Enteroendocrine Systems That Sense Nutrients in the Gut and Control the Body

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Summary Gut hormones produced and released from enteroendocrine cells have key roles not only in nutrient digestion and absorption, but also in control of appetite, nutrient deposition and storage in the body. Several types of enteroendocrine cells sense nutrients after meal ingestion and release specific gut hormones. Understanding how gut hormone responses are controlled and in turn regulate physiological outcomes is an area of active research. In addition, the role of the endocrine system in human-physiology and in pathophysiology (obesity, diabetes, and gastrointestinal diseases) has begun being investigated. The symposium was organized to present and discuss recent advances in this research field from the aspects of bench to bedside.

Key Words enteroendocrine cells, gut hormones, nutrient-sensing

Enteroendocrine system

The gastrointestinal tract functions not only as a digestive and absorptive organ. In the intestinal epithelium, there are 4 major kinds of cell types. More than 90% are absorptive cells. Absorptive cells take up luminal nutrients and transport nutrients, to the basolateral side. Goblet cells secrete mucus into the lumen, and Paneth cells support the stem cell niche and secrete lysozyme and defensins into the lumen, thereby protecting epithelia from luminal bacteria. Although only contributing 1% of the epithelial population, enteroendocrine cells play various important roles to control not only the gastrointestinal tract, but also control the whole body.

Enteroendocrine cells are found scattered through the intestinal epithelium and have a bell-like shape. In addition, the microvilli of open-type enteroendocrine cells reach the gut lumen. Such a morphological feature suggests that enteroendocrine cells are able to catch luminal nutrients with high sensitivity.

Morphologically, there are several types among enteroendocrine cells. The typical one is the open type, in which the apex of the cell reaches the intestinal lumen. Another one is the closed type. Because the apex of cell does not reach the intestinal lumen, this type of cell does not seem to directly sense luminal nutrients. The roles of closed type cells are unknown. Possibly, these cells may sense absorbed nutrients or mechanical stimuli in the epithelium.

The major role of enteroendocrine cells is sensing luminal information, including nutrients, and then they release gut hormones to the basolateral side.

Plasma concentrations of some of gut hormones increase immediately after meal ingestion, such as within 15–30 min. One exception is ghrelin, whose secretion is reduced in response to meal ingestion. Ghrelin is produced in X/A-like cells in the stomach, and it enhances appetite. In the stomach, gastrin is produced in G cells, and stimulates gastric acid secretion postprandially.

Because recent research technologies revealed that a single enteroendocrine cell expresses not only a single hormone but various hormones, the traditional “one hormone–one cell type classification” appears inadequate. However, the letter code for naming EECs (such as G cells, or S cells) is still used to specify a population of enteroendocrine cells expressing a particular hormone (1).

The nutrient-induced gut hormone secretions and the functions of these key gut hormones are summarized in Fig. 1. Secretin is produced in S cells in the duodenum and stimulates pancreatic bicarbonate and water secretion. Cholecystokinin, CCK, is produced in I cells in the proximal small intestine, and stimulates pancreatic enzyme secretion, and reduces appetite.

Glucose-dependent insulinotropic polypeptide (GIP, formerly called “gastric-inhibitory polypeptide”) is produced in K cells, mainly located in the proximal small intestine. GIP and glucagon-like peptide-1 (GLP-1) together are known as incretin hormones, based on their insulinotropic action.

GLP-1, and glucagon-like peptide-2 (GLP-2), are co-produced from the proglucagon gene in L cells in the distal small intestine and the large intestine. Not only stimulating insulin secretion, GLP-1 has multiple actions including suppressing appetite, suppressing gastric emptying, promoting pancreatic beta-cell proliferation, and neuroprotective and cardioprotective actions. Co-secreted GLP-2 promotes intestinal epithelial proliferation.

Peptide-YY (PYY) is also produced in L cells and suppresses appetite and gastric emptying.

Other hormones such as serotonin, motilin, neurtensin, oxyntomodulin, and leptin are also known to be produced in the gastrointestinal tract.

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Initial research on cellular nutrient-sensing mechanisms focused on CCK- and GLP-1-producing cells because of the availability of model cell lines such as murine STC-1 cells (2) and GLUTag cells, human NCI-H716 cells, and primary murine L cells (3).

Glucose triggers GLP-1 secretion via cellular transport through sodium-dependent glucose transporter 1 (SGLT1), similarly to glucose-induced insulin secretion in pancreatic beta-cells. GPR40 (FFRA1) and GPR120 (FFAR4) function as long chain fatty acid receptors, while GPR41 (FFAR3) and GPR43 (FFAR2) function as short chain fatty acid receptors. Dietary peptides are sensed by the extracellular calcium-sensing receptor (CaSR) and peptide transporter 1 (PepT1), but the specific feature of dietary peptides having potent gut hormone-releasing activity are largely unknown. Some amino acids stimulate gut hormone secretion thorough CaSR, GPR142, and GPRC6A.

As described above, regulatory mechanisms underlying nutrient-induced gut hormone secretions have been revealed by substantial efforts of enteroendocrine researchers around the world.

The symposium was organized to present and discuss recent advances in this research field from the aspects of bench to bedside.

Frank Reimann (University of Cambridge, UK) focuses on the cellular and molecular mechanisms; Tohru Hira (Hokkaido University, Japan) focuses on changes in nutrient-induced GLP-1 secretion in obese model rats; John McLaughlin (University of Manchester, UK) focuses on human health and gastrointestinal disease.

**Cellular and molecular mechanisms in the enteroendocrine system**

As introduced above, gut hormones modulate various physiological actions including local intestinal motility and nutrient absorption, pancreatic exocrine/endocrine secretion and appetite. The research is focused on understanding the basic physiology of the enteroendocrine system and its involvement in metabolism and food intake regulation.

By using fluorescent markers expressed under the control of specific prohormone promoters (GLU-Venus transgenic male mice), labelled enteroendocrine cells were isolated. The pioneered procedure enabled single enteroendocrine cell investigations.

Yet-to-be-published single cell transcriptome analysis identified different clusters of enteroendocrine cells in mouse intestine and human intestinal organoids. These enteroendocrine clusters expressed transporters and receptors specific for macro-nutrients.

Live-cell imaging and whole-cell electrophysiology revealed stimulus-secretion coupling pathways in murine and human L cells (4, 5), for example confirming the important role of SGLT1 for glucose sensing.

Transgenic mice with Cre-recombinase expression under the control of promoters for gut hormone receptors enabled the identification of target cells in the gut and the central nervous system (6, 7).

Such research will help to identify new drugs for type 2 diabetes and obesity that act by targeting gut endocrine-secreting cells or their target tissues.

**Adaptive changes in nutrient-induced GLP-1 secretion in diet-induced obese model rats**

Secretion of GLP-1 is acutely stimulated by luminal nutrients, which results in enhanced insulin secretion from the pancreatic beta-cells and various postprandial responses. For postprandial GLP-1 response, small intestinal GLP-1-producing cells rather than colonic ones are more likely responsible.

Changes in GLP-1 production/secretion under obese/diabetic conditions are not well characterized either in human or animal research (8, 9).

It was investigated whether nutrient-induced GLP-1 secretion is increased or diminished in diet-induced obese model rats. Compared to rats fed a normal diet, rats fed an obesogenic diet had higher glycemic, insulin and GLP-1 responses to meals (10). Blocking the GLP-1 signal further increased postprandial glycemia in rats.
fed the obesogenic diet (11). In genetically diabetic model rats, nutrient-induced GLP-1 secretion was not enhanced by chronic feeding of the obesogenic diet, while glycemic response was further increased (12). It was suggested that enhancement of the postprandial GLP-1 response during obesity development has a role in maintaining a normal postprandial glycemic response.

Because GLP-1 productions were not increased in the small intestine, the nutrient-sensing functions of GLP-1-producing cells could be modified by continuous feeding of an obesogenic diet.

**The enteroendocrine system in human health and in gastrointestinal disease**

The roles and integrated functions of the enteroendocrine system are not fully understood because of its inaccessibility and diffuse nature. It is well established that the enteroendocrine system plays key roles in the digestion and absorption of ingested food. A more recent focus has been on its potential role as a source of satiety hormones.

However, it has been unclear how much of a role gut hormones play in normal food intake regulation. The impact of normal postprandial gut hormones on appetite-related behaviors in humans is also uncertain (13).

In gastrointestinal diseases, there is growing evidence that supraphysiological levels of gut hormones have a major impact on appetite regulation, which may drive other symptoms (14). That is possibly an appropriate part of an intrinsic response to injury and inflammation.

Both in gastrointestinal diseases and in obesity, further research is required to better understand the mechanisms involved in appetite regulation/dysregulation and to recognize the potential impacts offered by targeting the enteroendocrine system.

**Disclosure of state of COI**

No conflicts of interest to be declared.

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**REFERENCES**


