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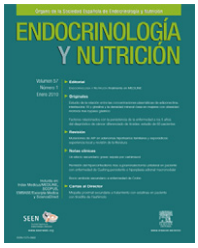

REVIEW ARTICLE

The role of gut hormones in controlling the food intake. What is their role in emerging diseases?

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Peptide YY (PYY)

Abstract Central nervous system (CNS) receives peripheral relevant information that are able to regulate individual's energy balance through metabolic, neural, and endocrine signals. Ingested nutrients come into contact with multiple sites in the gastrointestinal tract that have the potential to alter peptide and neural signaling. There is a strong relationship between CNS and those peripheral signals (as gastrointestinal hormones) in the control of food intake. The purpose of this review is to give updated information about the role of gut hormones as mediators of feeding behavior and of different nutrients in modulating gut hormones production. The role of gut hormones in the pathogenesis of emerging diseases as obesity and non-alcoholic fatty liver disease (NAFLD) is also discussed together with the possible role of these peripheral signals as targets of future therapeutic options.
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PALABRAS CLAVE
Hormonas intestinales;
Obesidad;
Péptido-1 similar al glucagón (GLP-1);
Esteatohepatitis no alcohólica (EHNA);
Colecistocinina (CCC);
Grelina;
Péptido YY (PYY)

El papel de las hormonas intestinales en el control de la ingesta alimentaria: su función en enfermedades incipientes

Resumen El sistema nervioso central (SNC) recibe cierta información periférica capaz de regular el equilibrio energético del individuo a través de señales metabólicas, neuronales y endocrinas. Los nutrientes ingeridos entran en contacto con varios sitios del tracto gastrointestinal que son capaces de alterar las señales nerviosas y pépticas. Existe una fuerte relación entre el sistema nervioso central y estas señales periféricas (hormonas gastrointestinales) en el control de la ingesta de alimentos. El objetivo de esta revisión es aportar información actualizada sobre el papel de las hormonas intestinales como mediadoras de la conducta alimentaria, y de los diversos nutrientes que modulan la producción de hormonas intestinales. También se analiza el papel de las hormonas intestinales en la patogénesis de enfermedades incipientes tales como la obesidad y la esteatohepatitis no alcohólica (EHNA), así como la posibilidad de que estas señales periféricas sean dianas en futuras alternativas terapéuticas.
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Introduction

The energy balance is regulated to defend a ''set point'' in body weight, whereas the food intake has a wide range of variations within each individual. New regulative mechanisms regarding gut–brain relationship have been recently discovered, allowing a better comprehension about the way in which energy homeostasis is regulated. Long-term and short-term hormonal signals connect periphery to the central nervous system influencing feeding behavior. Hypothalamus, specifically the arcuate nucleus and the dorsal vagal complex in the brain stem, are the most relevant structures involved in this function.[1] The role of the arcuate nucleus and the brain stem consists in an integration within signals coming from periphery and recognized in the gut hormones[2] (Fig. 1). Distinct subsets of neurons are involved, acting both as stimulants and as inhibitors toward food intake. Stimulant neurons are represented by neuropeptide Y (NPY) and agouti-related peptide (AgRP), while inhibitors include alpha-melanocyte stimulating hormone (alpha-MSH) and cocaine- and amphetamine-regulated transcript (CART). Typically, when one of these subsets is activated, the other is inhibited. Neurons responsiveness to hunger and satiety signals (as ghrelin, cholecystokinin, and PYY) are also modulated by body energy stores (represented by leptin and insulin).[3]

The aim of this article is to review the role of gut hormones as mediators of feeding behavior and of the different nutrients in modulating gut hormones production. The action and the burden of gut hormones in pathogenesis of emerging diseases as obesity and NAFLD are also emphasized as well as their possible role as future therapeutic targets.

Materials and methods

A medline and Pubmed search was performed to identify relevant past and recent (2000–2010) literature using the following keywords: control of food-intake, gut hormones and food intake, glucagon like peptide-1 (GLP-1), cholecystokinin (CCK), ghrelin, peptide YY (PYY), non-alcoholic fatty liver disease (NAFLD), and obesity.

Results

Gut hormones and food intake

During and after meal, ingested nutrients alter the release of gut peptides that may potentially modulate the food intake and contribute to a ''three-steps process'': *meal initiation, within-meal satiety and across-meal satiety influences*.[4]

Meal initiation

Ghrelin. Originally isolated as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) and for its capacity to stimulate growth hormone (GH) secretion, ghrelin is also the only orexigenic signal from the gastrointestinal tract and a long-term regulator of energy homeostasis.[5] This 28 amino acid peptide is modified post-translationally with an eight-carbon fatty acid by the enzyme ghrelin-O-acyl-transferase (GOAT). The acylation of ghrelin is required to activate the GHS-R and to mediate its effects on GH secretion and food intake.[6]

Ghrelin is mainly synthesized in the endocrine stomach cells and has a series of different biologic actions, including effects on glucose homeostasis, gut motility, pancreatic exocrine secretion, cardiovascular function, immunity and inflammation.[7] The physiological relevance of these actions remains unclear, and the major role of the ghrelin seems to be exerted in the regulation of energy balance. Ghrelin stimulates the synthesis of neuropeptide Y (NPY) and agouti-related protein (AgRP) in neurons of the arcuate nucleus of the hypothalamus, which in turn enhances food intake.[8] Ghrelin also stimulates appetite and food intake when it is administered systemically in humans.[9] Ghrelin also regulates the preprandial hunger. Plasma ghrelin peaks preprandially in human subjects, who have been deprived of time cues, initiating meals voluntarily.[10] In animal models, during postprandial period, plasma ghrelin is suppressed in proportion to the calories ingested, when macronutrient content and volume are kept constant.[11] Interestingly, fat appears to suppress ghrelin less potently per calorie than carbohydrates or proteins.[12,13] This may, in part, explain the reduced satiety and higher weight gain associated with high-fat diets.

Taken together, these data strongly suggest a role for ghrelin as a meal initiator. Whether ghrelin is the only hunger signal is yet undetermined. In addition, ghrelin appears to participate in long-term energy balance. Chronic administration of ghrelin in rodents results in fact in prolonged hyperphagia and weight gain.[14,15]

Within-meal satiety signaling

After a meal, nutrients pass into the stomach and intestine, and a number of gastrointestinal signals are released. Peptide signals also act to optimize the digestive process, and as short-term satiety signals. Three examples are: cholecystokinin (CCK), pancreatic glucagons and amylin.

CCK. CCK is widely distributed within the gastrointestinal tract, but the majority is synthesized in the duodenum and jejunum. It is rapidly released into the surrounding tissues and circulation in response to nutrients, in particular, fat and protein-rich meals in the gut, with levels rising approximately 5-fold postprandially.

Its main actions include delaying gastric emptying, stimulating pancreatic enzyme secretion and stimulating gall bladder contraction. Together with these actions, it also promotes the effective digestion of fat and protein in the small intestine by matching the delivery of nutrient with the capacity to digest it.[16] In addition it inhibits food intake. Administration of CCK, in humans and animals, inhibits food intake by reducing meal size and its duration.[17,18]

Recent work suggests that CCK-A receptors expressed by vagal afferent neurons are an important target for CCK in producing sensations of satiety, as well as inhibiting gastric emptying and stimulating pancreatic digestive enzyme secretion.[19] In animals it is thought that the reduction in food intake may be mediated by a paracrine/neurocrine effect since high concentrations of CCK occur only locally to the site of release.[20] Thus, locally released CCK may increase vagal tone, without a significant increase in plasma CCK level.

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