

# Interaction between diet and gastrointestinal endocrine cells (Review)

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**Abstract.** The gastrointestinal endocrine cells are essential for life. They regulate the gastrointestinal motility, secretion, visceral sensitivity, absorption, local immune defense, cell proliferation and appetite. These cells act as sensory cells with specialized microvilli that project into the lumen that sense the gut contents (mostly nutrients and/or bacteria byproducts), and respond to luminal stimuli by releasing hormones into the lamina propria. These released hormones exert their actions by entering the circulating blood and reaching distant targets (endocrine mode), nearby structures (paracrine mode) or via afferent and efferent synaptic transmission. The mature intestinal endocrine cells are capable of expressing several hormones. A change in diet not only affects the release of gastrointestinal hormones, but also alters the densities of the gut endocrine cells. The interaction between ingested foodstuffs and the gastrointestinal endocrine cells can be utilized for the clinical management of gastrointestinal and metabolic diseases, such as irritable bowel syndrome, obesity and diabetes.

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## 1. Introduction

An intake of nutrients is essential for maintaining life, as they provide energy to the body, and also trigger other

important body functions. The interaction between ingested foodstuffs and the gastrointestinal endocrine cells is a new emerging concept (1,2). Understanding this interaction is not only important for understanding the normal physiology and the role of ingested nutrients in gastrointestinal disorders and diseases, but also for managing certain gastrointestinal disorders (3-6).

New data on the interaction between ingested nutrients and the gastrointestinal endocrine cells obtained from basic science and clinical research have accumulated in the last few years. The present review aimed to interpret the newly gained knowledge so as to understand the role of this interaction.

## 2. Gastrointestinal endocrine cells

*General.* The gastrointestinal endocrine cells are scattered between the mucosal epithelial cells facing the intestinal lumen (Fig. 1) (7,8). There are  $\geq 10$  types of endocrine cell, and they are found in the stomach and the small and large intestines (8). Different segments of the gastrointestinal tract contain several different populations of gut endocrine cells (Fig. 2). Certain types of endocrine cells are located only in specific areas of the gastrointestinal tract. For example, serotonin- and somatostatin-secreting cells occur in the stomach and small and large intestines, while those producing ghrelin and gastrin are found only in the stomach, those producing secretin, cholecystokinin, gastric inhibitory peptide (GIP) and motilin are found only in the upper small intestine, and those producing polypeptide YY (PYY), pancreatic polypeptide and oxyntomodulin are located only in the lower small intestine and large intestine (7,9-11). The densities of these cells vary in different sections of the gastrointestinal tract, with the density being highest in the duodenum (12-16) (Fig. 3). The gastrointestinal endocrine cells regulate gastrointestinal motility, secretion, absorption, visceral sensitivity, local immune defence, cell proliferation and appetite (7,17-31). These endocrine cells interact with each other and also with the enteric nervous system, and the afferent and efferent nerve fibers of the autonomic nervous system and the central nervous system (CNS) (7,18,22,32). Depletion of gastrointestinal endocrine cells as in congenital malabsorptive diarrhea caused by mutant neurogenin-3 (33), or complete loss of these cells in mutant

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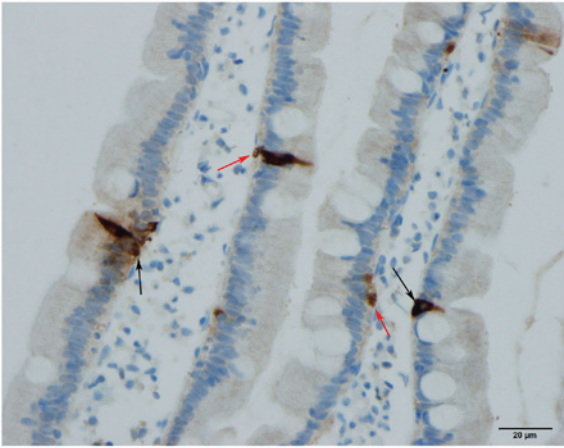


Figure 1. Gastrointestinal endocrine cells are scattered between the epithelial cells lining the gastrointestinal lumen (black arrows). A basal cytoplasmic process can occasionally be observed (red arrow). Chromogranin A cells in human duodenum.

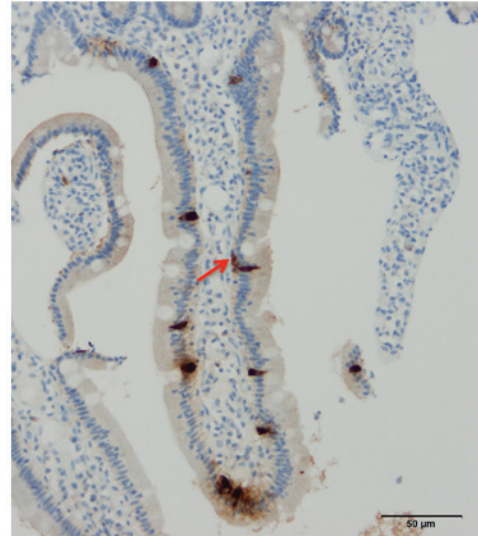


Figure 4. Human duodenal secretin cells. Some of these cells possess a basal cytoplasmic process parallel to the basement membrane (arrow).

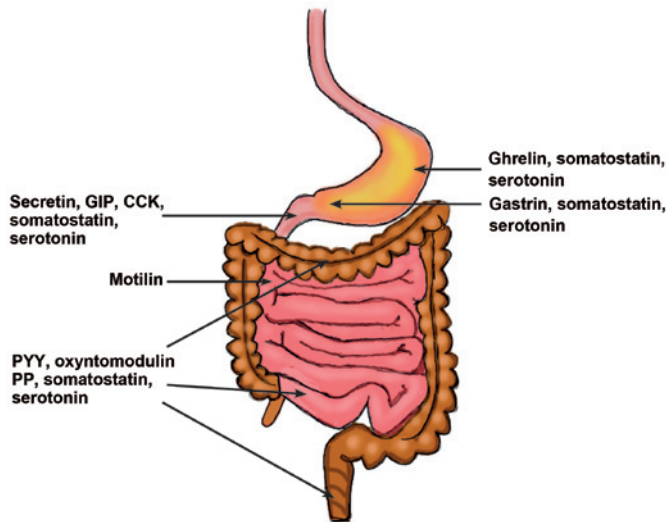


Figure 2. Distribution of different gastrointestinal endocrine cells in the gastrointestinal tract.

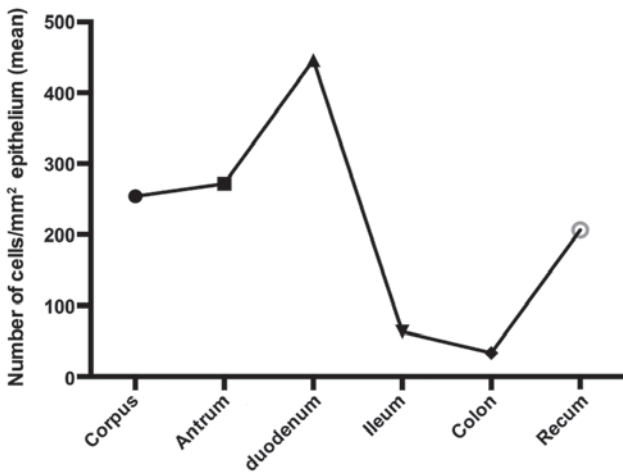


Figure 3. Densities of endocrine cells in different segments of the gastrointestinal tract as detected by chromogranin A. These segments were immunostained using the same method and the same antibody, and were quantified in the same way in the same laboratory by a single person (12-16).

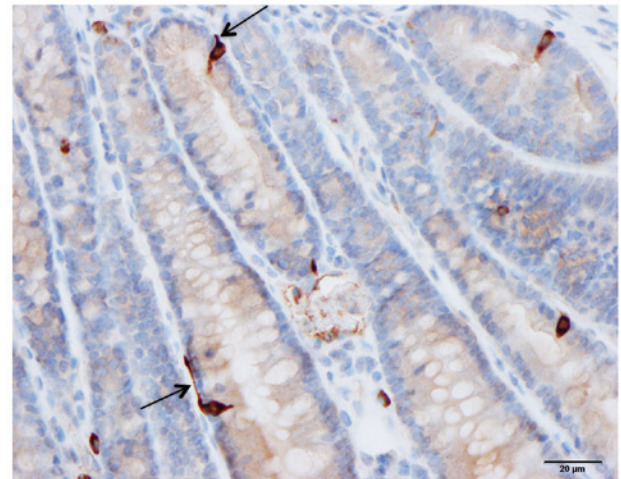


Figure 5. Polypeptide YY cells in the colon of a rat. These cells possess a cytoplasmic process (arrow) similar to that observed in the human small intestine.

mice with ablation of the transcript factor neurogenin-3 (34) show that the gastrointestinal endocrine cells are essential for life.

Immunohistochemical studies have shown that two hormones can be colocalized in the same endocrine cell type, such as glucagon-like peptide-1 and GIP in the small intestine as well as PYY and oxyntomodulin in the large intestine (34-38). Recent studies have further found that mature intestinal endocrine cells are capable of expressing several hormones (39,40).

*Gastrointestinal endocrine cells as sensory cells.* The gastrointestinal endocrine cells have specialized microvilli that project into the lumen and function as sensors of the gut contents (mostly nutrients and/or bacteria byproducts), and respond to luminal stimuli by releasing their hormones into the lamina propria (41-63). The gut intraluminal contents of carbohydrates, proteins and fats trigger the release of different

Table I. Hormones released from the gastrointestinal endocrine cells depending on the gastrointestinal luminal contents of carbohydrates, proteins and fats.

Process	Gastrointestinal nutrients		
	Carbohydrates	Proteins	Fats
Hormones released	Gastric inhibitory polypeptide and oxyntomodulin	Pancreatic polypeptide, neuropeptide Y, motilin, ghrelin, and cholecystokinin (CCK)	Peptide YY, oxyntomodulin, motilin, ghrelin, and CCK

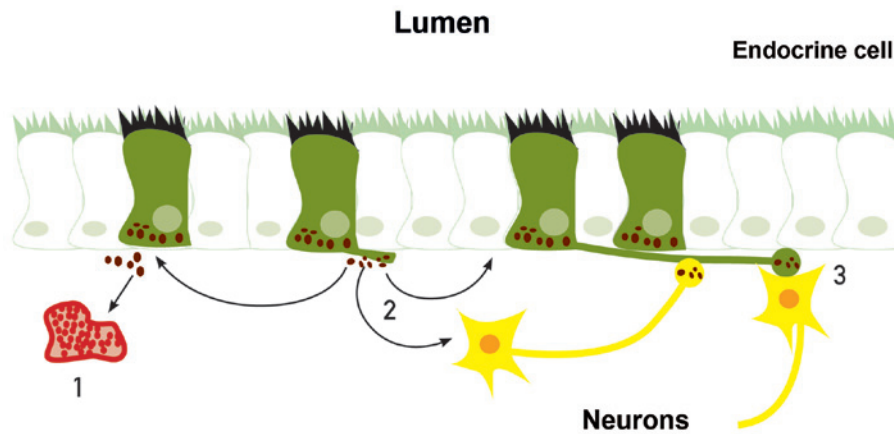


Figure 6. Gastrointestinal endocrine cells may exert their effects via three modes of action: 1, By entering the circulating blood and reaching distant targets (endocrine mode); 2, by acting locally on nearby structures (paracrine mode); or 3, via synaptic activity.

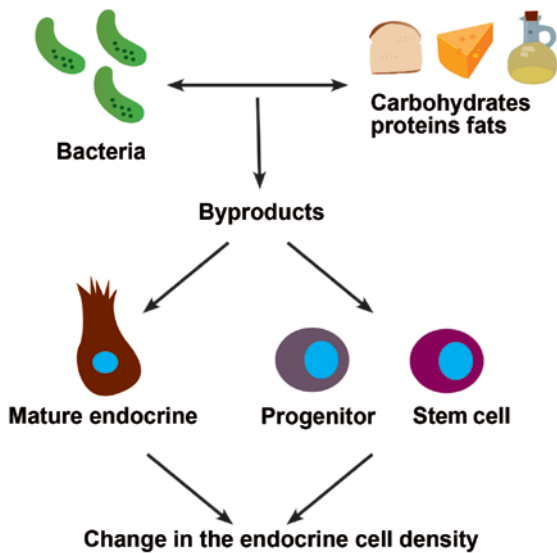


Figure 7. Schematic illustration of the possible ways by which a change in diet could affect the density of gastrointestinal cells.

signaling substances (such as hormones) from the gut endocrine cells (Table I) (41-53).

*Mode of action of gastrointestinal endocrine cells.* The signaling substances (hormones) released from the gastrointestinal endocrine cells may exert their actions locally on nearby cells or neurons (paracrine mode) or by entering the circulating blood and reaching distant targets (endocrine mode) (64-67).

The gastrointestinal endocrine cells possess a basal cytoplasmic process, which is believed to facilitate the paracrine mode of action (Figs. 4 and 5) (68-72). This cytoplasmic process extends  $\leq 70 \mu\text{m}$ , compared with the base of the endocrine cells being only  $10 \mu\text{m}$  in diameter (70). This process has certain similarities to neuronal axons, and has been named a neuropod (70,73-75). The neuropod has other axon-like characteristics, such as containing neurofilaments, being escorted by enteric glia cells, and expressing receptors for neurotrophins (74). Furthermore, gut endocrine cells have small clear synaptic vesicles, express several genes encoding for presynaptic proteins (synapsin 1, piccolo, bassoon, MUNC13B, regulating synaptic membrane exocytosis 2, latrophilin and transsynaptic neurexin), and also express post-synaptic genes (transsynaptic neuroligins 2 and 3, homer 3 and postsynaptic density 95) (75). Based on these data, it was concluded that the gut endocrine cells have the necessary elements for afferent and efferent synaptic transmission (75). Therefore, it appears that the gastrointestinal endocrine cells exert their effects via three modes of action: Endocrine, paracrine and synaptic (Fig. 6).

The recent findings of gastrointestinal endocrine cells exhibiting endocrine and neuron-like characteristics support and revive the old hypothesis on the evolution of the neuro-endocrine system of the gut (76). The observation that the mammalian gastrointestinal hormonal peptides occur in the CNS, but not in the gut of invertebrates (77-79), led to the hypothesis that the gastrointestinal endocrine cells of vertebrates originated in the nervous system of a common ancestor, and migrated during a later stage of evolution into the gut as scattered endocrine cells (76).

### 3. Interaction between diet and gastrointestinal cells

As aforementioned, the composition of the diet with different proportions of carbohydrates, proteins and fats is a trigger for the release of different gut hormones into the lamina propria. Furthermore, the ingested foodstuffs act as prebiotics for the intestinal microbiota, and the byproducts of the bacteria trigger also the release of hormones from the gut endocrine cells.

It has been shown recently that a change in diet is accompanied by a change in the density of gastrointestinal cells (3-6). This could be due to an ingested foodstuff acting as a prebiotic for the intestinal bacteria with the associated bacterial byproducts. These bacterial byproducts may act on the stem cells and/or differentiation progenitors, resulting in changes in the stem cell clonogenic activity and/or differentiation progeny. Alternatively, these bacterial byproducts could act on mature gastrointestinal cells to favor the expression of specific hormones (Fig. 7). Thus, the change in the density of a certain endocrine cell type could be caused by switching to the expression of a different hormone.

### 4. Conclusion

The diet is important for regulating the functions of gastrointestinal endocrine cells. It not only regulates the release of hormones from these cells, but also affects their densities. The interaction between nutrients and gastrointestinal endocrine cells could be useful for the clinical management of several diseases, such as irritable bowel syndrome, obesity and diabetes (17,80-85).

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