Roles of Gut Hormones in the Regulation of Food Intake and Body Weight

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Abstract

The gastrointestinal tract is extremely rich in endocrine cells and secretes a myriad of hormones, including ghrelin, glucagon-like peptide 1(GLP1), gastric inhibitory peptide (GIP), cholecystokinin (CCK), amylin, peptide YY (PYY), oxyntomodulin, and leptin. Mechanical distention of the stomach elicits mechanoreceptors within the gastric wall sensing tension, stretch, and volume, which then send brain signals through vagal and spinal sensory nerves.

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Both stomach and gut are tightly connected with the central nervous system where the fullness sensation is elaborated. Peripheral signaling hormones regulate appetite in the hypothalamic arcuate nucleus through anorexigenic and orexigenic signals. The gut–hindbrain axis is sufficient to drive the satiation sensation, although hindbrain also communicates with the forebrain where sensory and cognitive processes linked to meal anticipation and learned associations play a relevant role in the anticipation of food reward and pleasure.

We report an overview of the intestinal mechanisms regulating satiety and body weight with particular emphasis to the effects of drugs and bariatric/metabolic surgery on gut hormonal secretion.

Keywords
Gastrointestinal hormones · Nervous system · Satiety · Appetite

Introduction

Food ingestion promotes satiation trough two mechanisms: stomach distension and hormone release. The gastrointestinal tract is tightly connected with the central nervous system (CNS) where the fullness sensation is elaborated. Peripheral signaling hormones regulate appetite in the hypothalamic arcuate nucleus (ARC) through anorexigenic and orexigenic signals. The former are mediated by neurons expressing the neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), while the latter are mediated by neurons expressing the neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY). Projections of these neurons transmit the signals to secondary neurons located in the dorsomedial and paraventricular nuclei, in the lateral hypothalamus, and in the prefornical area.

The gut–hindbrain axis is sufficient to give the satiation sensation, although hindbrain also communicates with the forebrain where sensory and cognitive processes linked to meal anticipation and learned associations play a relevant role in the anticipation of food reward and pleasure.

Mechanical distention of the stomach elicits mechanoreceptors within the gastric wall sensing tension, stretch, and volume which then send brain signals through vagal and spinal sensory nerves (Ritter 2004).

When vagotomy was used, years ago, as a therapeutic approach to cure peptic ulcers, it was associated with a decline of appetite and consequently with weight loss (Irving et al. 1985). Therefore, the vagus nerve was regarded as a possible target for the treatment of obesity. The Maestro System (Enteromedics) has been recently approved by the Food and Drug Administration and consists of a subcutaneously implanted rechargeable battery connected with two electrodes that are laparoscopically implanted in the trunks of the vagus nerves just above the junction between the esophagus and the stomach. The leads are placed on the anterior and posterior intra-abdominal nerve trunks. Clinical studies have shown that Maestro System implantation determines a significant weight reduction of around 3 kg in 1 year (Shikora et al. 2013).

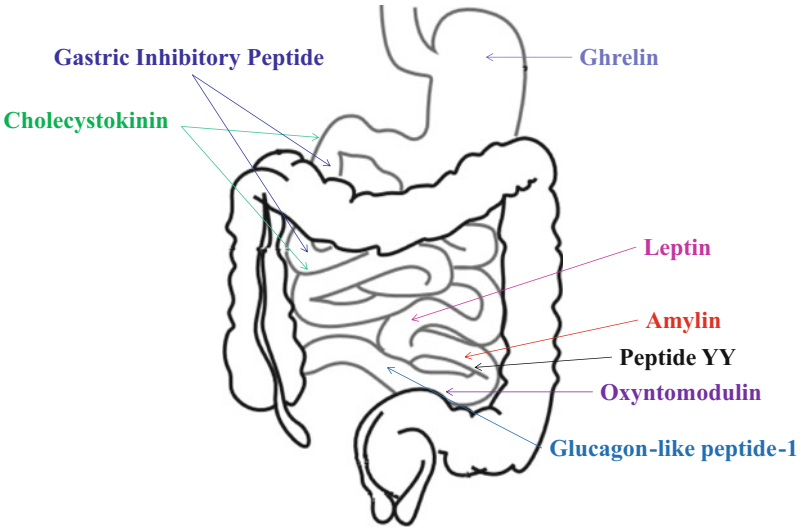

Fig. 1 Major hormones produced by the gastrointestinal tract

Nutrient delivery in the small intestine is able to reduce food intake (Powley and Phillips 2004) through the secretion of satiation hormones by entero-endocrine cells.

Entero-Endocrine Cells

Entero-endocrine cells (EECs), derived from pluripotent stem cells and located within the epithelial cells of the intestinal mucosa, sense the intraluminal nutrients and produce a series of hormones that regulate many functions including appetite, digestion, gut motility, and metabolism. Importantly, these cells are connected with nervous terminations and, thus, they can dialogue with the central nervous system.

At least 12 types of entero-endocrine cells have been identified until now and their location and type of hormone produced are summarized in Fig. 1. Single types of EECs are able, however, to produce more than one hormone as shown in transgenic CCK-eGFP mice, where six functionally different peptides (CCK, GLP1, GIP, PYY, secretin and neurotensin) can be coexpressed (Egerod et al. 2012).

In the following sections, the action of the major entero-hormones will be underlined.

CCK

Cholecystokinin (CCK) is produced by I endocrine cells of the duodenum and jejunum, but it is also produced in the enteric nervous system and in the brain. When injected before meals, CCK promotes satiety, but it has a short life (Lieverse

et al. 1995). Injection of CCK in the hypothalamus induces satiation. Long-term administration of CCK in both animals and humans is associated with ending of anorectic effects within 24 h.

CCK-1 receptors are expressed in the pancreas as well as in some sites of the brain (Hill and Woodruff 1990), while CCK-2 receptors are present in the gastrointestinal tract and are widely distributed throughout the brain (Hill and Woodruff 1990).

Otsuka Long-Evans Tokushima fatty (OLETF) rats, a model of congenital CCK1 receptor deficiency, develop hyperphagia and obesity (Takiguchi et al. 1997). In contrast, CCK1 receptor knockout (KO) mice are not hyperphagic or obese (Bi et al. 2004). These findings probably depend on the fact that in mice CCK2 receptors are predominant. In fact, $CCK2R^{(-/-)}$ mice develop obesity associated with hyperphagia (Clerc et al. 2007).

Few years ago, after the negative results, in terms of weight loss and cardiometabolic risk markers, of a 6-month phase II trial in 701 obese subjects using the selective CCK-A agonist GI181771X, GlaxoSmithKline terminated the development of this drug (West et al. 2008). However, interestingly, CCK shows a synergic satiation action with leptin enhancing weight reduction at least in experimental animals. Therefore, a combination of leptin and CCK might represent a promising pharmaceutical approach to obesity.

Studies investigating the changes in CCK levels after bariatric surgery are few and controversial. Rubino et al. (2004) did not find significant changes of CCK levels in the bloodstream after Roux-en-Y gastric bypass (RYGB). In another study, in contrast, RYGB patients had four time higher plasma CCK concentrations after a test meal than weight-matched control subjects (De Giorgi et al. 2015). In rats which underwent RYGB or sham operation, no difference in CCK circulating levels was found (Suzuki et al. 2005).

GLP1

Glucagon-like peptide-1 (GLP-1) is secreted by the enteroendocrine L cells distributed throughout the entire intestine but with a higher density in the ileum and colon (Gibbs et al. 1973; Jordan et al. 2008). It derives from proglucagon that is cleaved by the prohormone convertase 1/3 (PC1/3) (Fig. 2). In L cells, GLP1colocalizes with oxyntomodulin and peptide YY (PYY).

For the first time in 1987, Kreyman et al. (1987) found gut GLP-1 7–36-like immunoreactivity in humans and showed that GLP1 infusion enhanced insulin secretion. Similarly to glucose-dependent insulinotropic polypeptide (GIP), GLP1 is rapidly inactivated in the circulation by dipeptidyl peptidase-4 (DPP4).

GLP1 enhances insulin secretion and inhibits glucagon secretion; in addition, it stimulates β-cell proliferation and neogenesis, and inhibits β-cell apoptosis. Its inhibitory action on insulin secretion seems to be mediated by somatostatin (de Heer et al. 2008).

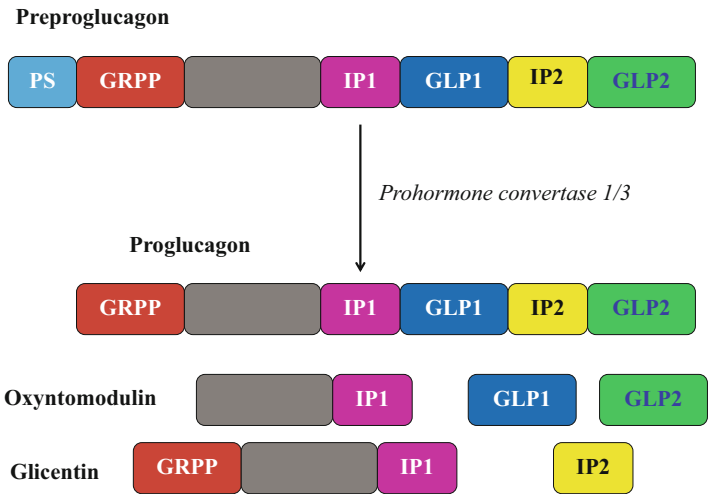

Fig. 2 Incretin synthesis pathway

Several reports show that GLP-1 reduces food intake in animals and humans, while blocking the GLP-1 receptor with exendin 9–39 determines hyperphagia in rodents (Williams et al. 2009).

The presence of GLP-1 receptors on neurons in the human hypothalamus, medulla, and parietal cortex has been recently demonstrated (Farr et al. 2016). Exenatide, an injectable GLP1 agonist, infusion increases activation in appetite- and reward-related brain areas in normoglycemic obese and in type 2 diabetic, obese subjects as compared with lean volunteers. Very recently, it has been shown that exenatide increases electrical activity of the dorsal raphe serotonin neurons (Anderberg et al. 2017).

Similarly to exenatide, liraglutide, another GLP1 agonist, decreases the activation of the parietal cortex in response to highly desirable visual food cues (Farr et al. 2016).

In a 56-week, double-blind trial involving 3731 patients with a BMI 38.3 $\pm$ 6.4 (Pi-Sunyer et al. 2015), 63.2% of the patients in the 3 mg once daily Liraglutide (commercial name, Saxenda) arm lost at least 5% of their baseline body weight as compared with 27.1% in the placebo arm ($P < 0.001$), while 33.1% and 10.6%, in the two groups respectively, lost more than 10% of their basal body weight ($P < 0.001$). The mid-term (3 years) results of this RCT in terms of transition from prediabetes to diabetes, published in February 2017 (le Roux et al. 2017), showed that 2% of the patients in the 3 mg daily liraglutide group progressed to diabetes versus 6% in the placebo group; the weight loss difference between liraglutide and placebo was −4.6 kg (95% confidence interval − 5.3 to 3.9 kg, $P < 0.0001$) with 49.6% of patients who lost $\geq$5 kg, 24.8% who lost $\geq$10 kg, and 11% who lost $\geq$15 kg in the liraglutide arm.

Oxyntomodulin

Preproglucagon is a polypeptide containing 179 amino acids; its fraction near the N-terminal contains glicentin while its fraction close to the C-terminal is the major proglucagon fragment (MPGF) (see Fig. 2). The latter contains GLP1 and GLP2. While in the pancreatic α-cells it is processed to the 29 amino acid glucagon and MPGF, in the intestinal L cells it forms glicentin, GLP1, GLP2, and oxyntomodulin (Fig. 2).

In experimental animals, oxyntomodulin injection reduces food intake and increases energy expenditure while its chronic administration reduces body weight gain (Wynne et al. 2005). Oxyntomodulin infusion for 4 weeks in humans reduces meal size by at least one-fourth, while its chronic administration determines a 0.5 kg/week average weight loss higher than with placebo (Brown and Pederson 1970).

It has been shown that oxyntomodulin binds the GLP1 receptor, although with an affinity 100 times lower than that of GLP1 itself (Wynne et al. 2005). Its action is at least partially mediated by GLP1 receptors; in fact, it does not modify appetite in GLP1 receptor knockout mice (Brown et al. 1970), and exendin 9–39, an antagonist of GLP1 receptor, blocks the effects of oxyntomodulin (Wynne et al. 2005). However, oxyntomodulin elicits anorexia in equimolar dose as GLP1 suggesting that it has a direct effect other than that mediated by its GLP1-R agonist action (Wynne et al. 2005). A possible direct action is that on the ventromedial hypothalamic satiety center (Wynne et al. 2005).

Oxyntomodulin linked at its N-terminus to a linear polyethylene glycol (PEG) chain is under study with the name of MOD-6031. Contrary to oxyntomodulin which has a very short half-life, MOD-6031 is a long-acting GLP-1/glucagon dual receptor agonist under development by OPKO Health Inc.

Gastric Inhibitory Peptide

Scientists noted that some nutrients, in particular fat, inhibit gastric acid secretion in a mechanism of negative feedback. In 1969, John Brown and Raymond Pederson (1970) published a paper in which two preparation of CCK, purified at 10% or 40% on the basis of gallbladder-stimulating potency, were studied on in vivo denervated stomach preparations of dogs. 40% purified CCK was more effective than 10% in stimulating gastric acid secretion suggesting that a gastric stimulant hormone was removed. In 1970, at the Karolinska Institute in Stockholm, Sweden, Brown et al. (1970) isolated the gastric inhibitory peptide (GIP) whose sequence was identified the following year. Later on, it was shown that the infusion of GIP during an oral glucose tolerance test potentiated insulin secretion. Indeed, the action of GIP on β-cells was found to be glucose dependent, a characteristic of the incretin action (Pederson and Brown 1976). Both GIP and GLP1 concur to the incretin effect, which is the much larger insulin secretion driven by an oral as compared with an intravenous glucose administration.

Similarly to GLP1, GIP is degraded by the enzyme DPP4. GIP, however, covers also a relevant action on modulating insulin sensitivity. In fact, genetic knockout of the GIP receptor protects from obesity-related diabetes (Miyawaki et al. 2002). Furthermore, chronic administration of (Pro^3GIP), a specific and stable GIP receptor antagonist, can prevent or reverse many of the established metabolic alterations, including insulin resistance associated to type 2 diabetes (Gault et al. 2002).

Peptides from the Pancreatic Polypeptide Family

The pancreatic polypeptide family includes the pancreatic peptide (PP), the peptide YY (PYY), and the neuropeptide Y (NPY).

PYY is cosecreted with GLP1 by endocrine L-cells. Circulating levels of PYY peak within 2 h of eating and are proportional to meal size and composition, with proteins having a stronger stimulating action than fat and carbohydrates, and fat larger that carbohydrates (Hill et al. 2011). PYY is an antilipolytic hormone as shown by Labelle et al. (1997).

The PYY response to meal ingestion is attenuated in obese subjects (Brownley et al. 2010).

PYY binds and activates at least three different G-protein-coupled receptor subtypes (Y_1, Y_2, Y_3, Y_4, and Y_5) dislocated in the brain, the subtype Y_5 is particularly expressed in the hypothalamus.

NPY is a 36 amino acid peptide with an anorexic action. It binds to Y_1 receptor that mediates its antilipolytic effect in the adipose tissue (Reichmann and Holzer 2016) and it is cleaved by dipeptidyl peptidase IV forming $NPY_{3–36}$ that can bind to the receptor Y_5 (Reichmann and Holzer 2016).

$PYY_{3–36}$ infusion reduces food intake in lean and obese individuals and decreases ghrelin levels in the bloodstream (Batterham et al. 2003).

PP acts by reducing food intake and delaying gastric empting; it is possible that PP transmits satiety signals to the satiety center via the vagus nerve (Wang et al. 2008). In fact, vagotomy reduces PP's satiation effects (Wang et al. 2008). Stomach distention during eating stimulates stretch receptors connected with vagal fibers. Therefore, PP can act by reducing gastric emptying and thus stimulating stretch receptors and vagal fibers, and also directly through PP receptors on the vagal afferents signaling to hypothalamus satiety center (Wang et al. 2008).

Amylin

In 1900, Opie described a hyaline degeneration of the Langerhans islets (Opie 1900) which later was recognized as a typical feature of type 2 diabetes and identified to be an accumulation of aggregates of fibrillar islet amyloid polypeptide (IAPP) or amylin.

Amylin, a member of the peptide calcitonin family, is mainly expressed by the pancreatic β-cells where it is stored together with insulin in 1:100 molar proportions,

but its expression has been also evidenced in the gut as well as in the hypothalamus and basal ganglia (Westermark et al. 2011).

Amylin is excreted in the urine but it is also degraded by the insulin degrading enzyme (IDE) (Gebre-Medhin et al. 1998); in fact, the in vitro addition of the IDE inhibitor bacitracin impairs amylin degradation. Another enzyme able to catabolize amylin is a type II zinc-containing metallo-protease known as neprilysin, which is mainly located in the β-cells (Gebre-Medhin et al. 1998).

Amylin has an action opposite to insulin; in fact, it inhibits insulin-mediated glucose uptake and glycogen synthesis in rat skeletal muscle. However, this effect is obtained with supraphysiological concentrations; thus, amylin cannot be considered as the hormone responsible of insulin resistance.

Amylin knock-out mice have an enhanced insulin response and a rapider plasma glucose clearance than wild-type controls (Gebre-Medhin et al. 1998). Amylin inhibits gastric emptying acting centrally in the brain (Gebre-Medhin et al. 1998).

Gastric bypass was not associated with amylin changes in nondiabetic patients (Jacobsen et al. 2012).

Leptin

Leptin is a 167 kDa polypeptide secreted by the adipocytes; it was discovered in 1994 by the Friedman's team (Zhang et al. 1994). Until now six different leptin receptors (ObR) have been identified, although ObR_b is considered to be the main functional receptor of leptin (Thon et al. 2016) and it is highly expressed in the hypothalamus.

In the central nervous system, leptin inhibits NPY/AgRP neurons and activates pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART) neurons located in the arcuate nucleus (Thon et al. 2016), thus inducing satiety.

Through its receptor ObR_b, which belongs to the class I cytokine receptor family, leptin activates Janus kinase signal transducer and activator of transcription (JAK-STAT), the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways (Thon et al. 2016).

Leptin regulates the autonomic nervous system circadian command mechanism. In fact, it is also secreted by the stomach (Liu et al. 2015) being stimulated by gastric wall distension and intragastric nutrients as well as by the CCK level raise. It potentiates the satiating effects of CCK and GLP1. Gastric overstretching, which is promoted by large and repeated meal ingestion, decreases leptin secretion, and this mechanism of action has been advocated in the reduced satiation of obese subjects (Mingrone et al. 2005). Adipose tissue leptin secretion contributes to signal to the satiety brain regions; in fact, feeding enhances leptin secretion from adipocytes (Thon et al. 2016).

Leptin counteracts the lipogenic and anabolic action of insulin and reduces fat ectopic deposition in the liver, skeletal muscle, and pancreas. Through the

sympathetic nerve system, it stimulates diet-induced thermogenesis by enhancing uncoupling protein (UCP1) gene expression in the brown adipose tissue (Thon et al. 2016).

As far as body weight increases during overeating, subjects become leptin resistant. In the leptin-resistant state, there is an excess of the suppressor of cytokine signaling 3 (SOCS3), which downregulates STAT3 (Mori et al. 2004) and thus reduces the effect of leptin on satiety. In fact, SOCS3-deficient mice show increased leptin-induced STAT3 phosphorylation in the hypothalamus. Protein tyrosine phosphatase 1B (PTP1B) inhibits leptin signaling by dephosphorylating JAK2. Adipose tissue PTP1B knockout mice increase body weight, while neuronal $Ptpn1^{(-/-)}$ mice are hypersensitive to leptin (Bence et al. 2006).

Leptin ultradian rhythm was studied before and after a malabsorptive type of bariatric surgery, biliopancreatic diversion (BPD), showing that the maximum leptin diurnal variation, i.e., the acrophase, decreased (10.27 ± 1.70 vs. 22.60 ± 2.79 ng $\cdot$ ml^{-1}; $P = 0.001$), while its pulsatility index increased (1.084 ± 0.005 vs. 1.050 ± 0.004 ng $\cdot$ $ml^{-1} \cdot min^{-1}$; $P = 0.02$) (Mingrone et al. 2005). Leptin changes negatively correlated with the changes of insulin sensitivity. It was suggested that insulin resistance reversion that follows BPD might allow reversal of leptin resistance and restoration of leptin pulsatility, thus increasing satiety (Mingrone et al. 2005).

Drugs improving leptin resistance have been proven to reduce body weight at least in rodents under a high fat diet and to lower hepatic fat deposition. Among these molecules, there are celastrol, a pentacyclic triterpene extracted from the roots of *Tripterygium Wilfordii* (thunder god vine) plant (Liu et al. 2015), and withaferin A that were shown to reverse leptin resistance in mice and to ameliorate the metabolic features linked with obesity.

Ghrelin

Ghrelin is a 28 amino acids acylated peptide mainly produced in the stomach and named after its ability to stimulate the secretion of growth hormone (GH). It is the only known orexigenic hormone; in other words, it stimulates food intake and is, therefore, associated with weight gain.

The binding of octanoic acid to the gherlin's serine 3 residue in its N-terminal confers to this hormone the capacity to bind its receptor, the GH secretagogue receptor 1 (GHSR1). This active form of ghrelin is promptly degraded to desacyl-ghrelin; in fact, the half-life of the acyl-ghrelin is only 10 min. Ghrelin circulates also bound to the immunoglobulins (IgG); in fact, ghrelin-reactive IgG are natural autoantibodies (Takagi et al. 2013) and protect ghrelin from acyl degradation.

In humans, ghrelin levels rise before a meal and fall after food intake. In addition, food proteins have a larger inhibitory effect than carbohydrates and fat on ghrelin secretion.

Ghrelin stimulates the dopaminergic regions of the limbic system, but it acts also on the amygdale and the orbitofrontal cortex, two brain regions that control eating

behavior addressing food choice toward high density energy, fat-rich food. Conversely, visual stimuli of hedonic foods stimulate ghrelin secretion.

Ghrelin, directly or through the vagus nerve, stimulates the neurons of the arcuate nucleus, which secrete NPY and AgRP, and inhibits the anorexigenic neurons secreting pro-opiomelanocortin and α-melanocyte-stimulating hormone.

The effect of ghrelin on appetite is larger in obese than in normal weight subjects. Nevertheless, total ghrelin plasma concentrations were found to be low and acyl-ghrelin to be normal in obese individuals, thus excluding a causative role of ghrelin in the pathogenesis of obesity. However, IgG seem to protect more ghrelin from degradation in ob/ob mice and in Zucker rats than in normal rodents, thus permitting the circulation of its active form in higher amounts.

Acylated ghrelin has also a strong gastric effect in increasing gastric secretion and motility.

Weight loss induced by dieting is associated with an increased ghrelin secretion, while gastric bypass dampens ghrelin secretion possibly contributing to the large weight reduction and marked appetite suppression observed after this kind of bariatric operation (Cummings et al. 2002). In contrast, after biliopancreatic diversion, a malabsorptive type of bariatric surgery that leads to massive lipid malabsorption and weight reduction without appetite changes, 24 h circulating ghrelin levels were unmodified from before surgery but its ultradian rhythm was disrupted (Mingrone et al. 2006). It is likely, therefore, that ghrelin secretion reduction after gastric bypass can contribute to the appetite reduction and weight loss observed after this type of bariatric surgery, while the weight loss observed after biliopancreatic diversion might be mainly driven by its associated massive lipid malabsorption.

Mechanisms Stimulating Gut Hormone Secretion

After food ingestion, its gastric presence is detected by vagal afferent fibers in the mucosa sensitive to mechanical touch, while the stretching of the gastric muscle layer due to stomach distention is sensed by vagal afferents in the external gastric musculature. The vagus nerve mediates the effects of many gut-satiating hormones which can however act also directly on the brain by stimulating the satiety center. In addition, enteroendocrine cells possess chemosensors, which belong to the family of G-protein-coupled receptor, that determine sweet (T1R) and bitter (T2R) taste in the mouth, as well as their common G-protein, α-gustducin (Mace et al. 2007).

In the rat jejunum, T1Rs regulate glucose uptake mediated by the sodium glucose cotransporter SGLT1. TIR2 and TIR3 have been found in entero-endocrine cells producing GLP1 and those producing GIP; while α-gustducin colocalize with PYY (Jang et al. 2007).

Food fats exert a potent satiating effect by stimulating the release of satiating hormones, including PYY, CCK, GLP1, and oxyntomodulin. However, fatty acids need to have a chain length longer than 12 carbon atoms and they act trough the binding to the GPR120 receptor (Hirasawa et al. 2005).

Interestingly, GLP1 producer L cells express receptors for leptin and insulin, the two long-acting adiposity hormones that control body weight, that stimulate GLP1 secretion. However, also L cells are subject to the phenomenon of leptin and insulin resistance.

Conclusion

The gastrointestinal tract communicates with the brain via the rich vagal mechanosensory innervation and by releasing entero-hormones to modulate appetite and satiety.

Efforts have been and are currently made by scientists to better characterize the molecular basis of the transduction cascades leading to gut hormone secretion, at both transcriptional and posttranscriptional level.

In addition, a better characterization of the nutrients stimulating satiety hormone synthesis and release is needed to choose those dietary nutrients with highest satiating effects and to design new drugs that reduce appetite and, thus, induce a long-lasting weight loss.

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