

# Role of gastrointestinal hormones in feeding behavior and obesity treatment

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**Abstract** Food intake regulation is generally evaluated by many aspects consisting of complex mechanisms, including homeostatic regulatory mechanism, which is based on negative feedback, and hedonic regulatory mechanism, which is driven by a reward system. One important aspect of food intake regulation is the peripheral hormones that are secreted from the gastrointestinal tract. These hormones are secreted from enteroendocrine cells as feedback to nutrient and energy intake, and will communicate with the brain directly or via the vagus nerve. Gastrointestinal hormones are very crucial in maintaining a steady body weight, despite variations in nutrient intake and energy expenditure. In this review, we provide an overview of the regulation of feeding behavior by gut hormones, and its role in obesity treatments.

**Keywords** Gastrointestinal hormone · Feeding behavior · Obesity · Clinical application

## Introduction

Currently, obesity and its comorbidities have become a critical problem throughout the world. Obesity is defined as an abnormal and excessive fat accumulation caused by an imbalance of energy intake and caloric expenditure that

may impair the health. Overweight is categorized by a body mass index (BMI) over 25 kg/m<sup>2</sup>, and obese is categorized by a BMI exceeding 30 kg/m<sup>2</sup>. However, in some Asian countries, the risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing World Health Organization (WHO) cutoff point for overweight. Thus, in different Asian populations, the cutoff point for observed risk varies from 22 to 25 kg/m<sup>2</sup>, while for high risk, it varies from 26 to 31 kg/m<sup>2</sup>. WHO has declared that obesity is one of the 10 at-risk conditions around the world and one of the 5 at-risk conditions in developing countries. In 2014, more than 1.9 billion adults are overweight and 600 million are obese.

In general, both overweight and obesity are associated with a high prevalence of comorbidities, including high blood pressure, metabolic syndrome, type 2 diabetes mellitus (T2DM), cardiovascular disease, and many others. A study suggested that a 1-kg weight gain increases the risk of diabetes by 4.5–9 % and cardiovascular disease by 3.1 %. [1]. Relating to obesity, the gastrointestinal tract is an important source of food intake. Gut hormones have a major role in controlling and regulating food intake. With the growing obesity crisis, gut hormones have become a hot topic of research among the scientists. Therefore, we are interested in the role of gut hormones in food intake regulation and in the treatment of obesity.

## Overview of neuroendocrine regulation in food intake

The food that we eat is broken down into small parts, which contains many nutrients. These nutrients may activate the G-protein-coupled receptors (GPCR) in the luminal side of enteroendocrine cells [2]. The

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gastrointestinal tract contains many types of enteroendocrine cells. Combined together, it becomes the largest endocrine organ in the body. When activated, it releases several hormones that have an impact on many physiological processes, including the food intake [3]. These hormones, including gut hormones, will pass median eminence and signal short-term nutrient availability to the hypothalamic arcuate nucleus (ARC) [4, 5]. Other circulating peptides, such as leptin released from the adipose tissue as well as insulin, are responsible for signaling the long-term energy stores and adiposity [6].

The ARC in the hypothalamus is known to regulate food intake and energy expenditure [7, 8]. It contains two populations of neurons that show an opposite effect to one another. The medial parts act as an orexigenic neurons that express neuropeptide Y (NPY) and agouti-related protein (AgRP) [9–11]. In the lateral side of ARC contains anorexigenic neurons that express alpha-melanocyte-stimulating hormone ( $\alpha$ -MSH) derived from pro-opiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) [12].

Moreover, other peripheral signals perform actions through the afferent neuron and brainstem that will indirectly influence the hypothalamus. The mechanoreceptors and/or chemoreceptors also contribute to control of the appetite. Both receptors activate the vagal afferent, and the neural signals converge

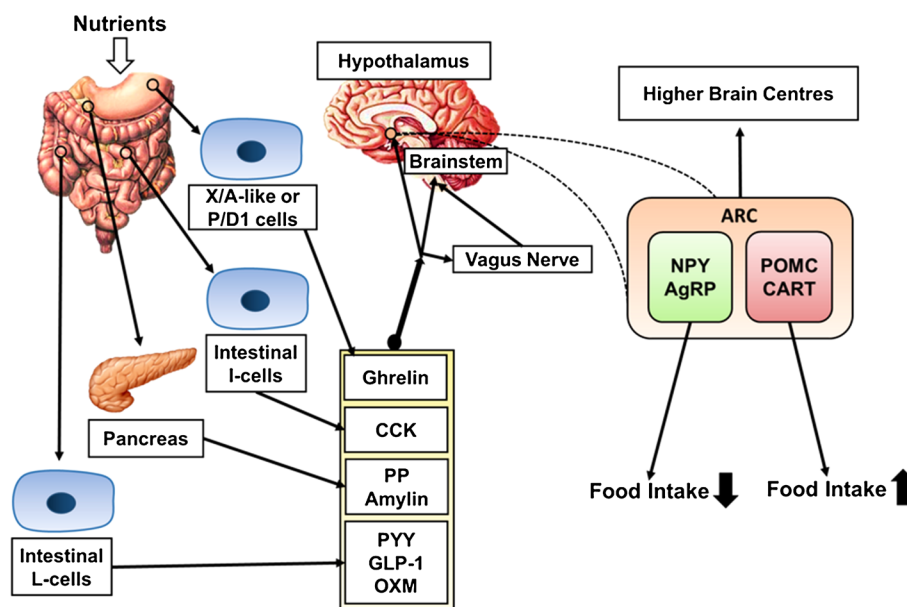
in the nucleus of tractus solitarius (NTS) of the brainstem. Then these signals are transmitted to hypothalamus [13]. Eventually, several gut hormones are also known to act via the ascending vagal pathway and brainstem [14].

Therefore, the orexigenic and anorexigenic neurons in the hypothalamus are regulated by many neural and hormonal signals (Fig. 1). These neurons will then project to other neurons in the extra-hypothalamic and intra-hypothalamic regions, such as the hypothalamic paraventricular nucleus (PVN), and lateral hypothalamus (LH) and perifornical area (PFA), where some of the important efferent pathways regulating hunger, satiety, and energy expenditure arise [15].

## Gut hormones and food intake regulation

### Ghrelin

Ghrelin, a peptide consisted 28 amino acids with n-octanoylated Ser3, was reported in 1999 as an endogenous ligand for the ‘orphan’ growth hormone secretagogue (GHS) [16, 17]. Ghrelin is predominantly found in the stomach, and was the first hormone to be identified for stimulating food intake [18]. It acts mainly as an orexigenic signal sending information about peripheral caloric intake to the brain center for energy homeostasis.



**Fig. 1** Neuroendocrine overview of food intake. Nutrients from food digestion will activate G-protein-coupled receptors on the luminal side of enteroendocrine cells. This leads to the release of gastrointestinal hormones, which will perform their action through three sites: the hypothalamus, brainstem, and vagus nerve. These hormones will signal short-term nutrient availability to the hypothalamic arcuate nucleus (ARC). The ARC in the hypothalamus is known to regulate food intake and energy expenditure. It contains two populations of

neurons that show an opposite effect to one another: the orexigenic NPY/AgRP neurons and the anorexigenic POMC/CART neurons. Both neurons will project to higher brain centers that control the hedonic aspects of food ingestion. ARC arcuate nucleus; AgRP agouti related peptide; CART cocaine and amphetamine-regulated transcript; CCK (Cholecystokinin; GLP-1 glucagon like peptide-1; NPY neuropeptide Y; OXM oxyntomodulin; POMC propiomelanocortin; PP pancreatic peptide; PYY peptide YY

Orexigenic NPY and AgRP-expressing neurons are involved in this mechanism because they express the ghrelin receptor [19, 20], which may respond to ghrelin by increasing the firing rate. Intracerebroventricular (ICV) administration of ghrelin increases body weight by increasing the cumulative food intake and energy expenditure reduction [21–24]. Ghrelin secretion is mainly regulated by feeding. In human studies, plasma ghrelin levels increase during fasting, and surge nearly twofold immediately preprandial, and drop within 1 h after food intake [25]. Prandial changes in the plasma ghrelin levels occur in association with the changes in hunger score, even when external cues related to time of day have been removed from environment [26]. These findings suggest that plasma ghrelin plays a role in short-term energy balance [27]. In addition to the regulation of appetite and energy balance, ghrelin also contributes to long-term body weight regulation. Ghrelin levels circulate in relation to the energy stores and manifest the compensatory changes in response to body weight alteration, increasing weight loss and vice versa [28].

Besides its direct effect on the brain, ghrelin is also suggested to act through the vagal neurons [29]. The existence of ghrelin receptors on vagal afferent neurons in the rat's nodose ganglion indicates that ghrelin signals from the stomach are transmitted to the hypothalamus through vagal neurons [30]. In animal models, vagotomy abolished the orexigenic effect of ghrelin [31]. The food intake stimulatory effect of ghrelin also disappeared in humans after vagotomy [32].

### Cholecystokinin

Cholecystokinin (CCK) is a gut satiating peptide that is produced by I cells in small intestine [33]. Basically, CCK is released post-prandially in response to saturated fats, long chain fatty acids, amino acids, and small peptides, and is reduced gradually upon fasting [34–36]. Peripheral administration of CCK before a meal may decrease the meal size in a dose-dependent manner, both in experimental animals [37, 38] and human subjects [39, 40]. CCK acts as a short-acting satiation signal, but not for long-term body weight regulation. It has a very short lifespan; according to a previous report, the peptide was not detectable when it was injected for more than 30 min before the meal [41].

There are several forms of CCK, ranging from 8 to 83 chain amino acids. The major circulating forms are CCK-8, CCK-22, CCK-33, and CCK-58, all having the same attribute, a C-terminal heptapeptide amide sequence for binding [42–44]. Although they have the same attribute, not all forms of CCK show equal bioactivity; for example, both CCK-8 and CCK-58 can reduce meal size after

administration, but only CCK-58 increases the intermeal interval time, while CCK-8 reduces this interval, as shown in previous studies [45, 46].

CCK performs its action through cholecystokinin-1 (CCK1) receptors and/or cholecystokinin-2 (CCK2) receptors [47]. CCK1 receptors are responsible for mediating the anorexigenic effect of CCK, mainly through vagal afferent fibers [48, 49], and this receptor is also located in brain [50, 51]. Subdiaphragmatic vagotomy and selective vagal deafferentation cause a decrease in the anorexigenic effects of peripheral CCK [52–54]. Furthermore, CCK1 receptors are also located in the hindbrain and hypothalamus, and microinjection of CCK into the hypothalamic nuclei may decrease food intake [55]. Additionally, lesions in the hindbrain Area Postrema (AP) proved to weaken the satiation effect of CCK [56]. These data indicate that to perform its action, CCK might communicate indirectly through the vagal nerve or directly to the brain.

### Peptide Tyrosine Tyrosine

Peptide tyrosine tyrosine (PYY) is a 36-amino acid peptide with tyrosine (Y) residues at the N and C terminals. It was isolated from porcine intestine in 1980 [57], and shares similar structure with NPY and PP, consisting of an  $\alpha$ -helix and a polyproline helix connected by a  $\beta$  turn, and together classified in the polypeptide-fold (PP-fold) family [58].

PYY is released from L-cells in the distal ileum and is increased along the intestine, reaching the highest levels in the colon and rectum. It is secreted following a meal, gradually rises, reaches the peak level within 1–2 h, and will remain elevated for 6 h [59, 60]. Meal composition has high influence on the release of PYY, with protein being greater than lipids and carbohydrates [61]. There are two main types of PYY, PYY<sub>1-36</sub> and PYY<sub>3-36</sub>, PYY<sub>1-36</sub> is proteolyzed by dipeptidyl-peptidase 4 (DPP4) to produce PYY<sub>3-36</sub> as the bioactive form [62, 63]. PYY performs its action through the Y receptor family (Y1, Y2, Y4, Y5, and Y6), where PYY<sub>3-36</sub> has a high affinity toward Y2 receptors and low affinity to Y1 and Y5 receptors [64, 65].

Peripheral administration of PYY<sub>3-36</sub> in rodents decreased appetite and food intake [66–68], and also reduced body weights in other experimental animals [69, 70]. In human, intravenous infusion of PYY<sub>3-36</sub> also showed the same results, indicating the role of PYY as an anorexigenic peptide [71]. This anorectic effect is mainly mediated through Y2 receptors in the hypothalamic ARC, and will inhibit the NPY/AgRP neurons, which activates the anorectic melanocortin-producing cells [66]. The anorexigenic effect of PYY<sub>3-36</sub> disappears in Y2 receptor-deficient animals [66, 72, 73]. Surprisingly, direct administration of PYY into the brain results in an increase

of food intake. This result might be due to the differential access to Y receptors, in which the orexigenic effect is predicted come from the interaction between PYY with Y1 and Y5 receptors in the brain [74, 75]. Furthermore, the vagal-brainstem-mediated pathway may also be involved in the action of circulating PYY<sub>3-36</sub>. Y2 receptors are located in vagal-afferent terminals. Several studies have confirmed that abdominal vagotomy or transection of hindbrain-hypothalamic pathways in rodent abolishes the anorectic effects and the ARC neuronal activation of PYY [76, 77]. In summary, PYY acts as a satiety signal that may reduce the food intake in rodents as well as in humans, and performs its action directly through Y2 receptors in the hypothalamic ARC and/or through the vagal afferent.

### Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a gut peptide derived from preproglucagon. It is produced in the body, mainly the intestinal L-cells, in response of glucose ingestion [78]. A study showed that high protein food intake increases the concentration of GLP-1 [79]. Cleavage of the preproglucagon resulted into two main bioactive forms of GLP-1, GLP-1<sub>7-36</sub> and the GLP-1<sub>7-37</sub> [80]. Both forms have a short biological half-life, because both of them are rapidly degraded during circulation by dipeptidil peptidase 4 (DPP4) [81].

Acute peripheral and central administration of GLP-1 reduced food intake in animals [82–84], and chronic administration proved to reduce weight gain [85]. In human subjects, intravenous injection of GLP-1 decreases the food intake in a dose-dependent manner [86–89], and it also activates the ileal break [90], a feedback in which ingested food activates distal-intestinal signals to inhibit the proximal gastrointestinal motility and gastric emptying. Beside of its anorexigenic property, GLP-1 also has an important role in glucose homeostasis. It acts as an incretin to induce glucose-dependent insulin release and enhance pancreas  $\beta$  cell growth in addition to reduced secretion of glucagon [91]. GLP-1 actions are mainly mediated through the GLP-1 receptors (GLP1R), located in pancreas, brainstem, hypothalamus, and vagal nerves. Peripheral injection of GLP-1 has been shown to activate neurons in the brainstem of rats [92]. The anorectic property of GLP-1 is diminished in vagotomized rodents [76]. Furthermore, using magnetic resonance imaging (MRI), scientists have confirmed that peripheral administration of GLP-1 increased the signal intensity in the brainstem's AP, and it also altered signal intensity in the hypothalamic PVN and ventromedial nucleus (VMN) [93]. Therefore, GLP-1 achieves its action both centrally through the hypothalamus and through the vagal-brainstem signalling pathway.

### Oxyntomodulin

Oxyntomodulin (OXM) is a gut peptide similar to GLP-1 and is derived from the same precursor, preproglucagon. It is cosecreted with GLP-1 from enteroendocrine L-cells postprandially in response to caloric intake [94]. OXM administration in rodents has been shown to decrease food intake and body weight [95, 96], and also to increase energy expenditure [97]. In normal weight humans, intravenous administration of OXM has been shown to reduce food intake [98], while in overweight and obese volunteers, administration of OXM increases energy expenditure and reduces energy intake [99, 100].

OXM has an affinity for both GLP-1 receptors and glucagon receptors. However, it is believed that the anorectic effect of OXM is mediated mainly through GLP-1 receptors [101], although recent data indicate that glucagon receptors are also involved in OXM action [102]. OXM has lower affinity to GLP-1 receptors than GLP-1, but it still has similar potency to GLP-1 in reducing food intake [95]. GLP-1 receptor knockout mice and administration of the GLP-1 receptor antagonist exendin 9-39 abolished the anorectic effect of OXM [101]. However, exendin 9-39 did not affect the anorectic effect of GLP-1 [96]. Similar to this, one study using manganese-enhanced magnetic resonance imaging (MEMRI) showed that intraperitoneally injected OXM reduces the neuronal activity in the ARC, PVN, and supraoptic nucleus (SON) [103]. Therefore, despite OXM and GLP-1 sharing similar attributes, these two hormones might act through different hypothalamic pathways.

### Pancreatic polypeptide and amylin

Pancreatic polypeptide (PP) is a 36-amino acid peptide that belongs to the "PP-fold" family of peptides. It is released from the pancreas postprandially in response to caloric load, and is controlled mainly by vagal cholinergic mechanism [104]. Many studies have shown that PP decreases food intake with a delay of gastric emptying after peripheral administration in humans and rodents [105–107]. PP can interact with all subtypes of the Y receptor family, while it has the highest affinity toward Y4 receptors, particularly in the VMN, PVN, AP, and ARC [107–109].

Amylin or islet amyloid polypeptide (IAPP) is a 37-residue peptide that is cosecreted with insulin from pancreatic  $\beta$  cells in response to food intake [110]. Amylin is known to slow down the gastric emptying and to inhibit gastric and glucagon secretion [111]. Peripheral and central administration of amylin decreased food intake [112, 113]. In humans, peripheral administration of amylin analogue pramlintide enhanced satiety and reduced food intake,

**Table 1** Summary of gut hormones in basic and clinical research effect on food intake and obesity

Gastrointestinal hormones	Basic research purpose	Basic research dosage	References	Clinical research	Clinical research dosage	Years	References
Cholecystokinin	Food intake experiment in rats with open gastric fistulas	0.06, 0.125, 0.25, or 0.5 µg/kg in saline	[37]	CCK-8	0.5 µg/ml of CCK-8 with 4 ng/kg/min (iv)	1981	[39]
	Comparing the meal pattern between CCK-58 vs CCK-8	0.45, 0.9, 1.8, 3.6 nmol/kg (ip) no dosage mention in the paper	[45]	CCK-33	1 idu/kg ideal weight/height (iv) *idu: ivy dog unit	1994	[40]
	Comparing the meal size and intermeal interval between CCK-58 vs CCK-8	0, 0.1, 0.5, 0.75, 1, 3, 5 nmol/kg (ip) dose: 0.5 ml	[46]				
Protein YY	Food intake experiment in rats and mice	500 µl (rats), 100 µl (mice) (ip)	[66]	PYY3-36	2 nmol/square meter of body surface area (90 m infusion)	2003	[71]
	Food intake experiment in mice	10 µg/100 g body weight (ip)	[67]				
	Food intake experiment in mice	0.3, 3, 10 µg/100 g	[68]				
	The safety and effectiveness of PYY3-36 for 14 days in New Zealand white rabbits	4.1, 41, 205 µg/kg/day	[69]				
GLP-1	Food intake experiment in rhesus macaques ( <i>Macaca mulatta</i> )	1) once-daily: 7 days of vehicle followed by 7 days of PYY3-36 0.3 pmol/kg/min and then 2 days of 0.8 pmol/kg/min 2) twice daily: 7 days of vehicle followed by 5 days of PYY 3-36 0.8 pmol/kg/min and 11 days of 1.6 pmol/kg/min (morning and afternoon) 3) continuous: 3 days of 1.6 pmol/kg/min	[70]				
	Food intake experiment in rats	1 µg (icv)	[82]	GLP-1	0.75 pmol/kg/min (iv)	1999	[86]
	Food intake experiment in lean and obese rats	1) once: 10 µg (ivt) 2) 4 days: 30 µm/days (ivt) 3) acute 15 µg (ivt) 9 nmol (icv)	[83]	GLP-1	0, 0.375, 0.75, 1.5 pmol/kg/min (iv)	1999	[87]
GLP-1	Food intake experiment in rats	9 nmol (icv)	[85]	GLP-1	4.8 pmol/kg/min (continuous subcutaneous infusion)	2002	[88]
	Food intake experiment in rats			GLP-1	2.4 pmol/kg/min for 24 h	1999	[89]



Table 1 continued

Gastrointestinal hormones	Basic research purpose	Basic research dosage	References	Clinical research	Clinical research dosage	Years	References
OXM	Food intake experiment in rats (central administration)	1) 3 nmol (icv) 2) 0.1 nmol (iPVN)	[95]	Human OXM	3 pmol/kg/min for 90 min (iv)	2003	[98]
	Food intake experiment in rats (peripheral administration)	3, 10, 30, 100 nmol/kg (ip)	[96]	Human OXM	400 nmol 3×/days	2005	[99]
	Food intake experiment in rats (repeated icv injection)	1 nmol twice a day for 7 days	[97]	Human OXM	400 nmol 3×/days	2006	[100]
	Food intake experiment in rats	0.1, 0.3, 1, 3 nmol (icv)	[106]	PP	10 pmol/kg/min	2003	[105]
Pancreatic Polypeptide	The role of PP in energy balance	100 µl (ip)	[107]				
	Food intake experiment in rats	1 µg/kg (ip)	[113]	Pramlintide (analogue of amylin)	120 mg (single subcutaneous injection)	2005	[114]
Amylin							

indicating the role of Amylin as an anorexigenic peptide [114]. Studies have shown that brain AP is the primary target of amylin for inducing the satiety action [115, 116].

## Gut hormones and obesity treatment

Currently, three main steps are widely applied in obesity treatment: lifestyle modification, pharmacotherapy, and bariatric surgery [117]. Lifestyle modification focuses on increasing physical activity while having a healthier diet and lower calorie meals, and is usually used in obesity intervention. If the lifestyle intervention has failed and the patients meet the requirements for anti-obesity medication, then the use of anti-obesity drugs should be considered. The requirements to use pharmacotherapy in treating obesity, according to the Food and Drug Administration (FDA), are patients with a body mass index (BMI) 30–27 kg/m<sup>2</sup> who have associated high-risk comorbid conditions [118]. In clinics, the use of prescriptions for anti-obesity is <3 %. Concerns regarding safety and adverse effects of anti-obesity drugs are the main reasons for this low prescription rate [119]. Several anti-obesity drugs have been withdrawn from the market due to adverse effects, such as: fenfluramin and dexfenfluramine in 1997, sibutramine in 2010 by the US Food and Drug Administration (FDA), and rimonabant in 2009 by the European Medicines Agency (EMA) [120]. The third option is bariatric surgery, usually targeted to severely obese patients (BMI ≥40 or ≥35 kg/m<sup>2</sup> with comorbidity). Until now, bariatric surgery has mostly been applied in obesity treatment that has shown long-term, sustained weight loss and improving metabolic comorbidities [121]. Unfortunately, the expensive cost and the complications make it impractical to treat the growing population of obese worldwide [122].

Interestingly, some studies have shown that the clinical benefits of bariatric surgery in achieving weight loss and metabolic comorbidity improvement are related to alterations in gut hormone production [123, 124]. Ghrelin level after bariatric surgery showed mixed results. Several studies showed a decrease in ghrelin level after sleeve gastrectomy (SG) [125–127], and a decrease and/or no change after the duodenojejunal bypass (DJB) and biliopancreatic diversion (BPD) [125, 128], while others reported an increase and/or no change after the adjustable gastric band (AGB) [129–133]. These different results may be due to the variability in the time at which blood sample was taken, or by the variation in bariatric surgery. In 2006, postprandial circulating levels of PYY and GLP-1 were increased after the Roux-en-Y gastric bypass (RYGB) in humans [134, 135]. Another study showed similar results in 34 patients after RYGB surgery, and the effect was

sustained for 2 years [136]. CCK production has also been altered after bariatric surgery; patients with jejunoileal bypass showed an increase in CCK-containing cells [137] and CCK levels [138, 139]. All together, this shows that gut hormones have an important role in tackling the obesity crisis.

Gut hormone-based therapy has an advantage in the development of anti-obesity drugs. Endogenous gut hormones physiologically regulate food intake; thus, hormone-based therapy will have fewer side effects than chemical drugs. Many studies have been done in the past to investigate the effect of gut hormone administration in obese subjects (Table 1), and resulted in promising outcomes [39, 40, 86–90, 114]. Furthermore, an additive effect could be achieved with a combined administration of gut hormones; for example, a combination of PYY3-36 and GLP-1 administration showed an additive anorectic effect in both mice and human [140]. This opens the possibility of a combination therapy of gut hormones in treating obesity.

Gut hormone-based therapy might become useful in treating obesity in the future, but it still has several drawbacks. The first one is the short half-life of gut peptides. Long-acting analogues of several gut hormones have been developed to overcome this problem; the exenatide (exendin-4), for example, is a GLP-1 receptor agonist that is resistant toward DPP4, resulting in longer action in vivo than GLP-1 [141–143]. Some are still at the clinical trial phase, such as Y242 (a PYY analogue) [ClinicalTrials.gov Identifier: NCT01515319], PP1420 (a PP analogue) [ClinicalTrials.gov Identifier: NCT02221765], or the Pfizer's OAP-189 (an OXM analogue) [ClinicalTrials.gov Identifier: NCT00970593], and we are awaiting trial results for all.

The other drawback is the rapid degradation of gut peptides in the upper digestive system, resulting in limited bioactivity through oral administration of gut hormones. Recently, orally administration of gut hormones has been achieved using the sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC) delivery technique, such as orally administered GLP-1 and PYY3-36 in human using the SNAC delivery technique to result in an additive anorectic effect [144]. This initial result suggests that oral administration of gut hormones could be applied in the near future. A new field in anti-obesity research is the study of nutrient sensing receptors. Studies have shown that targeting nutrient sensing receptors, such as the sweet taste receptor on the primary enteroendocrine L-cell cultures, causes the release of gut hormones [145, 146]. Oral administration of nutrient sensing agonists would be an effective way to treat obese patients. However, due to a lack of in vivo data, the physiological relevance of this application is still unclear and further research is required.

In summary, gastrointestinal hormones play an important role in energy homeostasis and food intake by

affecting the brain areas that are associated with the regulation of eating behavior and appetite; acting either directly from the blood stream or via the vagus nerve. Modifying and commandeering gut hormones and/or their signaling pathways provides a promising target for anti-obesity treatment in the future.

#### Compliance with ethical standards

**Conflict of interest** Akio Inui received a research grant from Vana H. The other authors have no conflict of interest to declare.

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