Regulation of Appetite, Satiation, and Body Weight by Enteroendocrine Cells. Part 1: Characteristics of Enteroendocrine Cells and Their Capability of Weight Regulation

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Key Words

Enteroendocrine cells · Satiation · Appetite · Obesity · Taste receptors · Macronutrients

Abstract

The gastrointestinal tract is the gateway for food in our body. Food ingestion and the ensuing digestive processes depend on the composition and amount of ingested nutrients. This complex process of nutrient digestion and absorption is effectively regulated by the enteroendocrine system. Enteroendocrine cells (EECs) reside scattered throughout the intestinal epithelium. They express nutrient receptors that face the lumen and secrete peptide hormones in response to food. Besides regulating digestion, gastrointestinal endocrine cells are involved in the regulation of appetite and satiety. The first part of this review describes the anatomical and biological characteristics of EECs and discusses the capability of their hormones to influence appetite, satiety, and body weight. In the second part, we then discuss the therapeutic potential of EECs in the treatment of obesity.

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Introduction

The gut plays a key role in the regulation of food intake in order to achieve efficient nutrient digestion and absorption. The perception of appetite and/or hunger leads us to eat, whereas gastric distension limits the extent of food intake and evokes the feeling of fullness, which is mainly mediated via vagal afferent stimulation. Interestingly, meals are typically stopped long before the gut capacity is reached [1]. Ingested food causes satiation not only by gastric distension but also by hormone secretion from enteroendocrine cells (EECs). The first studies of these secreted factors focused on the direct regulation of gastrointestinal (GI) function, such as secretin function on pancreatic secretion [2], cholecystokinin (CCK) on gallbladder contraction [3], and gastrin on gastric release [4]. The influence of CCK on appetite regulation was dis-

No grants or fellowships were received for the writing of this review; the authors have nothing to disclose.

Fig. 1. Intestinal epithelial cell types. Intestinal epithelial cells develop from common stem cells in the crypt and differentiate into absorptive enterocytes, or secretory Paneth, goblet, tuft, and enteroendocrine cells. Upon differentiation, all but the Paneth cells migrate towards the villus tip. EECs migrate slowly in contrast to enterocytes or goblet cells. They are found scattered along the intestinal tract and release their granules upon luminal stimulation from their base. Adapted from Moran-Ramos et al. [88].

covered in 1973 [5] and prepared the ground for many other studies demonstrating that gut hormones signal the central nervous system to regulate meal initiation and termination on one hand and energy expenditure on the other [6]. The gut-brain axis is illustrated in the context of obesity treatment in part 2 of our review; here we focus on the capability of EECs and their hormones to influence body weight.

EEC Development, Anatomy, and Biology

The gut is one of the largest hormone-producing organs in the human body in terms of the number of endocrine cells present as well as numbers of hormones produced.

The enteroendocrine system of the GI tract produces more than 20 hormones, but represent only ~1% of the intestinal epithelial cell population. EECs are scattered

throughout the GI tract between absorptive enterocytes, opioid-releasing tuft cells, and secretory goblet and Paneth cells (fig. 1) [7]. EECs are terminally differentiated cells that arise from pluripotent intestinal crypt stem cells (fig. 1) under the control of three basic helix loop helix transcription factors, Math1, neurogenin 3 (NGN3), and neurogenic differentiation 1 [8–10]; however, relatively little is known about the segregation into the different cell lineages.

There are at least 15 EEC subtypes and most of them display a characteristic distribution pattern within the GI tract as summarized in table 1. Upon activation they release the content of their basal storage organelles, which can stimulate afferent nerves or nearby cells in a paracrine fashion or enter the bloodstream as classical hormones (fig. 2) [11]. Initially, EECs were defined and named according to their morphology or the secreted peptide hormone, e.g. G cells secrete gastrin. It is nowadays well known that EECs can secrete more than one hormone, e.g. L cells produce glucagon-like peptide-1 (GLP-1), GLP-2, peptide YY (PYY), oxyntomodulin (OXM), and glicentin. Most EECs reach the lumen with their apical domain exhibiting microvilli and are called ‘open type’. In contrast, ‘closed-type’ EECs are separated by epithelial tight junctions (e.g. histamine-producing ECL cells). Over the past few years it became evident that the ‘open-type’ EECs act as sensors for the composition of the intestinal luminal content and regulate the secretion of gut peptides accordingly. This mechanism was already known, having been published in 1902 by Bayliss and Starling [2]. They demonstrated that duodenal acidification induced secretion of pancreatic digestive fluid via the release of the gut hormone secretin [2, 12]. In addition to a chemical trigger, EECs react on physical stimuli, e.g. distension of the gut, with serotonin (5-HT) secretion [13]. More recently, different nutrient receptors such as sodium-dependent glucose transporter 1 (SGLT1), G protein-coupled receptors (GPR), and others have been identified on EECs that trigger hormone release. EECs express two unrelated GPR families: the T1R and T2R receptor families [14]. The three T1R subtypes heterodimerize to sense sweetness (T1R2 and T1R3) and amino acids (T1R1 and T1R3), whereas the T2R family consisting of 25 subtypes act as bitter sensors and interact with the small G protein α -gustducin [14–17]. Other GPRs such as the long-chain fatty acid receptors FFA1 (GPR40) and GPR120, or the bile acid receptor GPR131, are exclusively expressed on EECs; others, e.g. the short-chain fatty acid receptor FFA3 (GPR41), are also expressed in adipose and pancreatic tissue (fig. 2) [18–20]. In addition,

Table 1. Summary of EEC subsets and their main localization, hormone secretion, function, stimuli and chemosensors in humans

Cell type	Main localization	Secretion products	Principal effects	Main stimuli	Luminal receptors
G cells	Pyloric antrum Duodenum	Gastrin	Stimulation of acid secretion, production of pepsinogen	Expansion of the stomach, alcohol, caffeine, protein Inhibition by somatostatin, secretin, GIP, NT, low pH	CaSR, GPRC6A LPAR5
P/D ₁ -like cells	Stomach	Ghrelin Obestatin Nesfatin-1	Stimulation of food intake, long-term body weight control Reduce food intake and body weight? Reduce food intake, body weight/induce insulin secretion	Fasting/inhibition: carbohydrates and lipids (LCFA)	T1R1–T1R3, T2Rs
D cells	Stomach, intestine	Somatostatin	Inhibition of GI hormone (e.g. gastrin) release, biliary secretion and exocrine function of the gut and pancreas, modulation of insulin release pancreas		CaR, GPRC6A LPAR5
I cells	Proximal small intestine	CCK	Activation of gallbladder contraction, pancreatic enzyme secretion Inhibition of food intake	Lipids, especially LCFA, not MCT, hydrolyzed protein (amino acids)	α-Gustducin, T2Rs FFA1, CaSR, LPAR5 PepT1
S cells	Duodenum	Secretin	Stimulation of pancreatic bicarbonate secretion, inhibition of gastric acid secretion, colonic contraction and motility, trigger insulin secretion	Low duodenal pH Digested proteins	Acid receptor
M cells	Proximal small intestine	Motilin	Enhancement of gut motility	Lipids, gastric distension, bile acids, low pH in the duodenum, neuronal nerves, serotonin	Bile receptors
K cells	Proximal small intestine	GIP Xenin	Enhancement of insulin secretion inhibition of gastric emptying and gastric acid secretion, reduction of LPL activity in adipose tissue Glucose homeostasis, reduction in food intake	Carbohydrates, fatty acids, proteins (certain amino acids)	α-Gustducin SGLT1, FFA1, GRP120, GRP119
N cells	Distal small intestine	NT	Stimulation of gastric acid, biliary and pancreatic secretion, inhibit gastric and intestinal motility Stimulate intestinal mucosal growth, reduce food intake?	Lipids	FFA1, FFA2, FFA3
L cells	Distal small intestine and large intestine	GLP-1 GLP-2 Glicentin PYY OXM	Reduction in gastric acid secretion and gastric emptying, decelerate ileal transit; induction of pancreatic cell proliferation, insulin transcription and GIP secretion; suppression of glucagon secretion; reduction in food intake Increase in mucosal growth, hexose transport; inhibition of food intake Increase in mucosal growth; inhibition of gastric emptying Reduction in gastric emptying, intestinal transit, food intake and appetite; increase in water and electrolyte absorption Enhancement of insulin secretion, induction of weight loss and energy expenditure	Carbohydrates (especially monosaccharides) and lipids (MCFA/LCFA), exercise Bile acids Lipids (LCFA, not MCT) > protein Low-carbohydrate diet Lipids	T1R2/T1R3; T2Rs GPR120, LPAR5 GPR131 α-Gustducin FFA2 FFA3 GPR119
EC cells	Stomach, small and large intestine	5-HT	Increase in gastric and pancreatic secretion and intestinal motility, accelerate intestinal transit, regulate appetite Insulin release	Chemical (pH), mechanical, neural stimulation SCFA, glucose intake, gastrin	FFA2, FFA3, TLR, TRPA1, toxin R

EEC types may have subgroups and contain different combinations of secretion products along the intestine, e.g., I and L cells may contain 5-HT. CaSR = Calcium-sensing receptor; FA = fatty acid; FFAR = fatty acid receptors; LPAR = lysophosphatidic acid receptor; TLR = Toll-like receptor; TRPA1 = transient receptor potential ankyrin 1; LCFA = long-chain fatty acid; SCFA = short-chain fatty acid; MCT = medium-chain triglyceride; LPL = lipoprotein-lipase.

Fig. 2. Luminal stimulation of EEC hormone release. Luminal contents stimulate EECs (violet) via their taste receptors. These receptors are mainly located at the apical domain, but are also found at the lateral membrane of EECs (indicated by the red serpentine symbol) and sense bile acids, protein components, sugar, and lipids via, for example, calcium-sensing receptors (CaSR), SGLT1, or GPRs (indicated by pink boxes). Taste receptors signal through α -gustducin. Altogether, this initiates a signaling cascade with elevation of intracellular cAMP and calcium (Ca^{2+}) or PLC β 2 activation, triggers membrane depolarization via TRPM5, and activates voltage-gated Ca^{2+} channels. Elevated intracellular Ca^{2+} is the primary trigger of exocytosis and the release of peptide hormones from the EEC base. The released gut hormones can act with neighboring cells in a paracrine fashion, stimulate neuronal cells, or act as classical hormones via the bloodstream. LCFA = Long-chain fatty acid; SCFA = short-chain fatty acid. Adapted and modified according to Engelstoft et al. [89].

the expression of the chemosensing machinery differs among EEC subtypes; therefore, a different gut peptide release is induced according to the dietary intake and composition. This emphasizes the impact of EECs as sensors of the gut luminal content and regulators of digestion, and suggests a major role in the regulation of appetite and satiety.

How EECs Regulate Appetite and Satiety

Historically, with the discovery of secretin in 1902 [2] gut endocrinology was the first field in endocrinology. The discovery of secretin was followed by John Edkins' finding of gastrin in 1905 [4], after which Ivy and Oldberg

[3] described CCK in 1928 as a stimulant of the gallbladder [21]. The anatomical dissemination and the variety of EEC subsets hampered research for many years. In the following section we focus on the interactions of EEC subtypes towards nutrients and the physiological consequences on appetite and intestinal satiation (table 1).

P/D₁-Like Cells: Acyl Ghrelin, Des-Acyl Ghrelin, Obestatin, and Nesfatin-1

P/D₁-like cells are distributed throughout the mucosal layer and account for 20% of the endocrine cell population in oxyntic glands [22]. Of note, in other species, such as rodents, these cells are termed X/A-like cells. They are

mainly located in the gastric fundus and have also been found in lower densities in the intestinal tract [22]. In the stomach they have a round shape without contact to the lumen. They release acyl ghrelin, des-acyl ghrelin, and obestatin, which are all encoded from the same gene, and in addition nesfatin-1. These hormones are involved in body weight homeostasis with a stimulatory role on food intake for acyl ghrelin and an inhibitory effect of des-acyl ghrelin and nesfatin-1 [23]. Thus P/D₁-like cells have the unique yin and yang properties to mediate opposed effects and may mediate hunger or satiety depending on the released hormones [23]. Of note, P/D₁-like cells store these peptide hormones in different vesicles.

The 28-amino-acid peptide ghrelin has a unique fatty acid modification on the third amino acid, which is essential for the binding to the ghrelin receptor. This acylation of the precursor proghrelin peptide is achieved by the enzyme ghrelin O-acyltransferase during posttranslational modification in P/D₁-like cells, but also later on in the plasma [24]. The ratio of acyl ghrelin and total ghrelin in the plasma varies between 1:5 and 1:19 [23]. Acyl ghrelin is the only known peripheral hunger-inducing hormone (orexin), which is released into the plasma during fasting. Short-term exogenous administration of acyl ghrelin effectively stimulates appetite and energy intake in humans [25, 26]. In addition, there is also evidence that it may stimulate gastric motility and emptying without inducing emesis [25]. Ingestion of monosaccharides and complex carbohydrates [27, 28], as well as long-chain fatty acids [29], reduces ghrelin expression, whereas protein stimulates ghrelin expression. However, after oral glucose tolerance testing there is no significant reduction of acyl ghrelin in obese children compared to lean children [30]. Distension of the stomach is not sufficient to regulate ghrelin response, but postgastric feedback via glucose-dependent insulinotropic peptide (GIP) influences ghrelin secretion [27].

Obestatin is a 23-amino-acid peptide and an alternative splicing product of proghrelin. In contrast to ghrelin, obestatin has anorexigenic effects and reduces gastric emptying [31]. The gastric peptide content and the plasma level of obestatin does not seem to be regulated by the metabolic state [23, 31, 32]. However, obestatin increased significantly during weight reduction in an intervention program [33], and after bypass surgery obestatin levels remained stable while the ratio of ghrelin and obestatin decreased [32].

The 82-amino-acid peptide nucleobindin-2/nesfatin-1 was described as an inhibitor of food intake. Repeated administrations reduced weight gain along with a reduction in fat mass [23]. There is also evidence that it

decreases dark-phase feeding by inducing satiety and satiety [34].

Obese humans have lower ghrelin levels compared to lean individuals [35]. In addition, obese patients have higher ghrelin O-acyltransferase protein levels in the plasma compared to normal-weight controls [24], thereby maintaining the unfavorable situation of obesity. Recent data provide evidence for a differential regulation of P/D₁-like cell hormones to counteract further body weight increase. Nesfatin-1 expression increases in obese patients with rising BMI, while acyl ghrelin expression decreases in P/D₁-like cells [36]. Thus, there are significant findings indicating that P/D₁-like cells are involved in the regulation of hunger, satiety, and body weight regulation.

I Cells: CCK

The triangular-shaped I cells are opened towards the intestinal lumen and contain in their basal-located granules the 27-amino-acid polypeptide CCK [37]. I cells reside in the duodenal and jejunal mucosa. Intestinal CCK secretion is stimulated in response to fat- and protein-containing meals. In order to facilitate nutrient digestion, CCK inhibits gastric emptying, reduces gastric acid secretion, and stimulates gallbladder contraction as well as pancreatic enzyme secretion. CCK was the first anorexigen gut hormone [21] shown to modulate appetite in humans. In accordance, exogenous administration of CCK decreases meal size in a dose-dependent manner, which is even more efficient in a distended stomach [38, 39]. However, this effect is only temporary as CCK is rapidly degraded with an approximately 13-min half-life in human plasma.

I cells secrete CCK in response to fat, especially fatty acids, and the secretion critically depends on fatty acid length. I cells detect long-chain fatty acids via FFA1 (GPR40) [40], while medium-chain triglycerides do not activate I cells. Protein in general, specifically hydrolyzed proteins and amino acids are strong inducers of CCK release in I cells via calcium-sensing receptors [41]. In contrast, I cells barely respond towards carbohydrates and the sensing mechanism is not yet known [42].

Pancreatic lipase insufficiency is associated with a poor CCK response to triglycerides, explaining at least in part the increased appetite and food ingestion in humans suffering from pancreatic lipase insufficiency [43].

L Cells: PYY, GLP-1, GLP-2, OXM, and Glicentin

L cells are open-type intestinal cells found scattered mainly in the distal ileum and colon. They received their name due to their L shape with a long extending base; however, in the colon they have a spindle- or sigmoidal-like form. Like I cells, they express fatty acid receptors. They synthesize a large precursor protein known as preproglucagon, which is processed into glucagon, GLP-1, GLP-2, OXM, and glicentin. In addition, L cells synthesize PYY. All five hormones induce an 'ileal break' by inhibiting gastric emptying and decelerating ileal transit, thereby decreasing food intake and preventing malabsorption and postprandial metabolic disturbances. In addition, GLP-1 and OXM are released after a meal and play a role in distal intestinal satiety signaling.

PYY is secreted as a 36-amino-acid peptide, which is enzymatically truncated by dipeptidyl peptidase-4 into PYY₃₋₃₆ [44]. Full-length PYY₁₋₃₆ reduces gastric emptying and, similar to GLP-2, induces an ileal break by increasing GI transit time and facilitates nutrient absorption in the small intestine [44]. PYY₃₋₃₆ is the major form released from L cells in proportion to caloric intake, and possess anorexigenic properties by reducing food intake and appetite [44–46]. Interestingly, endogenous PYY responses are reduced during oral glucose testing in obese children and after standard test meals in adults compared to normal-weight subjects [30, 47]. Moreover, double the caloric meal content is required in obese subjects to achieve equivalent PYY levels observed in normal-weight subjects [47]. Thus, impaired PYY release may relate to reduced satiety in obese subjects and contribute in the pathogenesis of obesity. PYY₃₋₃₆ selectively binds with high affinity to the neuropeptide Y subtype 2 receptor located in the arcuate nucleus in the brain and on the vagus nerve [48]. Exogenous infusion of an active PYY₃₋₃₆ peptide reduces food intake in normal-weight and obese humans [35, 45]. In addition, PYY infusion lowers ghrelin levels during and 3 h after infusion of PYY [45]. PYY₃₋₃₆ levels increase within 30 min after a meal and remain elevated for up to 6 h [45]. The sustained PYY secretion is supposed to be mediated by luminal stimulation of L cells. In accordance, carbohydrates, long-chain fatty acids, and especially protein-rich diets stimulate PYY release and in turn slow down gastric emptying [29, 49]. In particular, PYY₃₋₃₆ has more of an effect on food intake for the subsequent 12 h than the postprandial reduction in food intake [46]. Indeed, circulating levels of PYY are reduced in obesity and may support increased food intake [45, 50]. In addition, PYY levels decrease during midpuberty in

both genders, which correlates inversely with the growth hormone levels and may stimulate food intake to promote pubertal growth [51].

In 1985 the potent insulinotropic actions of the 30-amino acid peptide GLP-1 were first described [52]. Gut hormones which amplify nutrient-induced insulin secretion in response to food intake such as GLP-1, are named incretin hormones [53]. GLP-1 induces pancreatic β -cell mass, increases transcription and secretion of insulin, and suppresses glucagon secretion, thereby contributing to glucose homeostasis [53]. In addition, it decelerates gastric emptying and acid secretion.

GLP-1 secretion and plasma levels increase after a meal according to the amount and composition of food intake [54]. In accordance, fat- or carbohydrate-containing meals strongly induce GLP-1 release [49], especially during weight loss [55], but is negatively correlated to BMI [54, 55]. Thus, a decrease in GLP-1 secretion may contribute to the development of obesity [54]. GLP-1 is also widely expressed in the human brain and acts directly on GLP-1 receptors in the brain [56]. It is clear that the central GLP-1 system is important in appetite regulation; however, its relation to food intake is unclear [57]. In fact, there is also evidence that peripheral GLP-1 directly activates areas of the brain and is implicated in satiation [58]. Indeed, peripheral GLP-1 administration exerts anorexigenic properties by enhancing the sensation of satiety and reduces food intake after an energy-fixed breakfast [59]. Furthermore, physical exercise leads to an increase in GLP-1 [60]. However, humoral GLP-1 is rapidly degraded by dipeptidyl peptidase-4 and very little peptide actually reaches the circulation (half-life: 1.5–5 min). Thus, GLP-1 released from L cells may stimulate peripheral GLP-1 receptors located on vagal sensor afferents before entering the capillaries or activate sensory neurons in the hepatoportal region and liver [56].

The 33-amino-acid peptide GLP-2 is co-secreted with GLP-1 from L cells in response to nutrient ingestion. Like GLP-1, it is also rapidly degraded by dipeptidyl peptidase-4 [61]. GLP-2 reduces gastric motility and acid secretion [61], increases hexose transport activity, and is supposed to inhibit food intake [62]. In addition, GLP-2 has specific trophic properties, e.g. it enhances intestinal epithelial barrier function [63] and promotes mucosal growth and cell survival [61]. Furthermore, GLP-2 is suggested to reduce ingestion and slow down the GI food transit to increase nutrient absorption in the small intestine.

Like GLP-1, the 37-amino-acid OXM is derived from a preproglucagon precursor and contains the 29-amino-acid sequence of glucagon. It was named OXM as it in-

hibits gastric acid secretion. OXM increases after calorie intake and reduces food intake and appetite in humans [64]. These effects are not surprising since OXM signals through the GLP-1 receptor. Chronic administration of OXM causes weight loss and increases energy expenditure [65].

Finally, glicentin, the largest molecule processed from proglucagon, consists of 69 amino acid residues. It is co-secreted from L cells, along with GLP-1, GLP-2, and OXM. Like OXM, it possesses the sequence of glucagon. The biological actions include insulin secretion, inhibition of gastric acid secretion, gastric emptying, and stimulation of mucosal enterocyte proliferation [66].

Taken together, hormones released by L cells induce intestinal satiation signals, increase GI-transit time, and reduce food intake and appetite.

K Cells: GIP

K cells are open-type EECs located along the intestinal tract with an increase in the duodenum-producing GIP and xenin [67, 68]. They may coexpress GLP-1 in the midintestine and are therefore also referred to as K/L or L/K cells.

As an incretin, GIP is responsible for glucose-induced insulin secretion, but not for food intake [69]. However, GIP receptor knockout mice are resistant to obesity [70]. GIP receptors are expressed in different tissues and may be responsible for the multifaceted effects of the 42-amino-acid peptide GIP. Its secretion is stimulated in a meal-dependent manner by fat and carbohydrates through the action of SGLT1, FFA1 (GPR40), GPR120, and GPR119 [71]. In particular, fatty acids are sensed by FFA1 (GPR40), GPR120, and GPR119 receptors on K cells. In addition, there is evidence that proteins also induce GIP secretion, especially certain amino acids. The density of K cells corresponds to the GIP plasma level and may increase under conditions of a high-fat diet. However, to avoid an inappropriate insulinotropic response, this effect depends on the parallel administration of fat and glucose [71]. Obesity is associated with elevated GIP levels and increased K cell secretory response in humans [72, 73]. Accordingly, GIP mediates anabolic effects in adipose tissue, including stimulation of glucose uptake and fatty acid synthesis and deposition [74, 75]. It represents a link between overnutrition and obesity as GIP receptor antagonism has reversed obesity and metabolic changes in high-fat-fed mice [76].

K cells also secrete a 25-amino-acid neurotensin (NT)-related peptide, called xenin, which is involved in glucose

homeostasis. Xenin-25 increases the insulinotropic response to GIP, but has no effect when administered alone [77]. Xenin is structurally similar to NT, which is a satiety factor [78]. Recent studies suggest that xenin reduces food intake through a leptin- and melanocortin-independent mechanism [79].

N Cells: NT

N cells are mainly found in the jejunum and ileum of the GI tract. They secrete NT composed of 13 amino acids in response to intraluminal lipids. The 13-amino-acid peptide NT stimulates pancreatic and biliary secretion, inhibits gastric and small intestinal motility, and enhances fatty acid transport [80]. In addition, NT is a growth factor for GI tissues, e.g. the pancreas, colon, and small bowel [81]. NT receptor 1 is expressed in the intestine and brain and mediates the metabolic effect of NT and xenin [82]. Thus, NT may have the potential to ameliorate obesity by reducing appetite.

D Cells: Somatostatin

D cells are distributed throughout the GI tract with the highest frequency in the duodenum. D cells in the large intestine have a spindle shape with a small apical process and a wider basal extension, and differ from the appearance in the stomach. The large secretory vesicles contain somatostatin-14 and -28. It is the major inhibitory hormone of the GI tract and decreases the release of GI hormones and exocrine functions of the GI tract and pancreas by binding to 1 of the 5 existing somatostatin receptors which are ubiquitously expressed with high expression levels in the GI tract, pancreas, and brain [76, 83].

EC Cells: 5-HT

EC cells are the most common EEC type and are distributed throughout the GI tract. They have a pyramid shape with a slender apical process reaching the luminal surface. Interestingly, they store most of the entire body's 5-HT content in their granules. EC cells secrete 5-HT predominantly after neural, but also after chemical, stimulation, e.g. short-chain fatty acids may release 5-HT. It may act in an autocrine and/or paracrine, endocrine, and neurocrine manner, and increases secretion and intestinal motility, accelerates the intestinal transit, and regulates

appetite. These effects are mediated by the 5-HT receptor family. Targeting 5-HT receptors may provide a suitable strategy to regulate appetite and ingestive behavior. Administration of a 5-HT_{2C} receptor agonist in mice increases anorectic pro-opiomelanocortin mRNA and reduces body weight, body fat ratio, and initial food intake [84]. However, mice lacking the melanocortin 4 receptor do not respond to a 5-HT_{2C} receptor agonist, indicating that melanocortins acting on the melanocortin 4 receptor are necessary to mediate the effect on food intake downstream of 5-HT_{2C} [84]. Of note, lorcaserin, a selective 5-HT_{2C} receptor agonist, which has recently been approved by the FDA for the therapy of obesity, induces weight loss in obese humans [85, 86].

S Cells: Secretin

S cells secrete secretin and reside in the duodenum and in smaller numbers also in the jejunum and small intestine [2]. The 27-amino-acid peptide secretin is secreted postprandially into the circulation and regulates pH in the duodenum by inhibiting gastric acid secretion, delaying gastric emptying, and stimulating bicarbonate fluid production from the pancreas and liver. Secretin is now considered a neurally active peptide that exhibits a role in appetite regulation and fatty acid metabolism because central and peripheral administration of secretin inhibits food intake in mice by stimulating the melanocortin system [87].

Conclusion

This review demonstrates that EECs take on a special position in sensing the luminal contents and being involved in the complex regulation of food intake, appetite, and satiation. The hormones released by EECs in response to physical and chemical stimuli like ghrelin, nesfatin-1, GIP, CCK, GLP-1, OXM, PYY, and even secretin influence not only gastric emptying and intestinal transit, the release of digestive enzymes, and pancreatic insulin secretion, but also appetite and satiety, thereby ultimately influencing body weight. Indeed, peripheral administration of gut hormones such as nesfatin-1, CCK, GLP-1, OXM, PYY, 5-HT, and secretin reduces food intake in humans. In addition, gut hormone secretion in response to food intake differs between obese and lean subjects. Accordingly, gut hormone levels are altered in obesity, e.g. ghrelin and PYY levels are reduced and GIP and nesfatin-1 levels are elevated and probably promote the unfavorable state of obesity. In part 2 of our review, we will discuss the potential of EECs and their hormones as targets for new treatment strategies.

Medline Search Strategy

Articles were searched using the following keywords: enteroendocrine cells, obesity, taste receptors, satiation, gastrointestinal hormones, microbiota, differentiation, etc.

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