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Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2019 February ; 26(1): 3–10. doi:10.1097/MED.0000000000000448.

Gastrointestinal Hormones and Regulation of Gastric Emptying

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Structured Abstract

Purpose of the Review: This review examines the hormonal regulation of gastric emptying, a topic of increasing relevance, given the fact that medications that are analogs of some of these hormones or act as agonists at the hormonal receptors, are used in clinical practice for optimizing metabolic control in the treatment of type 2 diabetes and in obesity.

Findings: The major effects on gastric emptying result from actions of incretins, particularly GIP, GLP-1 and PYY, the duodenal and pancreatic hormones, motilin, glucagon and amylin, and the gastric orexigenic hormones, ghrelin and motilin. All of these hormones delay gastric emptying, except for ghrelin and motilin which accelerate gastric emptying. These effects on gastric emptying parallel the effects of the hormones on satiation (by those retarding emptying) and increase appetite by those that accelerate emptying. Indeed, in addition to the effects of these hormones on hypothalamic appetite centers and glycemic control, there is evidence that some of their biological effects are mediated through actions on the stomach, particularly with the GLP-1 analogs or agonists used in treating obesity.

Summary: Effects of gastrointestinal hormones on gastric emptying are increasingly recognized as important mediators of satiation and postprandial glycemic control.

Keywords

GIP; GLP1; ghrelin; glucagon; PYY; ghrelin; motilin; CCK; glycemia

Introduction

The stomach also plays an important role in regulating the amount and rate of calories that cross the pylorus into the duodenum. Therefore, gastric emptying is a significant determinant of the rate at which simple carbohydrates appear in the portal circulation and subsequently the systemic circulation, since most carbohydrate is absorbed in the first 70cm of the small intestine due to abundant expression of high affinity transporters [1]. It is not surprising, therefore, that a number of hormones act as regulatory mechanisms predominantly involved in the retardation of gastric emptying, and those mechanisms are collectively termed “brakes”. The hormones from the upper gastrointestinal tract also have

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Conflicts of interest:

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important effects on hypothalamic appetite centers and glycemic control, which are not considered here.

This review examines the hormonal regulation of gastric emptying, a topic of increasing relevance, given the fact that medications that are analogs of some of these hormones, or act as agonists at the hormonal receptors, are used in clinical practice for optimizing metabolic control in the treatment of type 2 diabetes and obesity. The major effects on gastric emptying result from actions of incretins, particularly GIP, GLP-1 and PYY, and the gastric orexigenic hormone, ghrelin. Comprehensive reviews of the hormones topic have been published elsewhere and the reader is referred to those articles for additional details [2**,3*]. In addition, many of these hormones are being tested in combination as potential new treatments of obesity, as reviewed elsewhere [4*].

Gastric Emptying

The solid and liquid two phases of a meal differ significantly in their distribution within the stomach soon after ingestion. Liquids tend to distribute throughout the stomach from the time of ingestion, whereas solids are retained within the proximal stomach, which acts as a food reservoir, during the early postprandial period. After some time, solid food is transferred to the distal stomach (the antrum), which triturates solid food down to 1–2mm size through the liquid shearing forces that are established by high amplitude body and antral contractions that propel the food against the closed pylorus. When the food is triturated, it can pass through the pylorus; the physical nature, particle size, fat and caloric content of food alter the emptying rate [5]. The rate of liquid emptying is much more rapid (time taken to empty 50%, $T_{1/2}$ is ~20 minutes) compared to emptying of solids ($T_{1/2}$ is ~120 minutes) [6]. Non-nutrient liquids empty exponentially, but calorie-containing liquid meals empty more slowly, and homogenized or liquidized solids empty almost linearly from the stomach.

The time before solid food starts to empty from the stomach is called the lag phase and its duration depends on the physical nature and fat content of the meal; thereafter, emptying follows a linear emptying profile over a period of 3–4 hours [6], depending on the volume, consistency and fat content.

Increased caloric content (e.g., in experiments using different sucrose concentrations) delays emptying irrespective of the volume of test meal ingested [7]. The presence of fat, such as oleate, in the meal results in stimulation of cholecystokinin (CCK) secretion in the duodenum; in turn, this inhibits antral motility, stimulates pyloric tone and delays gastric emptying [8]. CCK is the first of a repertoire of hormones that regulate gastric emptying. The next section details the effects of several gastrointestinal and other hormones on gastric emptying.

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Hormonal Control of Gastric Emptying

Gastrin

Gastrin is secreted by the G cells in the gastric antrum and by the parietal cells of the fundus and body. It is responsible for a significant proportion of postprandial acid release through direct activation of CCK2 receptors on parietal cells and through release of histamine from enterochromaffin-like cells [9]. It does not appear that gastrin has a significant effect on gastric emptying rate, but the induction of acid secretion and increase in intragastric volume may result in a slight prolongation of emptying of all gastric content. These studies were based on MR imaging and use of pentagastrin [10]. In patients with autoimmune gastritis that results in reduction in G cells that produce gastrin in the stomach, gastric emptying is delayed [11], and there is some evidence of an indirect relationship with serum gastrin [12]. Conversely, patients with Zollinger–Ellison syndrome (which is characterized by hypergastrinemia) have normal gastric emptying rates [13].

Gastrin-Releasing Peptide

Gastrin-releasing peptide (GRP), a 14 amino acid peptide, is not a circulating hormone and is released from nerves to stimulate gastric G cells to secrete gastrin. The closely related molecular entity, bombesin, which is derived from the skin of an amphibian, *Bombina bombina*, is a 14 amino acid peptide with identical 10 amino acid sequence in the N terminal, inhibited gastric emptying in humans with i.v. infusion [14]. On the other hand, blockade of bombesin receptors resulted in inhibition of gastric emptying [15]. Hence, the effects of endogenous GRP on gastric emptying are unclear.

Cholecystokinin

Cholescystokinin (CCK) is released from the intestinal I cells in response to dietary lipid and protein through mechanisms involving the G-protein-coupled receptors, GPR40 and calcium-sensing receptors. In particular, fatty acids of at least 12 carbon chain length are the most potent stimuli of CCK secretion. CCK has a multitude of effects inhibiting gastrin secretion, gastrointestinal motility and gastric acid secretion [16]; most of these effects are mediated through activation of the primary target of CCK, that is, vagal afferent fibers. CCK also controls the expression of receptors and peptide neurotransmitters by these neurons; these actions are potentiated by leptin and inhibited by ghrelin [17]. CCK causes relaxation of the proximal stomach (increasing its capacitance) [18] and inhibition of gastric emptying as demonstrated by the acceleration of gastric emptying with the CCK antagonist, loxiglumide [19]. This slowing of gastric emptying involves inhibition of antral contractility and stimulation of pyloric contractions, which have been demonstrated with infusions of CCK-octapeptide [20] or intraduodenal infusions of lauric (12-carbon) and oleic (18-carbon) fatty acids [21].

Gastric Inhibitory Polypeptide / Glucose-Dependent Insulinotropic Polypeptide

Gastric inhibitory polypeptide (GIP), also called glucose-dependent insulinotropic polypeptide, is a peptide hormone secreted by K cells in the duodenum and proximal jejunum. It signals through a specific receptor (GIPR) and, in the last two years, the

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discovery of a competitive antagonist of GIP has facilitated understanding of the actions of GIP in humans, in addition to physiological effects inferred from transgenic mice lacking the receptor [22]. GIP levels rise with nutrient ingestion, inhibiting gastric acid secretion and emptying. In humans, these effects are observed with supraphysiological concentrations of GIP. GIP also stimulates insulin secretion in the setting of hyperglycemia; however, the secretory response to infused GIP is impaired in diabetes.

Alternating processing of the precursor protein, pro-GIP, results in endogenous production of GIP(1–30)NH2. With cleavage by DPP-4, the metabolite GIP(3–30)NH2, a high affinity antagonist of the human GIPR, effectively inhibits GIP-mediated insulin, glucagon, and somatostatin release [23], and antagonizes the physiological actions of GIP in glucose metabolism, subcutaneous abdominal adipose tissue blood flow, and lipid metabolism in humans [24*]. It has been proposed that, because of increased fasting and postprandial glucagon in patients with type 2 diabetes, which are aggravated by GIP, a GIPR antagonist could improve the fasting and postprandial glycemia [25]. However, experimental infusion studies in humans showed that this GIPR antagonist did not inhibit plasma glucagon levels [26**], and more research on glycemic effects and effects on gastric emptying and secretion are required. Such studies will provide more direct evidence of any role played by GIP in control of gastric functions such as emptying, accommodation and acid secretion.

Glucagon-Like Peptide-1

GLP-1 is secreted from L cells in the small intestine and colon through post-translational processing of proglucagon (which also gives rise to GLP-2 – a trophic factor for intestinal mucosa). GLP-1stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent fashion. It has prominent effects on stomach functions such as retarding gastric emptying of solids and increasing fasting and postprandial gastric volumes [27]. These effects are dependent on vagal function; for example, the postprandial effect of GLP-1 is not observed in diabetics with evidence of vagal neuropathy [28]. Studies using the GLP-1 receptor antagonist, exendin-(9–39), in humans suggest that gastric compliance and tone are modulated by physiologic concentrations of GLP-1 signaling through cholinergic circuits [29]. The effects of GLP-1 on gastric function are also supported by the observation that genetic variation in transcription factor 7-like 2 (TCF7L2), a regulator of proglucagon processing, was associated with reduced fasting gastric volume and accelerated gastric emptying of liquids [30].

The effects on gastric emptying are attributed to a decrease in gastrointestinal motility by GLP-1 [31], and this is mediated through stimulation of inhibitory nitrergic myenteric neurons [32] in addition to activation of vagal afferents [33], which inhibit reflex vagal motor pathways [34]. Interestingly, the sensitivity of the nitrergic myenteric neurons to GLP-1 was impaired in mice fed a high fat diet, and required the presence of gut microbiota [35**].

GLP-1 receptor blockade accelerated emptying [36] in otherwise healthy humans. The impact of GLP-1 on gastric emptying is also illustrated by the effects of treatment of obesity and metabolic syndrome in humans. Thus, exenatide, a GLP-1 receptor agonist, and liraglutide and semaglutide, GLP-1 analogs, significantly retard gastric emptying [37,38**,

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39], with evidence of some tachyphylaxis to the effects of liraglutide between 5 and 16 weeks of daily administration [38**]. In addition, after Roux-en-Y gastric bypass (RYGB), there is evidence that the (high) postprandial concentrations of GLP-1 delay gastrointestinal transit of solids [40].

Glucagon-Like Peptide-2

GLP-2 is synthesized by alternating splicing of pre-proglucagon. Although its most prominent effects are related to its trophic effects on intestinal mucosa, there is also some evidence from studies that it retards gastric emptying of liquids [41,42] in healthy subjects, and the GLP-2 agonist, teduglutide, reduced overall gastric and small bowel emptying in patients with short bowel syndrome [43]. GLP-2 also inhibits gastric acid secretion [44]. A novel pharmacological entity, a GLP-1/GLP-2 co-agonist, GUB09–123, significantly improved glycemic control and showed persistent effects on gastric emptying in diabetic mice, and the effects were superior to monotherapy with the GLP-1 analog, liraglutide [45].

Ghrelin

Effects of ghrelin, an orexigenic hormone, are extensively reviewed elsewhere [46]. Ghrelin can accelerate gastric emptying of liquids and solids [47] at pharmacological doses, although a dose of synthetic human ghrelin used to stimulate physiological growth hormone secretion did not seem to alter gastric motor functions (emptying or postprandial accommodation) [48]. The potential for stimulating gastric motility and accelerating gastric emptying with ghrelin receptor agonists is best illustrated by the effects of the pentapeptide ghrelin receptor agonist, relamorelin [49,50,51,52,53*].

Leptin and Gastric Leptin

Leptin is a product in adipose tissue of the obese (ob) gene, which is located on chromosome 7 in humans and acts through its receptor OB-R. The stomach is the major source of leptin in the gastrointestinal tract. Secretion of leptin occurs in various physiologic states, including fasting or refeeding after fasting, increasing in both the serum and gastric mucosa [54]. Leptin and the soluble isoform of its receptor are secreted by gastric chief (parietal) cells in the gastric mucosa, are stable in the gastric acidic environment, and reach the duodenum either protein-bound or free [55]. Leptin receptors are abundant in the gastrointestinal system, especially in the proximal part of the intestine. These receptors can be found on the luminal and basolateral borders of intestinal cells [56].

Leptin interacts with the vagus nerve and cholecystokinin to delay gastric emptying. Leptin deficiency increases the rate of gastric emptying [57]. In obese, hyperglycemic, hyperinsulinemic female mice with mutation of the leptin receptor ($Lepr^{db/db}$), gastric emptying was accelerated and gastric interstitial cells of Cajal (part of the pacemaker apparatus in the stomach) and phasic cholinergic responses were increased [58].

Leptin has been shown to decrease the expression and secretion of ghrelin from gastric mucosa. Leptin cells are adjacent to ghrelin cells in the gastric mucosa, surrounding ghrelin cells in the lower half of stomach, possibly providing a paracrine regulation of ghrelin

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secretion. Leptin's effect on gastrointestinal tract motility is also generally opposite that of ghrelin [59,60].

Glucagon

Glucagon is a 29AA peptide secreted from pancreatic α-cells. Its main function is to maintain blood glucose by activating gluconeogenesis and glycogenolysis. Its effects are transduced by a G-protein-coupled receptor. Binding sites for glucagon have been demonstrated in liver, intestinal smooth muscle, brain, fat, heart and pancreatic β cells. Glucagon is required during fetal development for the differentiation of pancreatic islet β cells [61]. Glucagon reduces food intake and body fat mass and alters body energy expenditure, in addition to decreasing meal size [62]. Glucagon retards gastric emptying of liquids and inhibits motility throughout the gastrointestinal tract [63].

Amylin

Amylin is a peptide hormone co-secreted with insulin by the β-cell. Consequently, amylin is deficient in type 1 diabetes, while plasma levels are increased in obesity, in impaired glucose tolerance, and in type 2 diabetes. A synthetic analog, pramlintide, delays gastric emptying through inhibition of vagal signaling in a dose-dependent fashion [64], and this retardation of gastric emptying is confirmed in patients with type 1 or 2 diabetes without neuropathy [65]. Delayed gastric emptying induced by pramlintide improved total insulin sensitivity; however, it decreased total β cell responsivity [66]. Pramlintide is approved for the treatment of postprandial hyperglycemia in patients using intensive insulin therapy. Again, despite its pharmacologic effects, the physiologic contribution of amylin to the regulation of glucose metabolism is uncertain.

Peptide YY

Peptide tyrosine-tyrosine (PYY) is a 36 amino acid linear peptide that is a member of the neuropeptide Y family of peptides and circulates in two main forms, $PYY_{1–36}$ and $PYY_{3–36}$. The $PYY_{1–36}$ form is cleaved by dipeptidyl peptidase IV (DPP-IV) to produce $PYY_{3–36}$. Sixty percent of circulating PYY is (1–36), and 40% is (3–36). $PYY_{3–36}$, which crosses the blood brain barrier, has a high affinity for the Y2 receptors in the hypothalamus (e.g., arcuate nucleus). PYY is released from enteroendocrine L cells of the distal small intestine and colon on stimulation by intraluminal nutrients, glucose, bile salts, lipids, short-chain fatty acids, and amino acids. The release is also modulated by other gut peptides: vasoactive intestinal peptide (VIP), cholecystokinin (CCK), gastrin, and glucagon-like peptide-1 (GLP-1) [67]. PYY is an important mediator of the "ileal brake" that slows gastric emptying and intestinal transit in response to nutrients in the distal small intestine. It shares this action with GLP-1, GLP-2, serotonin (5-HT, through $5\text{-}HT_3$ receptors), melatonin, oxyntomodulin, glicentin, neurotensin, and enteroglucagon.

Peripheral injection of PYY inhibits gastric emptying of liquids and gastric acid and pancreatic exocrine secretion [68–70]. Intranasal $PYY_{3–36}$ administered preprandially induced nausea and vomiting, but the effect on gastric emptying was not measured [71]. Although there does not appear to be evidence that exogenous PYY retards gastric emptying

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of solids, there is association between endogenous PYY levels in peripheral blood and gastric emptying of solids in response to ileal lipid stimulation of PYY secretion [72].

Oxyntomodulin

Oxyntomodulin (or glicentin 33–69) consists of the entire (pancreatic) glucagon sequence (1–29) plus an octapeptide extending from the C terminus; both are derived from proglucagon. It is secreted by the L cells of the ileum and colon in response to glucose and other nutrients. In humans, oxyntomodulin delays gastric emptying of liquids (measured by intubated technique or by acetaminophen absorption), in addition to its inhibition of gastric acid and pancreatic enzyme secretion [73,74].

Bariatric Surgery or Endoscopy, Incretins and Gastric Emptying

Sleeve gastrectomy and Roux-en-Y gastric bypass (RYGB) are the most common bariatric procedures performed in North America [75]. Anatomic differences between the two procedures result in different rates of emptying, resulting in differences in enteroendocrine secretory responses: postprandial GLP-1 concentrations are lower after sleeve gastrectomy compared to RYGB in the comparative studies undertaken in humans [76–80]; nevertheless, sleeve gastrectomy significantly upregulates the secretion of GLP-1 in association with rapid emptying of both solids and liquids from the stomach [81]. There are other major changes in incretins and gut hormones including changes in PYY, ghrelin and leptin, and all may impact glycemic control, gastric emptying and satiety. These effects are beyond the scope of the current article and are reviewed extensively elsewhere [2**,82,83**]. Clearly, alteration of the gastric anatomy prevents the important inhibition of gastric emptying by hormones such as GLP-1 and PYY in response to these restrictive bariatric procedures. This differs from the effect of endoscopic sleeve gastroplasty, which creates a proximal pouch with increased gastric retention and increased satiety [84]. Effects of sleeve gastroplasty on gastrointestinal hormones are the subject of ongoing investigation.

Conclusion

The upper gastrointestinal tract integrates intraluminal nutrients and neural, mechanical and hormonal mechanisms to modulate the response to caloric ingestion. In addition to the effects of the hormones from the upper gastrointestinal tract on hypothalamic appetite centers and glycemic control, there is evidence that some of their biological effects are mediated through actions on the stomach, particularly with the GLP-1 analogs or agonists that are used in treating obesity and postprandial glycemia. These hormones modulate integral functions that are critical for life and health, in part through their effects on gastric emptying. Although the therapeutic applications to date have been dominated by GLP-1 receptor modulation, novel pharmacological agents targeting other hormones or their receptors are in development and include GIP antagonists, ghrelin agonists and “twincretins”, that is, single molecules that act as agonists of both GLP-1 and GIP receptors [85]. It is anticipated that interaction of these hormonal mechanisms with the gut microbiota will also provide further avenues of mechanistic understanding and therapeutic applications of the gastrointestinal hormones.

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Acknowledgements

The author thanks Mrs. Cindy Stanislav for excellent secretarial assistance with the manuscript.

Funding: This work is supported by grant R01-DK67071 from National Institutes of Health.

Dr. Camilleri has consulted for Rhythm Pharmaceuticals with the consulting fee paid to his employer, Mayo Clinic. He has received research funding for studies on relamorelin from Rhythm Pharmaceuticals. He received some medication supplies from Novo Nordisk for studies on liraglutide.

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gastrointestinal motor functions; this ushers the discussion of the potential role of microbiota and the interaction of high fat diet with resistance to the effects of GLP1, possibly through alterations of the microbiota.

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Key Points

- Several upper gastrointestinal hormones alter gastric emptying; the most important are CCK, GIP, glucagon, GLP-1 and PYY which retard gastric emptying. These hormones also reduce appetite or induce satiation.
- The hormones, ghrelin and motilin, and their receptors are associated with acceleration of gastric emptying and are targets of novel therapy for gastroparesis, e.g., the pentapeptide ghrelin agonist, relamorelin, and the motilide, erythromycin.
- Many of the current or promising therapies for obesity act on these hormones or their receptors to reduce appetite and induce satiation.
- Prominent effects of bariatric surgery or endoscopic procedures alter gastric emptying and act on these hormonal mechanisms to reduce appetite and induce satiation.

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Table 1.

Summary of peptides and hormones involved in gastric emptying (original)

Peptide / Hormone	Predominant Site of Synthesis/ Release	Main Functions	Effects on Gastric Emptying and Other Organs in Digestive Tract
Gastrin	17-AA peptide from gastric mucosa	- Blood-borne regulator of gastric acid secretion, interacting with somatostatin and EC cells - Regulates gastric epithelial organization, proliferation, and function	- No direct effect on GE; increased acid secretion may be associated with modest increase in time for complete emptying
CCK	I cells in duodenal mucosa, particularly with fatty acids ≥12 carbon chain length; multiple molecular forms	- Activates vagal afferents directly and modifies the response of vagal mechanosensitive fibers to gastric and duodenal nutrients	- Relaxes the proximal stomach to increase its reservoir capacity - Inhibits GE and acid secretion - Induces gallbladder contraction and exocrine pancreatic secretion
Ghrelin	28-AA peptide expressed mostly in stomach	- Growth hormone secretagogue that stimulates pituitary release of growth hormone and stimulates hypothalamic centers to increase appetite - Effects mediated through vagus nerve	- Stimulates gastric emptying and contracts gastric fundus - Stimulates gastric acid secretion - Other actions: vasodilatation, inhibition of insulin, anti-proliferative
Leptin and Gastric Leptin	Leptin circulating (167 AA protein) secreted by adipose tissue, placenta, skeletal muscle; gastric leptin by fundic glands, and chief cells	- Hypothalamic regulation of feeding behavior, food intake and energy balance - Storage of fat and insulin signaling	- Gastric leptin reduced during fasting, rapidly released after food intake by vagal cholinergic stimulation, CCK and secretin, or in response to satiety factors (e.g., CCK and insulin)
Amylin	Co-secreted with insulin from pancreatic β-cells	- Suppresses glucagon release in response to caloric intake - Stimulates brain satiety centers to limit caloric intake	- Retards GE of solids
Glucagon	29AA peptide secreted from pancreatic α-cells	- Maintains blood glucose by activating gluconeogenesis and glycogenolysis - Affects energy expenditure, reduces meal size	- Retards GE of liquids - Inhibits GI motility
GLP-1	Co-secreted with PYY from intestinal L cells:	- Two biologically active forms: GLP-$1_{7–37}$ and GLP-$1_{7–36\ amide}$ (the major circulating form) - Incretin hormone that enhances insulin secretion stimulated by oral nutrients - Control of appetite and energy intake in humans	- Retards GE of solids and liquids and inhibits antral motility - Increases gastric reservoir capacity - Reduces postprandial glycemia - Increases satiety and fullness
PYY	Co-secreted with GLP-1 from ileocolonic L cells; active form $PYY_{3–36}$	- Stimulates Y_2 receptors in hypothalamic ARC nucleus circuitry to regulate food intake	- Activates ileal brake and other feedback control of regional motor function, and delays GE liquids - Inhibits gastric acid, pancreatic exocrine and bile acid secretion
OXM	37-AA peptide from intestinal L cells	- Acts via GLP-1 receptors to decrease food intake	- Inhibits gastric acid secretion - Modest delay in GE liquids

AA: amino acid; ARC: arcuate nuclei of the hypothalamus; CCK: cholecystokinin; EC: enterochromaffin cells; GE: gastric emptying; GLP-1: glucagon like peptide-1; OXM: oxyntomodulin; PYY: peptide tyrosine-tyrosine

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2020 February 01.