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Regulation of Appetite and Satiety by Gastrointestinal Peptides

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Abstract

In recent decades, global obesity has increased significantly, causing a major health problem with associated complications and major socioeconomic issues. The central nervous system (CNS), particularly the hypothalamus, regulates food intake through sensing the metabolic signals of peripheral organs and modulating feeding behaviors. The hypothalamus interacts with other brain regions such as the brain stem to perform these vital functions. The gut plays a crucial role in controlling food consumption and energy homeostasis. The gut releases orexigenic and anorexigenic hormones that interact directly with the CNS or indirectly through vagal afferent neurons. Gastrointestinal peptides (GIP) including cholecystokinin, peptide YY, Nesfatin-1, glucagon-like peptide 1, and oxyntomodulin send satiety signals to the brain and ghrelin transmit hunger signals to the brain. The GIP is essential for the control of food consumption; thus, explain the link between the gastrointestinal tract (GIT) and the brain is important for managing obesity and its associated diseases. This review aimed to explain the role of gut peptides in satiety and hunger control.

Keywords: Obesity, Gastrointestinal peptides, Ghrelin, Oxyntomodulin.

تنظيم الشهية والشبع بواسطة الببتيدات المعدية المعوية

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الخلاصة

في العقود الأخيرة ، زادت السمنة العالمية بشكل كبير ، مما تسبب في مشكلة صحية كبيرة مع المضاعفات المرتبطة بها والمشاكل الاجتماعية والاقتصادية الرئيسية. يلعب الجهاز العصبي المركزي ، ولاسيما تحت المهاد ، دورا حاسما في تنظيم تناول الطعام عن طريق استشعار اشارات التمثيل الغذائي للأعضاء الطرفية وتعديل سلوكيات التغذية. يتفاعل المهاد مع مناطق أخرى في الدماغ مثل جذع الدماغ لأداء هذه الوظائف الحيوية. تلعب القناة الهضمية دوراً حاسماً في التحكم في استهلاك الغذاء وتوازن الطاقة. تطلق القناة الهضمية هرمونات التي تتفاعل مباشرة مع الجهز العصبي المركزي او بشكل غير مباشر من خلال الخلايا العصبية .

الببتيدات المعدية المعوية بما في ذلك كوليسيستوكينين ، الببتيد ، الببتيد ١ الجلوكاجون و أوكسيتومودولين ترسل اشارات الشبع الى الدماغ و جريلين يرسل اشارات الجوع الى الدماغ . هرمون الببتيد المشتق من الأمعاء ضروري للسيطرة على استهلاك الطعام. وبالتالي ، فإن شرح العلاقة بين الجهاز الهضمي والدماغ مهم لإدارة السمنة والأمراض المرتبطة بها. تهدف هذه المراجعة إلى توضيح دور الببتيدات المعوية في الشبع والسيطرة على الجوع.

الكلمات المفتاحية: السمنة ، الببتيدات المعدية المعوية ، جريلين ، أوكسينتومودولين

Introduction

The control of food intake in healthy individuals is done by gastrointestinal peptides (GIP) that stimulate hunger or satiety. Disturbance of GIP metabolism can lead to obesity [(1)]. The coordination of central and peripheral signals that control energy homeostasis is vital to understand appetite control. In the body's energy balance, the central nervous system (CNS) that receives signals from the digestive tract and adipose tissue plays an indispensable role. Hunger and satiety are controlled by the brain-gut axis [(2)]. GIP monitor food consumption, stomach evacuation, and bowel movements, collectively control body weight over the long term [(3)].

Several peptides originated from the gut inhibit food intake, specifically cholecystokinin (CCK), peptide tyrosine (PYY), glucagon-like peptide 1 (GLP-1), and nesfatin-1. In contrast, ghrelin which is centrally acting and peripherally delivered peptide stimulate food intakes [(4)].

The worldwide spread of obesity and the major complications associated with it have induced greater necessity to understand the processes of energy balance. The present review aimed to explain the role of GIP Involved primarily in hunger and satiety regulation.

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Brain-Gut Food intake Regulation

The hypothalamus is critical in the relaying of afferent signals from the gut and brainstem as well as processing efferent signals that modulate food intake and energy expenditure. The hypothalamus arcuate nucleus (ARC) is a structure located at the base of the hypothalamus, adjacent to the median eminence (ME). The latter has a more permeable blood-brain barrier (BBB), which makes the ARC neurons exposed to nutrients and gastrointestinal peptides. The ARC transmits circulatory signals to other hypothalamic zones, as well as to extrahypothalamic areas such as the mesolimbic reward system and to the hunger and satiety sites in the nucleus tractus solitaries (*NTS*) [(5)]. The ARC contains two neuronal populations in the ARC implicated in the regulation of feeding. Orexigenic neurons (i.e. stimulating appetite) express neuropeptide Y (NPY) and agouti-related protein (AgRP). Whilst anorexigenic neurons (i.e. inhibiting appetite) in the ARC express cocaine -and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC). Neuronal projections from these two populations then communicate with other hypothalamic areas involved in appetite regulation such as the Paraventricular nucleus (PVN), Dorsomedial nucleus (DMN), and Lateral hypothalamic area (LHA) [(6)] . Table 1 explains the role of GIP in food intake control

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Table1. GIP activities in food intake control [(6)]

GIP	Receptor	Site of action	Effects on food intake
Ghrelin	ghrelin receptor	Vagal nerve Brain stem Hypothalamus	orexigenic ↑ appetite ↑ gastric motility
Nesfatin-1	Melanocortin receptor	Vagal nerve Brain stem Hypothalamus	Anorexigenic ↓ appetite
CCK	CCK1	Vagal nerve Brain stem Hypothalamus	Anorexigenic ↓appetite ↑ gallbladder emptying ↓ gastric emptying
Peptide YY	Y2R	Vagal nerve Brain stem Hypothalamus	Anorexigenic ↓gastric emptying ↓ intestinal motility
GLP-1	GLP-1	Vagal nerve Brain stem Hypothalamus	Anorexigenic ↑insulin release ↓gastric acid secretion
OXM	GLP-1 Glucagon	Hypothalamus	Anorexigenic ↑ energy expenditure ↓ gastric emptying and secretion

↑, increase; ↓, decrease; GIP " gastrointestinal peptides" , GIT " gasterointestinal tract ", CCK "cholecystokinin ", GLP-1"glucagon like peptide-1", PYY "Peptide YY", OXM "oxyntomodulin" , Y2R " neuropeptide Y2 receptor ".

Gastrointestinal Peptides Coordinating Satiety and Appetite

1- Ghrelin

Ghrelin is biosynthesized and secreted from the stomach, small intestine, pancreas and brain [(7)]. Ghrelin is found in the bloodstream in two forms. First is deacyl-ghrelin (desacyl-ghrelin) which is more stable and higher levels than other forms. Second is the acylated form (acyl-ghrelin AG) which is the product of post-translational acylation of the hydroxyl group of the ser3 residue of the nascent ghrelin, catalyzed by ghrelin-o-acyltransferase (GOAT), This acylated form corresponds to around 20 % of the total circulating ghrelin and is responsible for the biological activity of ghrelin. GOAT is responsible for the acylation of the preproghrelin and converted to proghrelin that is proteolytically cleaved by the prohormone convertase. [(8)]. The biological activities of acyl-ghrelin are mediated by binding to the growth hormone secretagogue receptor (GHS-R1a) [(8)]. Acyl-ghrelin has several functions in many tissues. Acyl-ghrelin stimulates the secretion of growth hormones from the anterior pituitary gland and activates the hypothalamic orexigenic axis by induction the secretion of neuropeptides such as

NPY, stimulating food intake and reducing energy expenditure. [9] Thus, ghrelin exhibits orexigenic properties and has been targeted for the treatment of obesity. Chronic administration of ghrelin promotes weight gain and obesity [10]. The circulating concentration of orexigenic ghrelin increased in obese patients with Prader – Willi syndrome [11]. In addition to its orexigenic effect mediated by neuropeptide Y, ghrelin contributes to obesity by stimulating GH secretion from the pituitary gland [12].

The dimerization property of GHS-R1a with multiple G-protein coupled receptors allowing the cross-talk between many other neuropeptide systems of serotonin and dopamine. Hence, ghrelin has the potential to engage various neuropeptide systems in mood, food, and obesity [13,14].

The ghrelinergic system mediates the non-homeostatic hedonic rewarding and motivational aspects of food intake via mesolimbic dopaminergic circuitry [15,16].

Ghrelin receptors spread widely throughout the body, with high levels of pituitary and hypothalamic expression with lower levels of expression in peripheral tissue, especially in the pancreas, GIT, immune cells, and the heart. Further, ghrelin enhances GIT motility and diminishes insulin secretion [17].

Patterson *et al.* reviewed many studies cored about antagonizing ghrelin action by competitive inhibition or by neutralizing ghrelin, as targets for the treatment of obesity [18,19]. Also, the antagonizing ghrelin action may be used as a treatment of nutritional disorders like cachexia and anorexia nervosa [3].

2- Nesfatin-1

Nesfatin-1 (NF-1) was first identified in 2006 as an anorexigenic peptide. Its precursor protein, non-esterified fatty acid / nucleobinding 2 (NUCB2) is expressed in CNS and peripheral tissue. [20]. NF-1 is secreted centrally from the hypothalamus and freely crosses the BBB. In addition, it is released peripherally from gastric mucosa, adipose tissue, pancreas, and testis tissue [21]. Many studies have shown that central or peripheral NF-1 injection significantly reduce food intake in rodents [22,23,24]. Also, NF-1 may affect absorption and digestion of food which is explained by reduced NUCB2 mRNA expression in GIT and hindered fasting gastric emptying [25]. Injection of NF-1 in brain of leptin-receptor mutant rats can suppress food intake by activating the melatonin system, irrespective of the leptin pathway [22].

Direct inhibition of an orexigenic substance is a possible mechanism for understanding the inhibition of food intake by NF-1. In vitro study has shown that NF-1 induces hyperpolarization in ARC nuclei that are responsible for the secretion of NPY [26]. Studies on various physiology parameters are ongoing to clarify differences in the NF-1 pathways. NPY and the α-melanocyte-stimulating hormone (α-MSH) have a controversial effect on the NF-1/NUCB2 neurons of the PVN that are activated by α-MSH and inhibited by NPY; both effects are mediated by regulating cytosolic calcium ion levels [27]. Finally, NF-1 has been reported to regulate gastric motility through its effect on the PVN and the LHA [28]. Peripheral effects of NF-1 seem to be more concerned about decreasing gastric motility and increasing the glucose-stimulated release of insulin [29,30].

3- Cholecystokinin

Cholecystokinin (CCK) is biosynthesized and released by endocrine I cell in the mucosal lining of the small intestine, as well as neurons of the enteric nervous system, and neurons in the brain [31]. Circulating CCK levels are increased at 14 minutes after food intake and persist about 3 hours; CCK is inactivated by tripeptidyl peptidase II. Fat and protein-rich foods are strong release stimuli. While, duodenal bile acids are powerful biological CCK release suppressors [32].

CCK actions are mediated via binding to two G protein-coupled receptors, CCKA and CCKB. CCKA exists in many tissues, including GIT, the pancreas, hepatitis, and vagal afferents, whereas CCKB is the dominant type in the CNS, especially the brain [33]. The CCK-induced satiation by linking CCKA receptors on the vagus nerve [34]. So, the CCK can, directly and indirectly, transmit satiation signals to the brain. The CCK's physiological functions are to promote enzyme release, facilitate GIT motility, and defer gastric emptying. CCK and leptin produce short-term food inhibition and promote long-term body weight loss, which can be considered as a potential target for obesity treatment [4]. The primary clinical area of focus for CCKA receptor agonists was obesity treatment [35]. Variability in CCK-1 receptors can enhance obesity propensity. CCK seems to be more important in satiation than satiety [36].

The manipulation of CCK-satiation signals by drugs has been found to impact eating behavior by influencing meal size but not the number of meals [37]. Nevertheless, the study shows that CCK has an essential role as an anti-obesity counterbalanced by reducing the food intake via raising the number of meals without altering body weight [38]. Administration of CCKA receptor agonists to obese subjects has failed to reduce body weight [39]. However, coadminstration of CCK and leptin in rats has shown to have a synergistic effect on weight loss [40]. It is worthy to mention that both CCKA and leptin receptors are expressed on vagal afferent neurons that may explain the synergistic effect between CCK and leptin in weight reduction [41].

4- Peptide tyrosine-tyrosine

Peptide tyrosine-tyrosine (PYY) is anorexigenic peptide that consists of thirty-six amino acid residues. Structurally, it is characterized by the

presence of pancreatic polypeptide (PP)- fold, similar to other peptides like NPY, GIP, and PP. PYY is synthesized by the intestinal enteroendocrine L-cells of the ileum and colonalong with other gut like GLP-1 and oxyntomodulin (OXM), and is secreted in response to food intake [42]. PYY secretion is proportional to meals' quality, and its circulatory levels increase to up to 6 hours within 2 hours of food intake [43]. There are two significant forms of PYY found in circulation, PYY1-36 and PYY3-36. PYY1-36 is cleaved into PYY3-36 by dipeptidyl peptidase 4 (DPP4). PYY3-36 may act centrally by completive inhibition of NPY Y2 receptor (Y2R) on NPY neurons suppressing food intake. Decreased endogenous levels of PYY in obese subjects when compared to lean subjects [44]. Obese people have lowered PYY3-36 levels while fasting PYY3-36 levels have been elevated since gastric bypass operation and other conditions associated with reduced appetite [43]. It is suggested that increased fast and postprandial levels of PYY in massively obese individuals play a significant role in their dramatic weight loss after gastric sleeves [45].

5- Glucagon-like peptide-1

Glucagon-like peptide-1(GLP-1) formed by differential processing of the proglucagon gene in ileum cells and colon L cells [46]. Central and peripheral GLP-1 behaviors are essential to appetite control. In normal conditions, GLP-1 secretion triggered by intake of food rich with glucose and fatty acid, it is serving as an "incretin" and causing increased insulin secretion after food intake, thus, influencing glucose homeostasis. Other GLP-1 actions involve repression of glucagon secretion, impaired gastric emptying, and GIT motility suppression. The half-life of GLP-1 is short due to the quick degradation of an active form into inactive form, following dipeptidyl peptidase-4 (DPP-4) disconnecting 2 terminal amino acids. [47]. GLP-1 has anorexigenic effects via the large-scale receptors in the GIT, pancreas, and brain [48]. Also, it reduces the rate of food absorption into circulation by decrease the gastric emptying rate [49].

GLP-1 was the first reliable GIT hormone utilized for human medicine. Many preparations of GLP-1 receptor agonists and DPP-IV blockers for type 2 diabetes mellitus (type 2 DM) treatment are presently available [50]. The effectiveness of GLP-1 receptor agonists in promoting weight loss at doses used to regulate diabetes has restricted effectiveness [51].

Obesity preserves the anorectic action of GLP-1. Consequently, diminished GLP-1 secretion may lead to obesity pathogenesis. The impact of GLP-1 on appetite and food intake may help weight loss [52].

The GLP-1 normalizes glycosylated fructosamine, decrease glycated hemoglobin, and reduces body weight after 6 weeks of treatment in type 2 DM patients. [53]. Therefore, GLP-1 is considered good medicine to control appetite and treat obesity and type 2 DM [45].

6- Oxyntomodulin

Oxyntomodulin (OXM) is a pro-glucagon 37-amino acid peptide product, it is synthesized and secreted from the intestinal L-cells with a response to caloric consumption. OXM reduces pancreatic secretions and gastric motility and secretions and stimulates glucose metabolism [54]. OXM joins both the glucagon and GLP-1 receptors, while its effect on appetite mediated by GLP-1 receptor since the treatment with a GLP-1 receptor blocker prevents the anorectic effects of OXM [54].

OXM offers an exciting possibility as an anti-obesity because of its binary actions on food intake reduction and increased energy expenditure. It is acts as a glucagon receptor agonist to raise energy expenditure without effect on glucose levels. The agonist action of OXM on both GLP-1 and glucagon receptors confirmed by reduced body weight without disruption of glycemic control, and an improved lipid profile in diet-induced obese animals, which gives suggestions the future expansion of obesity therapies [55, 56].

Obesity Control with Gut Peptide Therapies

Obesity is a worldwide health problem, which is a major contributor to cardiovascular disease and cancer. The World Health Organization has forecast an overweight of about two billion adult populations and million obese by 2015 [57]. Obesity is defined as an imbalance between consumption and expenditure of energy. Food intake is regulated via orexigenic and anorexigenic peptides. A chronic imbalance between signals of hunger and satiety increases the risk of obesity [58].

Nearly every medicine and compartmental treatment for obesity lead to weight reduction and weight recovery. Conversely, gastric sleeve is a treatment of obesity that provides safe weight loss control for an extended period. The mechanisms following the bariatric surgery for long-term weight loss have yet to be identified; however, numerous gut hormones are involved in this; ghrelin decreases and increases in PYY and GLP-1 levels are noted after bypass surgery [59]. Inhibiting the response of PYY and GLP-1 gave rise to appetite and increases food intake. Thus, high levels of PYY and GLP-1 play an essential role in weight loss after stomach bypass surgery [60]. Gastric bypass surgery can not consider alone for the treatment of obesity due to its costly and major complications associated with each surgery. Pharmacotherapy is necessary, leading to substantial, treatable, continuous loss of weight, diabetes, and cardiovascular health improvement [60].

For the following reasons, gut hormones have developed as the main type of target management of obesity. Also, surgical treatment of obesity is known to increase the postprandial release of GIP like GLP-1, oxyntomodulins, PYY, and it is supposed to lead to many of the metabolic perks of this surgery [60,61]. The restriction of these hormones in patients with gastric bypass surgery inverts some advantages of surgery such as decreased appetite [62]. The PYY and OXM combination causes a preferable decrease of appetite relative to the hormone alone [63]. Also, when giving oral PYY3-36 together with GLP-17-36 amide in conjunction with sodium N-caprylate to 12 healthy human-caused a significant reduction of energy consumption in the dinner served 15 minutes later [64]. Oxyntomodulin and PYY hormones can also reproduce the levels of post-prandial intestinal hormones shown after gastric bypass when given to 10 obese healthy individuals as a subcutaneous infusion for 10 hours [65]. Dual and even three-fold agonists of the intestinal hormones can serve as the basis for optimal body weight loss and a new obesity treatment strategy.

However, many remedies do not produce a dramatic weight loss of over 5 percent and cause serious side effect like fatigue, heart disease, and neurological effects [66,67]. Thus, hormones must control food consumption, digestion, and, therefore, bodyweight without systemic administration's dangerous effects. Due to the administration of nutrients or medication compounds, the enter endocrine network could raise weight reduction efficiency and mimic physiological sensors of feeling full and appetite control [68]. To induce endogenous gut hormone discharge, nutritional stimulation of the enter endocrine L cell taste receptors into the distal small intestine and colon must be regarded. In reality, sweet taste receptor in vitro stimulation in immortalized and primary L cell crops induces hormone release, including OXM, GLP-1, and PYY [69]. Thus, it is promising to specifically target nutrient receptors via oral or rectal administration with further study is required. Endogenous secretion of GIP may have an appropriate therapeutic choice for diabetes type 2 and obesity [70].

Conclusion

The hypothalamus combines GIT signals with signals of other peripheral tissues or external environments. The processing of all input signals in CNS produces different compensatory responses to maintain energy homeostasis. The role of peptide hormones derived from the GIT is controlling body weight and energy homeostasis. Decrease appetite increases satiety with enhancing energy expenditure are criteria required to control the body weight. The characteristic of GIP fulfills these criteria make them more effective therapeutic approaches against obesity and obesity-related diseases. Further research needed to explain the effectiveness of gut peptide as an effective therapeutic strategy for weight gain to reduce morbidity and mortality related to obesity.

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