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Gut hormones regulating Apetite

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Abstract

Obesity is a global health crisis resulting in major morbidity and premature death. The obesity epidemic has been recognized by the World Health Organization (WHO) as one of the top 10 global health problems. No currently available medical therapy delivers substantial, sustainable weight loss. Over the last 20 years, peptide hormones released from the gastrointestinal tract in response to nutritional stimuli have come to be recognized as important physiological regulators of appetite. Hormones such as peptide YY, pancreatic polypeptide, glucagon-like peptide-1 and Oxyntomodulin are thought to act as postprandial satiety signals. Here, we review the state of current knowledge of these hormones for future research and development.

Key words: cholecystokinin, ghrelin, peptideYY, glucagon-like peptide-1, Oxyntomodulin

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INTRODUCTION

Obesity: Definition and scope of the problem

Obesity is defined as a condition associated with the accumulation of excessive body fat resulting from chronic imbalance of energy whereby the intake of energy exceeds expenditure [1]. Obesity develops within the context of a sustained positive energy balance, due to a combination of reduction in activity related energy expenditure and increased dietary energy intake[2].Obesity is a global epidemic which is associated with an increased risk for type 2 diabetes and cardiovascular disease, musculoskeletal disorders, sleep apnea, and some forms of cancer[3,4,5]. Children are also increasingly overweight, with estimates as high as 20 million globally. More than 90% of obese individuals regain lost body fat within 2 yr. Emerging scientific concepts provide a new basis for understanding the multiple causes of obesity as well as the underlying mechanisms involved in weight dysregulation.[4,6] Many advances have been made recently in the understanding the regulation of body weight by homeostatic system. For most people, the amount and composition of food eaten differs considerably from meal to meal and from day to day. Thus, food intake, both meal frequency and meal size, must also be highly

regulated [7, 8,15]. Better understanding of appetite regulation improves understanding of the etiology of debility or obesity [9]. No single and/or combination therapy has yet been fully successful. Novel therapeutic targets are urgently required [10]. Successful pharmacologic treatment for obesity may be possible only by simultaneously targeting the interlocking, redundant systems that drive food intake and act to resist the loss of body fat [11]. The need to better understand the mechanisms of appetite regulation is therefore clear. Over the last 20 years, peptide hormones released from the gastrointestinal tract in response to nutritional stimuli have come to be recognized as important physiological regulators of appetite. Hormones such as peptide YY, pancreatic polypeptide, glucagon-like peptide-1 and Oxyntomodulin are thought to act as postprandial satiety signals. These physiological pathways of appetite control offer a promising basis for anti-obesity therapies [12].

Gut hormones:

The gastrointestinal tract is the largest endocrine organ in the body .Gut hormones which are Secreted from the GI tract either before or after each meal, function to optimize the process of digestion and absorption of nutrients by the gut. In this process, their local effects on gastrointestinal motility and secretion have been well characterized. By altering the rate at which nutrients are delivered to compartments of the alimentary canal, the control of food intake constitutes another point at which intervention may promote efficient digestion and nutrient uptake. Because they occur naturally, they are almost free from undesirable side effects that would result in reduced tolerability and safety. Therefore, they are regarded as potential novel therapeutic agents in obesity treatment. However, further studies are required to explore their efficacy, safety and tolerability, particularly in the long-term treatment [7,13]. Eating releases a number of gut hormones, including Oxyntomodulin, Glucagon-like peptide 1(GLP1), peptide YY (PYY3-36) and pancreatic polypeptide .These hormones have been found to inhibit appetite. They also inhibit release of the ‘hunger hormone’ ghrelin. Ghrelin is a peptide hormone released from the endocrine cells of the stomach when you’re hungry and ghrelin release is reduced after a meal. Thus gut hormones produce a co-ordinated satiety response.

Many gut peptides have been shown to influence energy intake. The most well studied in this regard are cholecystokinin (CCK), pancreatic polypeptide, peptide YY, glucagon-like peptide-1 (GLP-1), Oxyntomodulin and ghrelin. With the exception of ghrelin, these hormones act to increase satiety and decrease food intake. The mechanisms by which gut hormones modify feeding are the subject of ongoing investigation. Local effects such as the inhibition of gastric emptying might also contribute to the decrease in energy intake. The global increase in the incidence of obesity and the associated burden of morbidity has imparted greater urgency to understanding the processes of appetite control. As physiological mediators of satiety, gut hormones offer an attractive therapeutic target in the treatment of obesity. [13]

Cholecystokinin was the first to be implicated in the short-term control of food intake and other appetite-regulating hormones have subsequently been characterized. Of these, ghrelin is the only known orexigenic gut hormone, whereas a number of satiety factors exist, including glucagon-like peptide-1 (GLP-1), Oxyntomodulin (OXM), peptide YY (PYY) and pancreatic polypeptide (PP).these gut hormones act as meal initiators and terminators. Their role as agents of appetite regulation has been investigated by both observational and interventional studies. Characterization of the release patterns of different gut hormones in relation to nutrient ingestion

can provide insights into their effects on appetite. Furthermore, alterations in levels of gut hormones following bariatric surgery may contribute to the appetite suppression and sustained weight loss seen in patients undergoing this procedure and supports the development of these hormones as therapeutic targets. Administration of exogenous peptide to animal models and human volunteers, and measurement of their effect on food intake, also illuminates the actions of these hormones on appetite. [12]

Cholecystokinin

Cholecystokinin CCK is the prototypical satiety hormone, produced by mucosal enteroendocrine cells of the duodenum and jejunum secreted into the lumen of the gut in response to the presence of was demonstrated to have appetite regulatory effects, acting primarily to promote meal termination via the vagus nerve and also controls the expression of both G-protein coupled receptors and peptide neurotransmitters. [9, 14, 15, 16]Multiple biologically active forms of CCK coordinate postprandial gall bladder contraction and pancreatic secretion with gastric emptying and gut motility. Reduction in meal size is mediated by CCK1 receptors, which preferentially bind sulfated CCK on vagal afferent neurons; hence, vagotomy reduces the effect of CCK on satiety. Gastric emptying is also inhibited by CCK1 receptors on the pyloric sphincter, which may contribute to satiety [16]. Infusion of CCK in human subjects suppresses food intake and causes earlier meal termination [15, 16] In rats, continuous intraperitoneal infusion produces tolerance after 24 h. Acute studies in rats reveal that CCK acts to initiate early meal termination but that this is ultimately compensated for by an increase in meal frequency.[15]

Since CCK only intermittently preserves its anorexigenic activity between injections of exogenous CCK, compensatory overeating occurs, so it is unlikely that this peptide could be useful in anti-obesity therapy [9]. However, the physiological or pharmacological nature of the actions of CCK on food intake also awaits further clarification. [13]

PYY

PYY is a a naturally occurring peptide belonging to the NPY family. It is produced by the gut and is released into the circulation after meals. The major metabolic form of PYY both stored and in circulation is PYY 3-36 and this is an N-terminally truncated form of the full-length peptide [9, 17]. PYY3-36, acts via Yl, Y2, Y3 and Y5 receptors [9, 15]. Peripheral injection of PYY3-36 in rats inhibits food intake and reduces weight gain [9, 18], where as Central administration of PYY3-36 stimulate food intake [9]. Obesity does not appear to be associated with resistance to PYY (as it is with leptin), and exogenous infusion of PYY 3-36 results in a reduction in food intake by 30% in an obese group and 31% in a lean group. After a meal, PYY is released shortly after food intake; this is likely to be under neural control because it occurs before ingested nutrients reach the distal small intestine and colon, where the greatest concentrations of PYY 3-36 are found. Further release is seen when the nutrients arrive at this region of gut and is particularly stimulated by carbohydrates and lipids. PYY is likely to affect appetite via a direct central effect and also via its effects on gut motility; it acts as an “ileal brake” and so leads to a sensation of fullness and satiety [8] Future studies investigating the chronic use of steady-state preparations of PYY are warranted. A more detailed understanding of the Y-receptor system and the highly complicated neuronal circuitry involved in the appetite

regulatory effects of PYY is vital for the development of optimally targeted antiobesity drugs of this nature. [15]

Pancreatic polypeptide:

Pancreatic polypeptide Sharing some common structural features with PYY3-36, PP is principally secreted by a population of cells located at the periphery of pancreatic islets.[12,13] It is released into the circulation in response to nutrient ingestion and is subject to control by the vagus nerve [12], in proportion to calories ingested and levels remain elevated for 6 h[15] Chronic administration of PP to rodents reduces food intake, increases energy expenditure and results in a loss of bodyweight The anorexigenic effect of intra-peritoneal administered PP in rodents is abolished by vagotomy[15]. The role of PP in the regulation of energy balance is unclear. Studies have shown that circulating levels are reduced in the context of obesity, and there is abnormal release following a meal, whereas levels are elevated in anorexic patients. However, these findings have not been universally replicated. PP reduces food intake when administered to rodents and humans. It remains to be evaluated whether this effect is preserved in obese humans. Work in those with Prader–Willi syndrome, characterized by overeating and morbid obesity, is encouraging, but not necessarily applicable to the more general, non-syndromic obese population.[12]

Glucagon-like peptide-1

Glucagon-like peptide-1 is a product of proglucagon cleavage [13] and is released from the L-cells of the GI tract post-prandially [15] in proportion to the amount of energy ingested. GLP-1 and longer-acting GLP-1 receptor agonists, such as exendin-4,reduce food intake in rodents when injected into the CNS or peripherally.[12] it is an incretin hormone which stimulates postprandial insulin release[15].it is an incretin hormone which stimulates postprandial insulin release.[12] In addition to its pancreatic glucoregulatory effects, the active form of GLP-1, GLP7–36amide, also inhibits food intake in a number of species when given centrally or peripherally[15].A major hurdle to the therapeutic use of native GLP-1, and one common to many gut hormones, is its short circulating half-life. Metabolism by the enzyme dipetidyl peptidase IV (DPP-IV) is the principal means by which circulating GLP-1 is inactivated. A number of DPP-IV-resistant GLP-1 receptor agonists, such as liraglutide and exenatide have therefore been developed and are currently in various stages of testing as agents for the treatment of diabetes and obesity [12]. Oral GLP-1 (2-mg tablet) alone and the combination of oral GLP-1 (2-mg tablet) plus PYY3–36 (1-mg tablet) induced a significant reduction in calorie intake [15].

Ghrelin

Ghrelin, a 28 amino acid peptide, is produced by the stomach with appetite-stimulating and growth hormone– releasing activities mediated by the growth hormone secretagogue receptor and its level is highest in the fasting state, rising sharply before, and falling within one hour of, a Meal [11, 16]. Ghrelin, a newly discovered gut peptide is potentially an important new peripheral signal to the brain to stimulate food intake in human.[17] . Defective ghrelin signaling from the stomach could contribute to abnormalities in energy balance, growth, and associated gastrointestinal and neuroendocrine functions [19]. Wren and colleagues demonstrated that intravenous ghrelin infusion stimulates appetite and food intake potently in human and recent research showed that circulating ghrelin levels decreased in normal weight subjects after a meal[17] Low concentrations of circulating ghrelin have been associated with obesity, insulin

resistance, and type 2 diabetes[20].Chronic ghrelin administration induces adiposity without attenuation of the effects on food intake .Ghrelin also has local gut effects in addition to its effects on appetite, stimulating gastric emptying and decreasing gastric acid secretion in rodents[21] drugs that can block ghrelin will be very effective to overcome obesity without much disturbance in the physiological homeostasis of our body. Intense research is going on in this regard for a breakthrough drug in obesity [9]

Oxyntomodulin

Oxm is produced by processing of preproglucagon in the gut and brain and is released after eating .Central administration of Oxm inhibits food intake in the rat with greater potency than does GLP-1 .Oxm appears to act via a GLP-1-like receptor because its anorectic actions are blocked by co administration of the GLP-1 receptor antagonist, exendin 9-39 .[9] Recently, it was shown that Oxm is also a potent inhibitor of food intake when administered ip to rats . Intraperitoneal administration of Oxm results in c-fos expression in the arcuate nucleus, a region partially outside the blood-brain barrier, but there is little activation of neurons in the nucleus of the solitary tract in the brain stem. These experiments demonstrate that Oxm has a very different pattern of neuronal activation from that of GLP-1. When the antagonist exendin 9-39 is injected into the arcuate nucleus, circulating Oxm no longer inhibits food intake, suggesting an arcuate site of action. By contrast, the effect of circulating GLP-1, acting via the brain stem, is unaffected. In humans, iv infusion of Oxm reduces food intake at a free-choice buffet meal by 19.3%, with the total calorie intake remaining lower at 12 h after infusion. Further work is needed to establish a role physiologically for reduction in appetite after a meal and for homeostatic regulation of body weight.[8] subcutaneous self-administration of Oxyntomodulin three times daily in the community reduced body weight, decreased food intake, and altered the levels of adipose hormones in overweight and obese nondiabetic human subjects.[10] OXM offers another promising target in the development of a therapy for obesity[13].

CONCLUSION

Successful pharmacologic treatment for obesity may be possible only by simultaneously targeting the interlocking, redundant systems that drive food intake and act to resist the loss of body fat. Evidence suggests that the gut acts as a nutriment sensor, resulting in the release of several hormones. Gut hormones as part of their function to optimize the digestive process, it was perhaps inevitable that they should also act to regulate appetite and food intake. As physiological mediators of satiety, gut hormones offer an attractive therapeutic target in the treatment of obesity.

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