The role of gastrointestinal hormones in the pathogenesis of obesity and type 2 diabetes

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Abstract

Obesity, influencing the increase of incidence of type 2 diabetes, cardiovascular complications and cancer is a growing medical problem worldwide. The feelings of hunger and satiety are stimulated by the “gut-brain axis”, where a crucial role is played by gastrointestinal hormones: glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide, pancreatic polypeptide, peptide YY, oxyntomodulin, cholecystokinin and ghrelin. These hormones affect not only the functioning of the digestive tract, but also might have effects on insulin secretion and are mediators which affect brain areas involved in the regulation of food intake. The effect of their actions can be antagonistic as well as an additive or synergistic, and their secretion is dependent on many factors, such as dietary nutrients or the energy state of the body. Changes in circulating gut hormones concentrations result in activation of various pathways primarily within the hypothalamus and brain stem areas, which modulate feeding behaviour and a number of metabolic processes.

Brain – gut axis regulation

The central nervous system (CNS) (the paraventricular nucleus and the hypothalamic arcuate nucleus), which receives signals from the alimentary tract as well as from adipose tissue, plays a key role in the body’s energy balance. The feelings of hunger and satiety are regulated in the CNS via the brain-gut axis, with a number of hormones playing critical roles (Table I). Ghrelin is the main and, as it seems, the only known appetite-stimulating gastrointestinal hormone. Its levels increase after overnight fasting, they rise approximately two-fold immediately before a meal and decrease to their lowest values 1 h after each meal (Figure 2) [8, 9]. Postprandial decrease of ghrelin levels is further dependent on meal calorie value and composition; for example, the decrease is lower after fat-based meals compared with carbohydrate- or protein-based meals [10, 11]. Basic ghrelin levels respond in a compensatory manner to the energy deficit/excess: low ghrelin levels are observed in obesity, whereas high levels in anorexia (Figure 2) [12, 13]. A lower decrease in ghrelin levels in relation
Ghrelin is acylated at position 3 into an active, acylated form that can pass the blood-brain barrier and bind to a receptor that stimulates growth hormone (GH) secretion. In the CNS, ghrelin stimulates hypothalamic production of neuropeptide Y (NPY) and Agouti-related peptide (AgRP) by influencing mitochondrial uncoupling proteins (UCP2) [15–17]. Acylated ghrelin neutralization reduces food intake and leads to weight-loss in diet-induced obese mice [18]. Long-term ghrelin administration in experimental animals leads to weight gain, resulting from hyperphagia, and increased expression to fasting values is observed in postprandial obese individuals [14].

Table I. The main mechanisms of action of gut hormones and “adiposity signals” (modified according to Suzuki et al. Endocr J 2010) [6]

| Gastrointestinal hormones – “satiety signals” regulating the beginning, end and intervals between meals |
|-----------------------------------------------------------------------------------------------------|
| GLP-1                                                                                                |
| Incretin effect, satiety regulation, delayed gastric emptying |
| GLP-2                                                                                                |
| Affects gastrointestinal motility and trophic effect in the intestinal tract |
| Ghrelin                                                                                                |
| Hunger stimulation |
| PYY                                                                                                  |
| Satiety regulation, delayed gastric emptying |
| PP                                                                                                    |
| Affects gastric motility, satiety regulation |
| OXM                                                                                                   |
| Satiety regulation, affects HCl secretion, incretin properties |
| CCK                                                                                                   |
| Affects gastrointestinal motility, exocrine pancreatic enzyme secretion, secretory function of the gallbladder |
| GIP                                                                                                   |
| Incretin effect |
| Amylin                                                                                                |
| Affects glucose homeostasis, gastric motility |

| “Adiposity signal” hormones – role in regulating the formation of energy reserves |
|----------------------------------------------------------------------------------|
| Insulin                                                                          |
| Affects glucose homeostasis, glycogen synthesis |
| Leptin                                                                           |
| Regulates energy metabolism |

Figure 1. Hunger/satiety regulation in CNS (“gut-brain axis”)

--- anorectic effect, → orexigenic/stimulatory effect,
NPY – neuropeptide Y, AgRP – Agouti-related peptide, POMC – pro-opiomelanocortin, CART – cocaine- and amphetamine-regulated transcript, GLP-1 – glucagon-like peptide-1, GIP – glucose-dependent insulinotropic peptide, PP – pancreatic polypeptide, PYY – peptide YY, OXM – oxyntomodulin

Figure 2. Mean 24-hour plasma ghrelin profiles in normal-weight and obese subjects (modified by Cummings et al. NEJM 2002) [9]
of enzymes that promote fat accumulation in the adipocytes [19].

**Cholecystokinin**

Cholecystokinin (CCK) was the first gastrointestinal hormone found to act as a hunger suppressant [20]. Cholecystokinin is mainly produced in the L-cells of the duodenum and small intestine [21] in response to a meal, to stimulate pancreatic hormone secretion, bile secretion [22] and inhibition of gastric emptying [23]. An increase in CCK blood levels is observed approximately 15 min after meal initiation [22]. Therapeutic use of CCK is restrained due to its 1–2-minute half-life. Administering CCK earlier than 15 min before a meal does not result in meal size reduction [20].

There are several known bioactive forms of CCK, such as CCK-8, CCK-22, CCK-33 and CCK-58, which differ in the number of amino acids. Cholecystokinin-33 is the prevailing form found in plasma and the intestines [24]. Cholecystokinin is widely distributed in the CNS, including the hypothalamus, where it is most abundantly present in the dorsomedial nucleus and the median eminence of the hypothalamus [25].

Two types of CCK receptors, CCKA and CCKB, are known [26, 27]. CCKA (also known as CCK1) seems to play a more important role in food intake regulation. Administering selective antagonists for this receptor in experimental animals abolishes the inhibitory effects of intraperitoneal CCK-8 infusion [28]. Rats, lacking CCKA expression (Otsuka Long Evans Tokushima Fatty Rats), present with high food intake, obesity and hyperglycaemia [29]. However, studies in knockout mice do not confirm long-term effects on body weight [30]. CCKA receptors are expressed in the pancreas, afferent and efferent neurons of the vagus nerve, the nucleus of the solitary tract (NTS), the area postrema and the hypothalamic dorsomedial nucleus, which are the key regions regulating food intake [26].

The influence of exogenous CCK on the reduction of food intake is hormone-dose dependent, both in rats [20] and in humans [31].

Gastric or abdominal vagotomy abolishes the effect of satiety induced by CCK-8 administered peripherally, indicating that vagus nerve CCKA receptors may play a crucial role in food intake regulation [32]. Peripheral CCK administration decreases food intake by reducing meal duration as well as the quantity of the ingested food [31]. It was shown that CCK administered in high doses causes nausea and taste aversion [33–35]. However, the anorectic effect of low doses and malaise in experimental animals are not correlated [36]. Centrally administered CCK also decreases food intake, and the effect is potentiated by concomitant administration of leptin. CCK, along with leptin, is likely to play an important role in long-term weight regulation [37].

Studies on the use of CCK in obesity treatment showed that intermittent infusions of CCK for 6 days reduced ingested meal size by at least 44%; however, it increases meal frequency by 162% or more, but with no effect on body weight [38]. Furthermore, it was shown that a 2-week continuous intraperitoneal CCK infusion resulted in the rapid development of tolerance, and thus a lack of effect on food intake or body weight [39].

Studies show that in lean individuals the increase in postprandial CCK levels is high and fast, which may result in earlier occurrence of satiety, while in obese individuals, postprandial CCK levels remain increased for longer [40]. Postprandial CCK levels may also be sex- and meal composition-dependent. Higher CCK levels are observed after high-fat meal ingestion. The increase of CCK levels is higher in females [41].

**Peptide YY**

Peptide YY is a 36-amino-acid protein with NPY and pancreatic hormone-like structure, produced in the gastrointestinal L-cells, mainly in the colon and rectum. Its name derives from two tyrosine molecules (Y) at the initial and terminal portion of the peptide. The PYY3-36 fragment, which is an active form, is mainly detected in peripheral circulation [42, 43].

The physiological role of PYY is associated with the meal “termination” signal; PYY levels are low after overnight fasting, at their highest in the 2nd h after meal initiation and gradually decrease within 6 h from reaching their highest value. Peptide YY acts mainly via the Y2R receptor in neurons producing NPY in the hypothalamic arcuate nucleus [42, 44].

Peptide YY shows “satiety peptide” properties. Previous studies reveal low PYY levels in obese patients [45]. Peripheral administration of PYY to humans results in a 30% or higher reduction in the calorific value of a meal consumed 2 h after PYY infusion and a 33% reduction in the quantity of consumed food over 24 h [44, 45]. Postprandial PYY peak further depends on meal calorie value and food composition (Figure 3) [46].

**Pancreatic polypeptide**

The pancreatic polypeptide (PP) is a peptide secreted by PP cells in the islets of Langerhans and, in smaller amounts, by colon and rectum cells. It acts through the Y receptors, particularly Y4 and Y5 [47, 48]. Pancreatic polypeptide does not pass through the blood-brain barrier, but it affects the CNS via Y receptor activation in the area postrema of the brain stem with high expression of the Y5 receptor (where the “tight” blood-brain...
Oxyntomodulin

The name ‘oxyntomodulin’ (OXM) derives from its function to modulate the gastric oxyntic glands producing HCl. Oxyntomodulin is secreted by the L-cells, depending on the calorie value of the ingested meal, in parallel with GLP-1 production, and has an influence on the GLP-1 receptor in the hypothalamic arcuate nucleus [57, 58]. Oxyntomodulin, which has a 50-fold lower affinity for receptor GLP-1R, compared with GLP-1 [59], also shows effects independent of the receptor stimulation (an OXM-specific receptor has not been identified so far). As with GLP-1, OXM is also inactivated by the DPP-IV enzyme [60].

Oxyntomodulin shows an incretin effect as well as β-cell protective properties [61]. Studies have revealed that in healthy individuals oxyntomodulin reduced appetite and the amount of ingested food by 19.3% [62], and in obese individuals it reduced body weight by 2.3 kg in 4 weeks [63] and increased energy expenditure by 9.4% (as opposed to most weight loss treatments) [64]. It has been shown that the appetite suppressing effects of OXM are partly due to the inhibition of ghrelin secretion (a decrease in secretion by 44% after IV infusion of OXM) [62]. A reduction in food intake (42.7%) in obese individuals following oxyntomodulin and PYY (3-36) administration was also observed, indicating an additive effect of both hormones [65].

Gastrointestinal hormones affecting the secretion of insulin (incretin)

The incretin effect involves meal-induced stimulation of insulin secretion. The effect was observed when insulin secretion increased more after oral glucose administration than after the intravenous infusion of an equivalent glucose dose, while maintaining stable plasma glucose levels [66]. Incretins are gastrointestinal hormones increasing postprandial insulin secretion by β-cells in the islets of Langerhans. Incretin hormones include:

1) glucagon-like peptide-1 (GLP-1),
2) glucose-dependent insulinotropic polypeptide (GIP); previous name: gastric inhibitory polypeptide.

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is encoded by a gene producing preproglucagon – a 160 amino acid fragment post-translationally generating the following peptides: GLP-1, GLP-2, glucagon, glicentin and OXM, depending on the site of expression, i.e. pancreatic α-cells, intestinal L-cells or the central nervous system [67, 68] (Figure 4).
Glucagon-like peptide-1 is mainly synthesized by L-cells in the duodenum, small and large intestine, and less by the pancreas and the hypothalamus. Its secretion in the gastrointestinal tract is influenced by glucose and fatty acids after food ingestion or as a result of vagus nerve stimulation. In peripheral circulation, GLP-1 has a very short half-life ($T_{1/2} = 1–2$ min) due to degradation of the active form (7-36) into inactive form (9-36) after disconnection of 2 terminal amino acids by dipeptidyl peptidase-4 (DPP-4) [70, 71].

The main mechanisms of action involve stimulating insulin secretion by $\beta$-cells in the islets of Langerhans and inhibiting glucagon secretion by $\alpha$-cells (Figure 5). Increased insulin secretion is the result of its increased synthesis. Substantial evidence exists to prove that the native GLP-1 increases $\beta$-cell mass and inhibits their apoptosis [72]. Glucagon-like peptide-1, via the GLP-1 receptor in the central nervous system, shows also central effects, suppressing appetite and reducing the rate of food absorption into the blood by lowering the rate of gastric emptying [72–74]. Glucagon-like peptide-1 secretion depends on meal composition, and higher concentrations are observed after high-fat meals [75] (Figure 5).

**Figure 5.** The main effects of GLP-1 actions (based on Baggio, Drucker, Gastroenterology 2007) [72]

Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP) is a 42 amino acid peptide secreted by K cells in the mucosa of the duodenum, jejunum and the proximal portion of the ileum. Both GIP and GLP-1 show incretin activity – stimulating food intake mediated insulin secretion by $\beta$-cells in the islets of Langerhans [72, 76]. Postprandial GIP levels depend on the basic nutrient content of a meal. Higher values are observed after the ingestion of carbohydrates, compared with proteins [77].

Glucose-dependent insulinotropic polypeptide receptors are found not only in $\beta$-cells in the islets of Langerhans, but also in the adipose tissue, the central nervous system, the heart, the adrenal cortex and on the vascular endothelium. Additionally, GIP stimulates D-cells in the pancreatic islets to secrete somatostatins [72, 78, 79] and glucagon [80]. Both GIP and GLP-1 are rapidly ($T_{1/2} = 2$ min) degraded by dipeptidyl peptidase-4 [71]. Resistance to GIP is observed in diabetic patients, which may be caused by a defect at the receptor level [81, 82].
Conclusions
Recent studies indicate an important role of gastrointestinal hormones in appetite and satiety regulation. Evidence exists to prove that brain-gut axis disorders result in excessive energy accumulation and development of overweight and obesity. Peptides released from the gastrointestinal tract affect the activity of the hypothalamus and brain stem, both involved in food intake regulation and food habit modulation. Applying the knowledge of the brain-gut axis mechanism of action and implementing the data on physiological bases of food intake regulation in clinical practice may allow for more effective management of the obesity epidemic.

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