was specified when the nutrient load initiated the release of hormone from the intestinal cells and resulted in glucose dependent insulin response.[13] The insulin response to oral glucose load is greater compared to the intravenous glucose load and this was identified as the incretin effect.[14] The insulinotropic and glucagonostatic effects are outweighed by the action of GLP-1 in slow gastric emptying which confirms the ileal brake pathways.[15] This inhibition of gastric emptying occur through vagal afferent mediated central mechanisms. The glycaemic control in type 2 diabetes is improved by the development of GLP-1 analogues like exenatide and liraglutide along with DPP-4 inhibitors like sitagliptin and vildagliptin.[16] The migrating motor complex plays an essential role in maintaining the gastrointestinal motility by means of peristalsis during fasting (fasting motility) or segmented contractions during postprandial state (fed motility).[17] GLP-1 interacts with GLP-1R and reduces the contractions in fed motility and by this ROSE-010, a stable GLP-1 analogue was investigated to reduce the exacerbations in irritable bowel syndrome.[18] A single blinded parallel study conducted on GLP-1 inhibited prandial GI relaxation through myenteric neuronal mechanisms in humans.[19] The regulation of GLP-1 towards gastric[20] as well as colonic motility[21] were studied through the antagonistic effect of exendin (9-39) amide, a potential GLP-1R blocker.

Gastrosecretory cells and their functions.

Type of delivery	Cells of secretion	Hormone secreted	Secretion	Signalling Pathway	Stimulators	Inhibitors	Function
Endocrine (diffuse into blood stream directly for distant action)	Enteroendo-crine cells	Gastrin	G cells in the antrum of stomach, duodenum and pancreas	GPCR- IP3 pathway	Gastrin releasing peptide, amino acids in the stomach	Somatostatin	Controls the gastric acid function
		Cholecystokinin	I cells of small intestine (mostly duodenum)	GPCR- IP3 pathway	Hydrochloric acid, amino acids, fatty acids	Somatostatin, pancreatic peptide	Release of bile into intestine, inhibits gastric emptying and favours digestion
		Secretin	S cells of duodenum and jejunum	GPCR- AC pathway	Gastric acid, fats and protein	pH above 4.5	Regulates water homeostasis
		Glucose-dependent insulinotropic peptide (GIP)	K cells in duodenum and jejunum	GPCR- AC pathway	Glucose, lipids	-	Stimulation of insulin secretion
		Motilin	Enterochr-omaffin cells and Mo cells of stomach, small intestine and colon	GPCR- IP3 pathway	H+ ions and ingested fat	Ingested glucose	Stimulation of gastric activity, maintenance of myoelectric activity of stomach
Paracrine (diffuse into extracellular space to act locally)	Enteroendo-crine cells	Somatostatin SST 14 (hypothalamus); SST 18 (GIT)	D cells of stomach, duodenum, pancreas and also as a response to acid in the stomach	GPCR-cAMP pathway inhibition	Fatty acids, amino acids, glucose and GI hormones	gastric acid, vagal nerve,	Involvement in the neuroendocrine inhibitory effects
		Histamine	Enterochromaffin like cells (ECL cells)	GPCR- cAMP pathway stimulation	Gastrin, pituitary adenyl cyclase-activating peptide	Somatostatin	Stimulation of gastric acid secretion
Endoparacrine (act through both endocrine and paracrine mechanisms)	Enteroendocrine cells	Glucagon like peptide (GLP-1)	L cells of small intestine	GPCR-cAMP pathway stimulation	Food intake, intestinal glucose	Somatostatin	Stimulation of insulin secretion
		Glucagon like peptide (GLP-2	L cells of small intestine	GPCR-cAMP pathway stimulation	Nutrient intake	Somatostatin	Enteric nervous system and m TORC1 mediated a.a absorption and transport.
		Pancreatic polypeptide	PP or F cells of pancreas	GPCR- IP3 pathway	Food intake, exercise	Somatostatin, ingested glucose, vagus nerve	Action against cholecystokinin, regulation of pancreatic exocrine secretion
		Peptide YY	L cells of intestine	GPCR- IP3 pathway	Fat and protein diet	Somatostatin, ingested glucose, vagus nerve	Suppression of appetite, suppression of pancreatic secretion, stimulation of water and electrolyte absorption in colon
Neurocrine (neuron mediated paracrine signalling)	Post-ganglionic non-cholinergic neurons of the enteric nervous system	Vasoactive intestinal peptide (VIP)	Cells of gut, pancreas and hypothalamus	GPCR-AC pathway	Neurotransmitters (ACh, DE), prostaglandins (PGD, PGE), nerve growth factor	Somatostatin, vagus nerve	Regulation of gastrointestinal function
		Gastrin release peptide (GRP)	G cells of stomach	GPCR-IP3 pathway	Vagal reflex	Somatostatin	Regulation of gastrin function, enteric motor function
		Enkephalins	Mesenteric plexus	GPCR-IP3 pathway	GI distension	-	Maintenance of food and liquid consumption



Production of intestinotropic hormones (GLP-1 and GLP-2).

Hepatic system

GLP is released according to the quantity of the meal. So the effect of GLP on liver depends on the meal ingested. It arrests the production of hepatic glucose by stimulating the secretion of insulin and inhibiting the secretion of glucagon.[22] Liraglutide ameliorated hepatic steatosis and cardiac hypertrophy in C57BL/6J mice fed with western diet for 8 weeks.[23] The administration of GLP-1 agonist, AC3174 for 4 weeks at 30μg/Kg/day resulted in the reduction of hepatic weight as well as liver content.[24] Uncontrolled open label study for 3 year period decreased ALT levels in subjects with T2DM (Type 2 Diabetes mellitus) treated with Exenatide 10 μg twice daily.[25] GLP-1R activation regulates hepatic lipid synthesis, secretion, uptake or oxidation which results in reduced hepatic lipid content independent of changes in the body weight.[26]

Central nervous system

The regulation of food intake by central (intracerebroventricular) GLP-1 and its antagonistic action by prior administration of exendin was observed in the rat paraventricular nucleus of hypothalamus and central nucleus of amygdala[27] because circulating GLP-1 has the accessibility to blood-brain barrier free areas which relay their nerve supply to these nuclei and thereby control nutrient homeostasis. GLP-1 administration in humans assessed by peroneal nerve microneurography increased the skeletal muscle sympathetic nerve activity (MSNA) after 60 min of administration without affecting cardiac sympathetic and parasympathetic nerves.[28] Exenatide increased cerebral glucose metabolic rate in the brain regions working on food reward system, glucose homeostasis as well as appetite whereas it reduced glucose uptake in hypothalamus.[29] GLP-1 receptor activation decreases anticipatory food reward which reduce cravings for food and controls overeating.[30]

Renal system

GLP-1 intravenous infusion enhanced sodium excretion and reduced H^+ secretion suggesting the renoprotective activity.[31] GLP-1R agonists reduced tubular sodium excretion through protein kinase A dependent Na (+)/H (+) exchanger isoform 3 (NHE3)-mediated bicarbonate reabsorption[32] in kidney cell line and rodent kidney preparations.

Disease conditions

The protective effects of GLP-1 and GLP1R agonists like exenatide were investigated in diseases like Parkinsonism, Alzheimer's disease and amyotropic lateral sclerosis. GLP-1 analogues like semaglutide and liraglutide showed promising protection of dopaminergic neurons in substantia nigra and striatum by improving 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) induced motor impairments.[33] GLP-1R activation initiated neurotrophic effects, neuroprotection, anti-inflammation, neurogenesis and synaptic plasticity by evaluating disease progression in gut-brain axis.[34] A case report was submitted for acute pancreatitis that reported as a side effect with GLP-1R agonist treatment.[35] The multisystemic role of GLP-1R agonists is due to their multiple pleiotropic effects in patients with other comorbidities. The influence of GLP-1R agonists in medication compliance in terms of cost, adverse effects, nonadherence etc., due to polypharmacy in elderly patients with diabetes was reported.[36]

GLUCAGON LIKE PEPTIDE -2 (GLP-2)

The GLP-2 receptor gene is present on chromosome 17 and is produced in the pancreas, intestines and brain by the posttranslational processing of proglucagon with the help of proconvertases. GLP-1 and GLP-2 are secreted in a 1:1 ratio from intestinal L-cells.[37] Ingestion of nutrients releases the GLP-2 in circulation in biphasic manner that is a rapid early phase for 10-15 min followed by prolonged phase for 30-60 min.[38] This release is facilitated by GIP (glucose-dependent insulinotropic peptide), GRP (gastrin releasing peptide) as well as vagus nerve stimulation as similar to GLP-1 release.[39] The biological functions of GLP-2 are stimulation of mucosal growth in the small and large intestine, inhibition of enterocyte and crypt cell apoptosis, stimulation of enterocyte glucose transport and GLUT-2 expression, increased nutrient absorption, inhibition of gastric emptying and gastric acid secretion, reduction of intestinal permeability, stimulation of intestinal blood flow, relaxation of intestinal smooth muscle. GLP-2 is more stable when compared to GLP-1 with an approximate

half-life of 5-7 min[40] and gets cleaved by DPP-IV enzyme[41] which shows renal clearance. The receptor location of GLP-2R is confined to GIT and brain[42] unlike GLP-1R located in GIT, brain, heart lung and kidney.

Actions of GLP-2

Gastrointestinal system

GLP-2 activates mTORC1 signalling pathway and facilitates amino acid transport through enteric nervous system to proclaim optimal energy absorption.[43] GLP-2 administration alleviated the negative effects of feed restriction and improved the intestinal morphology as well as ameliorated the circulating inflammatory markers in cows.[44] GLP-2 promotes intestinal epithelial homeostasis and function, enhances intestinal nutrient absorption and blood flow and inhibits gastrointestinal motility, thus controls the energy intake whereas in hypothalamus and brain stem, GLP-2R plays physiological roles in regulating food intake and glucose homeostasis, which are mediated through vagal outputs via neural circuits.[45] Nutrient absorption, fluid retention, body weight and lean body mass were significantly improved by exogenous GLP-2 administration in human subjects with short-bowel syndrome.[46] Co-administration of exogenous GLP-2 together with a DPP-IV inhibitor improved the intestinotrophic response when compared to GLP-2 alone.[47] Exogenous GLP-2 administration also expands the mucosal surface area of the small bowel by stimulating crypt cell proliferation and inhibiting enterocyte apoptosis.[48] Vasoactive intestinal peptide (VIP) is implicated as a downstream target of GIP-2 action on blood flow, inflammation, cell proliferation and survival.[49] A potential degradation resistant GLP-2 analogue, Teduglutide (h[Gly2] GLP-2) treatment for 24 weeks reduced the parenteral support in SBS-IF (short bowel syndrome with intestinal failure) patients.[50] GLP-2 administration for 14 days as intravenous infusion at 50 μg/kg/d significantly reduced gross and histological intestinal mucosal damage and reduced the levels of the cytokines TNF-alpha and IFN-gamma in rats with antigen induced enteritis.[51] Human GLP-2 analogue (h [Gly2] GLP-2) significantly reverses weight loss, reduces interleukin-1 expression and increases colon length, crypt depth and both mucosal area and integrity in the colon of mice with acute DS colitis.[52]

Hepatic system

Hepatic uptake mechanism for GLP-2 was detected through a positive extraction of inactive metabolite of GLP-2 in pig liver by using mass spectrometry.[53] The treatment of metabolic disease by GLP-2-GLP-2R-gall bladder axis via decrease in the gall bladder smooth muscle activity reported a enhancement in the gall bladder filling.[54] GLP-2 plays a lipogenic role in the liver by increasing lipogenic gene expression and inducing hepatic steatosis, fasting dyslipidemia and VLDL over-production. In contrast, the lack of GLP2R appears to interfere with VLDL secretion, resulting in enhanced hepatic lipid accumulation.[55] A randomized, single-blind, cross over study on 10 healthy male volunteers confirmed that teduglutide, a GLP-2 analogue rapidly increased the mesenteric blood flow and triglyceride concentrations in plasma, triglyceride rich lipoproteins and chylomicrons by means of systemic nitric oxide independent mechanism. GLP-2 enhances epithelial barrier function and ameliorates inflammation and gastrointestinal stasis in postoperative ileus murine model,[56] thereby possibly contributing to suppression of the development of NAFLD/NASH.[57] Mice treated with GLP-2 exhibit an accelerated and more extended process of liver regeneration as shown by the increase in Ki-67 labelling and the upregulated expression of cell cycle-regulated genes.[58] Short-term treatment of long acting GLP-2 analogue, glepaglutide in a randomized phase 2 trial restored the disturbed homeostatic feedback in the gut-liver axis in terms of liver biomarkers might show therapeutic potential for the reversal of intestinal-failure associated liver disease (IFALD).[59]

Central nervous system

The gastrointestinal peptides released from the gut maintains various physiological mechanisms associated with brain. Signals from gut hormones affect the hypothalamic pathways of brain. Gut-brain axis regulates the energy balance with the help of gut hormones.[60] Along with the endocrine cells GLP-2R is also expressed in enteric neurons, vagal sensory neurons[61] as well as central neurons.[62] Circulating GLP-2 CNS GLP-2 mediated through melanocortin system (POMC/Pro-opiomelanocortin neurons) acts as a key signal for physiological short-term feeding behaviour and gastric motility and a key regulator for long-term energy homeostasis.[63] Central GLP-2 also activates P13K signalling in POMC neurons and thereby enhances hepatic insulin sensitivity.[64] GLP-2 was found to increase nNOS expression by modulating the nitrergic neurotransmission[65] and thereby influence the neutrally induced responses in mouse gastric fundal strips.

Respiratory system

GLP-2 receptors were present on the cell membrane of type II pneumocytes and interstitial cells. The cytoprotective and reparative effects of teduglutide, a long-acting synthetic GLP-2 analogue were analysed on mouse

model with lung injury that received TNF-α/Act D. Teduglutide pretreatment regressed the structural damage, cell apoptosis and oxidative stress by reducing lipid peroxidation.[66]

Renal system

GLP-2R signaling in baby hamster kidney (BHK) cells expressing a transfected rat GLP-2 receptor (BHK-GLP-2R cells) suggested mitogenic signaling in heterologous cell types independent of protein kinase A (PKA) pathway.[67] Characterization of the independent and cellular mechanisms mediated by agonist-induced GLP-2R desensitization and trafficking was done by using heterologous BHK cells transfected with GLP-2R[68] by means of lipid-raft dependent pathway.

Disease conditions

Preclinical evaluation proved that GLP-2 or teduglutide injection twice daily dosing in preclinical models increase the intestinal length and weight, villus height, crypt depth and crypt cell proliferation in both normal rodents and during intestinal adaptation in surgical models of short bowel syndrome[69] whereas GLP-2 administration by clinical evaluation reduced faecal weight and maintained intestinal fluid as well as electrolyte absorption with 28% improvement in creatinine clearance in patients with short bowel syndrome.[70] The enterocrinin GLP-2 like GLP-1 exhibits benefits on lipid metabolism, atherosclerosis formation, plasma glucose levels and maintenance of gastric mucosa integrity[71] in Inflammatory Bowel Disease (IBD). The intestinotrophic efficacy of GLP2-2G-XTEN, a novel, long-acting form of GLP2-2G in rat's Crohn's disease model with lower molar dose and less frequent dosing in relation to GLP-2G was demonstrated for better therapeutic benefit (Susan E. Alters *et al*. 2012).[72]

CONCLUSION

The hormones that control the gastrointestinal functions are secreted by enteroendocrine cells. These hormones are the secretory peptides that are synthesized by means of peptide processing through enzymatic modifications. The essential intestinotropic hormones GLP-1 and GLP-2 are secreted from enteroglucagon cells present in the ileum and colon via proglucagon gene processing mediated by organ specific proconvertases. GLP-1 behaves responsible for its incretin effect and ileal break pathways, glycaemic control, gastrointestinal motility in GIT; controls the lipid content in liver; regulates nutrient homeostasis in CNS; facilitates reabsorption in kidneys. GLP-2 on the other hand promotes intestinal epithelial homeostasis, cytokine function in GIT; maintains lipogenic profile in liver; regulates energy balance in CNS via gut-brain axis; mitogenic signalling independent of protein kinase pathway in the kidney. Thus both the peptides maintain the homeostatis and physiological functioning of organs in health and disease.

ABBREVIATIONS

AC: Adenylate cyclase; **ACh:** Acetylcholine; **BHK:** Baby Hamster Kidney; **cAMP:** Cyclic adenosine monophosphate; **CCK:** Cholecystokinin; **D cells:** Delta cells; **DS colitis:** Dextran sulfate induced colitis; **DE:** Dopamine; **EC cells:** Enterochromaffin cells; **ECL cells:** Enterochromaffin like cells; **EPAC:** Exchange Protein directly activated by cAMP; **G cells:** Gastrin releasing cells; **GRP:** Gastrin releasing peptide; **GIT:** Gastrointestinal tract; **GRPP:** Glicentin related pancreatic polypeptide; **GCG:** Glucagon coding gene; **GLP-1:** Glucagon like peptide -1; **GLP-1R:** Glucagon like peptide-1 receptor; **GLP-2:** Glucagon like peptide -2; **GIP:** Glucose-dependent insulinotropic peptide; **GPCR:** G protein (Guanine nucleotide binding protein) coupled receptor; **GLUT-2:** Glucose transporter-2; **I cells:** Cholecystokinin secreting cells; **IBD:** Inflammatory Bowel Disease; **IP3:** Inositol 1,4,5 triphosphate; **IFN-ϒ:** Interferon – ϒ; **IFALD:** Intestinal-failure associated liver disease; **IP:** Intervening peptide; **K cells:** Gastric inhibitory secreting cells; **L cells:** Glucagon like peptides releasing cells; **mTORC1:** Mammalian target of rapamycin complex-1; **MPTP:** 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; **M/Mo cells:** Motilin secreting cells; **mRNA:** Messenger ribonucleic acid; **MSNA:** Muscle sympathetic nerve activity; **nNOS:** Neuronal nitric oxide synthases; **N cells:** Neurotensin releasing cells; **NAFLD/NASH:** Nonalcoholic fatty liver disease/Nonalcoholic steatohepatitis; **NHE3:** Sodium (Na+)/hydrogen (H+) ion exchanger isoform-3; **PYY:** Peptide tyrosine tyrosine; **PI3K:** Phosphoinositide 3-kinase; **PC:** Proconvertase; **POMC:** Proopiomelanocortin; **PG:** Prostaglandin; **PKA:** Protein Kinase A; **S cells:** Secretin secreting cells; **SBS-IF:** Short bowel syndrome with intestinal failure; **SST:** Somatostatin; **TNF-α:** Tumor necrosis factor-α; **T2DM:** Type 2 Diabetes Mellitus; **VIP:** Vasoactive Intestinal Peptide.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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