Distribution of Endocrine Cells in the Gastrointestinal Tract of Piglets and Chemosensory Function Postprint

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Abstract

Gastrointestinal endocrine cells (EECs) are specialized epithelial cells of the gastrointestinal mucosa, whose total number exceeds that of all endocrine cells in other parts of the organism, thereby constituting the largest endocrine organ of the body. Research has demonstrated that the mammalian gastrointestinal tract harbors at least 20 distinct types of EECs, and the gastrointestinal hormones they secrete exert critical functions in regulating gastrointestinal physiological processes, energy homeostasis and feeding behavior, gastrointestinal chemosensing, nutrient metabolism, and immune modulation. This review comprehensively summarizes the classification of EECs, research methodologies for studying EECs, and recent advances in the distribution of EECs in piglets. Furthermore, it consolidates progress in understanding the chemosensory roles of EECs, the interaction between EECs and immune function, and the crosstalk between intestinal microbiota and gastrointestinal chemosensing, thereby providing a scientific foundation for implementing nutritional regulation strategies aimed at improving intestinal health and growth performance in piglets.

Full Text

Distribution and Chemosensing Role of Enteroendocrine Cells in Piglets

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Abstract: Enteroendocrine cells (EECs) are specialized epithelial cells of the gastrointestinal mucosa whose total number exceeds that of all other endocrine cells in the body, collectively forming the largest endocrine organ. Research has identified at least 20 distinct EEC types in mammals, whose secreted gut hormones play crucial roles in regulating gastrointestinal physiology, energy balance, feeding behavior, gut chemosensing, nutrient metabolism, and immune modulation. This review summarizes the classification of EECs, methodological approaches for their study, and recent advances in understanding EEC distribution in piglets. We further examine the chemosensing functions of EECs, their interactions with immune function, and the influence of gut microbiota on gastrointestinal chemosensing, aiming to provide a scientific basis for nutritional strategies to improve gut health and growth performance in piglets.

Keywords: enteroendocrine cells; gut hormones; chemosensing; piglets; gut microbiota; immune

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The gastrointestinal tract serves as the primary interface for environmental substance exchange and interacts with the central nervous system to influence gastrointestinal motility and secretion, nutrient digestion and absorption, immunity, and systemic metabolism. These functions depend on interactions among various epithelial cell types, including absorptive enterocytes, enteroendocrine cells, goblet cells, Paneth cells, and M cells. Although EECs constitute less than 1% of all gastrointestinal epithelial cells, their total number surpasses that of all other endocrine cells in the body, making them the largest endocrine organ. EECs secrete a variety of hormones collectively known as gut hormones, which regulate gastrointestinal motility and secretion, energy balance and feeding behavior, gut chemosensing, nutrient metabolism, and immune modulation. While substantial progress has been made in understanding EECs in humans and rodents, particularly regarding gut hormone and receptor genes, EEC-immune interactions, and microbial metabolite sensing, research on piglets remains limited. This review outlines the distribution and chemosensing roles of EECs in piglets to provide insights for regulating gut health and disease prevention.

1 Classification of EECs

EECs differentiate from intestinal stem cells and are diffusely distributed throughout the gastrointestinal mucosa, forming the body' s largest endocrine organ. Mammalian gastrointestinal tracts contain at least 20 EEC types, including G cells, D cells, EC cells, X/A-like cells, K cells, L cells, and I cells (Table 1). Most EECs are open-type cells whose apical microvilli extend into the lumen to sense food stimuli and pH changes, thereby modulating their endocrine activity. A minority are closed-type cells whose apical surfaces are covered by adjacent cells, primarily responding to gastrointestinal motility, neural regulation, and hormonal signals.

Table 1 Gastrointestinal Endoendocrine Cells and Their Secreted Hormones

Cell Types	Distribution	Hormone	Function	References
G cell	Gastric antrum, pylorus, duodenum	Gastrin	Strongly stimulates acid secretion from parietal cells	[4-6]
D cell	Fundus, pylorus, intestine	Somatostatin	Inhibits gut hormone secretion, relaxes intestinal smooth muscle	[4,7]
D1 cell	Fundus, pylorus, intestine	Vasoactive intestinal peptide (VIP)	Inhibits gut hormone secretion, relaxes intestinal smooth muscle	[9,11]
EC cell	Fundus, pylorus, intestine	Serotonin (5-HT)	Stimulates intestinal smooth muscle contraction, regulates GI motility	[12-13]
ECL cell	Fundus, pylorus, intestine	Histamine	Acts on parietal cells to indirectly promote HCl secretion	[16-17]
X/A-like cell	Stomach, duodenum, jejunum	Ghrelin	Regulates appetite, hormone release, acid secretion, GI motility, energy homeostasis	[9,14,18]

Cell Types	Distribution	Hormone	Function	References
K cell	Duodenum, jejunum	Glucose-dependent insulinotropic peptide (GIP)	Inhibits acid secretion, stimulates insulin release	[9,14,18]
M0 cell	Jejunum, ileum	Motilin	Promotes GI motility	[9,14,18]
N cell	Jejunum, ileum	Neurotensin	Reduces vascular tension	[9,14,18]
L cell	Distal small intestine and colon	GLP-1/2, PYY	Promotes insulin secretion, inhibits feeding, secretion and motility	[9,14,18]
PP cell	Fundus, pylorus, jejunum	Pancreatic polypeptide (PP)	Inhibits gastrin-induced acid secretion	[9,14,18]

Each EEC type synthesizes and secretes one or more regulatory peptides or active molecules, with distinct chemosensing mechanisms. Over 40 bioactive peptides have been identified in the gastrointestinal tract, including gut hormones, neurotransmitters, and growth factors. Currently, more than 20 gut hormones are known to act on target cells through four primary mechanisms: (1) endocrine secretion into circulation (e.g., cholecystokinin, secretin); (2) paracrine diffusion through intercellular spaces (e.g., somatostatin); (3) luminal secretion directly into the gut lumen (e.g., gastrin, pancreatic polypeptide); and (4) autocrine action on membrane receptors. Upon binding to specific receptors, gut hormones regulate gastric emptying and acid secretion, GI motility, appetite and feeding behavior, intestinal fluid secretion, and mucosal protection.

2 Methodological Approaches for Studying EECs

EECs are diffusely distributed throughout the gastrointestinal tract, typically appearing as irregular cone-shaped cells with basal attachments to the basement membrane and lateral processes contacting neighboring cells. Their cytoplasm contains numerous secretory granules that vary in size, shape, and density among different EEC types. Since EECs are difficult to identify in

conventional hematoxylin-eosin stained sections, immunohistochemistry (IHC) and immunofluorescence (IF) are the primary detection methods. Monoclonal or polyclonal antibodies against secreted hormones or cell surface receptors are used to visualize EECs under fluorescence or confocal microscopy. Some EECs can also be identified by electron microscopy based on the chromaffin, argyrophilic, or argentaffin properties of their secretory granules. Recent studies have employed fluorescence-activated cell sorting (FACS) to isolate mouse intestinal EC cells. Additionally, RT-PCR and Western blotting are used to comprehensively analyze marker molecules and receptor gene expression in EECs.

3.1 EC Cells

Over 90% of gastrointestinal serotonin is stored in EC cells, which are distributed throughout the mucosal epithelium from stomach to colon. Serotonin acts directly on smooth muscle and neurons to modulate intestinal motility. In three-way crossbred piglets, EC cells are most abundant in the jejunum. However, in Meishan piglets, an excellent indigenous Chinese breed, EC cells are present in the epithelium of duodenum, jejunum, ileum, and colon, with significantly higher numbers in the duodenum than other segments. These cells appear conical, round, or fusiform. Studies in Large White pigs across different ages (0, 5, 15, and 100 days) and intestinal segments (duodenum, jejunum, ileum) revealed significant effects of age, segment, and their interaction on EC cell density. At 5, 15, and 100 days, EC cell density was highest in the duodenum. Within the same segment, duodenal EC cell density peaked at 15 days, while jejunal and ileal densities decreased progressively along the intestinal tract. Immunohistochemical studies in growing pigs showed D cells, EC cells, and L cells primarily distributed among gastric and intestinal gland epithelial cells, with occasional cells scattered in the mucosal epithelium and rare cells in duodenal glands, following the abundance pattern: EC cells > D cells > L cells.

3.2 G Cells

Gastrin, primarily secreted by G cells, stimulates acid secretion and regulates gastric emptying, appetite, feeding, stress responses, and memory. In pigs, G cells are located mainly in the middle region of the gastric antral glands and pyloric area, with numbers lower than in mice but higher than in humans. Both G and D cells express G protein-coupled receptor family C group 6 member A (GPRC6A), calcium-sensing receptor (CaSR), and G protein-coupled receptor 92 (GPR92). In humans, chimpanzees, and rats, G and D cells co-localize in the same regions of the antral epithelium. Tong et al. investigated the developmental patterns of gastrin and serotonin-secreting cells in piglets at various ages (0, 7, 28, 35 days, 2 months, and 4 months), finding G cells predominantly in the pylorus with occasional scattered cells in other intestinal tissues. Their spatiotemporal distribution correlates with breastfeeding and weaning stress.

3.3 X/A-like Cells

Ghrelin, a multifunctional gut hormone secreted primarily by X/A-like cells, regulates appetite, hormone release, acid secretion, GI motility, energy homeostasis, and cell proliferation through its functional receptor growth hormone secretagogue receptor-1a (GHSR-1a). Ghrelin levels typically rise before meals and fall after feeding. Our previous research found X/A-like cells in the gastric glandular region, pylorus, duodenum, and jejunum of both Meishan and Landrace piglets. X/A-like cell density was significantly higher in the pylorus of Landrace pigs but higher in the jejunum of Meishan pigs. GHSR-1a expression levels correlated with X/A-like cell distribution patterns, decreasing along the intestinal tract in both breeds. Ghrelin is detectable throughout the digestive tract from stomach to cecum in pigs of different ages, with X/A-like cell density following the pattern: stomach > small intestine > large intestine, peaking in the gastric body, pylorus, and cardia. Notably, X/A-like cell density in the gastric body was significantly higher at 28 days of age during weaning. These findings indicate that X/A-like cell distribution is influenced by age, feed intake, weaning stress, and breed differences.

3.4 L Cells

L cells are essential components of the EEC population, secreting critical peptide hormones including glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2), and peptide YY (PYY). Basal GLP-1 levels are low but increase rapidly within one hour after feeding. Circulating GLP-1 stimulates insulin secretion from pancreatic -cells and suppresses glucagon secretion from -cells, thereby controlling appetite and blood glucose. Only approximately 25% of secreted GLP-1 reaches the portal vein, with 40-50% degraded in the liver and merely 10-15% entering systemic circulation. Comparative studies of GLP-1-positive cells in fetal intestines of rats, pigs, and humans revealed predominant distribution in the distal intestine, with higher numbers in the ileum of rats and pigs. Another study reported greater GLP-1-positive cell numbers in rats than in pigs or humans. Our previous work identified GLP-1-positive cells throughout the duodenum, jejunum, ileum, and colon of Meishan piglets, with density following a parabolic pattern along the intestinal tract, peaking in the ileum. Clinically, impaired GLP-1 secretion occurs in type 2 diabetes, and receptor antagonists that block GLP-1 action can reduce satiety signals for therapeutic applications.

GLP-2, another important peptide hormone secreted by L cells, exerts multiple biological functions in the GI tract, including promoting intestinal epithelial cell proliferation, inhibiting apoptosis, increasing small intestinal weight, protecting and repairing damaged mucosa during various intestinal diseases, and maintaining intestinal barrier integrity. GLP-2 also inhibits acid secretion and GI motility while increasing intestinal blood flow. In pigs, rapid intestinal development begins three weeks prenatally, with piglet intestinal weight increasing within 24 hours after birth accompanied by elevated plasma GLP-2 levels. No-

tably, different zinc sources and levels significantly affect GLP-2 gene expression in porcine IPEC-J2 cells. In vitro studies demonstrate that GLP-2 supplementation increases expression of tight junction proteins occludin and ZO-1 in colonic epithelial cells. Additionally, intestinal L cells secrete not only GLP-1 and GLP-2 but also PYY, cholecystokinin, and neurotensin. In rats, PYY is secreted primarily by L cells in the distal small intestine, while mouse duodenum and jejunum contain few L cells. However, in pigs, over 40% of EECs in the duodenum co-secrete PYY, with most also secreting GLP-1 or GIP, suggesting that traditional K and L cell classifications may need revision.

3.5 Other EEC Types

Beyond the well-studied EC, G, X/A-like, and L cells, few reports exist on other EEC types in piglets. Using immunohistochemistry and electron microscopy, researchers identified distinct granule sizes for S cells, I cells, and D cells in porcine intestinal mucosa, with D cells most abundant in duodenum, pylorus, and fundus, while S and I cells predominantly localized to duodenal mucosa. Orexin-positive cells co-localize with X/A-like and G cells, and the hormones orexin, gastrin, and ghrelin are expressed throughout the stomach, duodenum, jejunum, cecum, colon, and rectum, suggesting cooperative regulation of gastric secretion, energy balance, body weight, and feed intake. Dietary sodium butyrate supplementation in weaned piglets significantly increases the number of chromogranin A-positive cells and D cells in gastric mucosa.

4.1 Gut Chemosensing

Gut chemosensing refers to a nutrient-sensing system involving interactions between EECs and visceral vagal neurons, comprising complex regulation by neurons, gastrointestinal chemosensory cells (taste receptor cells), luminal chemoreceptors, and the immune system. As primary chemoreceptors in the gut, EECs respond to luminal contents by secreting hormones and neurotransmitters that activate target cells and neural pathways. This system includes afferent and intrinsic neurons that detect luminal contents and generate reflexes affecting GI motility, blood flow, and water/electrolyte secretion. Luminal chemoreceptors (taste receptors) are primarily G protein-coupled receptors (GPCRs) and solute carrier transporters (SLCs) expressed on various gastrointestinal cell types, with particularly high numbers on the luminal side of EECs (Figure 1 [Figure 1: see original paper]). Mammalian chemoreceptors belong mainly to the GPCR superfamily, including taste receptor family 1 (T1Rs or TAS1Rs) and family 2 (T2Rs or TAS2Rs). The T1R family comprises T1R1, T1R2, and T1R3, where T1R1+T1R3 functions as an umami receptor, T1R2+T1R3 as a sweet receptor, and T2Rs as bitter receptors.

As shown in Figure 1-b, EECs sense carbohydrates through T1R2/T1R3, sodium-glucose cotransporter 1 (SGLT1), and ATP-sensitive potassium channels. Carbohydrate binding to sweet receptors activates -gustducin and phospholipase C, causing membrane depolarization, increased intracellular

Ca^2 , and release of hormones and neurotransmitters including serotonin, GIP, and GLP-1. Sweet substances stimulate satiety signals (GLP-1, PYY, cholecystokinin) that are transmitted via the vagus nerve to the hypothalamus to inhibit feeding. Protein digestion products (peptides and amino acids) are sensed primarily through CaSR, T1R1/T1R3, and GPRC6A, inducing membrane depolarization and hormone secretion mediated by the mTORC1 signaling pathway. Paneth and tuft cells also express T1R1/T1R3 to sense luminal proteins and amino acids. Lipid sensing by EECs involves chylomicron formation, while free fatty acid sensing depends on receptors including FFAR1/2/3/4, GPR119, GPR120, OLFR78, and CD36.

These nutrient-sensing pathways enable EECs to detect luminal nutrients and secrete gut hormones (cholecystokinin, GLP-1/2, GIP, PYY, serotonin, somatostatin, gastrin, ghrelin) that initiate vagal signals to the hypothalamus and adjacent cells, thereby regulating physiological functions, nutrient absorption and metabolism, intestinal barrier integrity, and immunity. As understanding of EECs and gut hormones advances, targeting the gut endocrine system offers promising strategies for nutritional regulation, pharmaceutical development, and disease intervention in pig production.

4.2 EECs and Immune Function

EECs are recognized as crucial regulators of intestinal immunity and integral components of the gut barrier. Serotonin acts on multiple immune cells (mast cells, monocytes, dendritic cells, T cells, B cells, eosinophils, neutrophils) to activate cytokine secretion, bridging innate and adaptive immunity, and directly stimulates goblet cells to induce mucin production. Inflammatory conditions significantly alter EEC numbers and hormone secretion in humans and rodents, with inflammatory bowel disease increasing ileal serotonin, GLP-1, and PYY cells, as well as GLP-2 secretion. Notably, EECs from inflammatory bowel disease patients exhibit increased production of the pro-inflammatory cytokine IL-17C. Cholecystokinin directly affects T and B cell function, promoting type 2 helper T (Th2) and regulatory T cell generation. Ghrelin activates PI3K and PKC signaling pathways to promote T cell proliferation and reduce Th17 cell activity, participating in anti-inflammatory responses. Thus, the immunoendocrine axis represents a potential therapeutic target for intestinal infections and inflammatory disorders.

4.3 Gut Microbiota and Gastrointestinal Chemosensing

Gut microbiota plays a vital role in host chemosensing. Microbial metabolites such as short-chain fatty acids (SCFAs) activate EEC sensing to influence the brain via the microbiota-gut-brain axis, regulating feed intake and systemic metabolism. EECs express Toll-like receptors (TLRs) to recognize pathogens and specific metabolite receptors to respond to beneficial bacteria, maintaining gut homeostasis. Bacterial metabolites stimulate EECs to produce GLP-1, PYY, and cholecystokinin, and can modulate bile acids to activate farne-

soid X receptor (FXR) and TGR5 (GPBAR1), stimulating GLP-1 secretion. Lipopolysaccharide and flagellin activate TLR4, TLR5, and TLR9 to induce cholecystokinin secretion from EECs. L cells express SCFA receptors (GPR41, GPR43, GPR119, TGR5) to induce GLP-1, GLP-2, and PYY secretion, regulating energy balance, glucose metabolism, intestinal barrier function, and metabolic inflammation. Recent studies show that propionate and butyrate significantly increase PYY gene expression and secretion in human EEC lines (NCI-h716). In mice, small intestinal EC cells indirectly sense luminal nutrients primarily through paracrine stimulation of GLP-1 from L cells, whereas colonic EC cells express numerous microbial metabolite receptors to directly sense SCFAs, secondary bile acids, ketones, and aromatic acids. Interestingly, germ-free mice exhibit significantly altered EEC numbers. L cells express the bile acid receptor TGR5 to sense bile acid stimulation and promote GLP-1 and GLP-2 secretion, prompting researchers to target TGR5 to regulate GLP-2 secretion in weaned piglets.

5 Summary and Outlook

In summary, multiple EEC types and their secreted hormones have been identified in piglet gastrointestinal tracts, exerting critical regulatory effects on appetite, feeding behavior, digestive physiology, nutrient absorption, intestinal barrier function, and immunity. As primary components of gut chemosensing, EECs express diverse chemoreceptors that recognize luminal nutrients, toxins, and microbial metabolites, transmitting taste signals to the central nervous system and releasing hormones and neurotransmitters that act on target cells and vagal nerves to regulate physiological functions. Targeting EECs offers promising strategies for addressing weaning stress in piglets by modulating chemoreceptors and hormone secretion to stimulate appetite, improve intestinal development, enhance mucosal barrier function, reduce inflammation, and optimize growth performance through regulation of gut microbiota, SCFA production, and bile acid metabolism.

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Note: Figure translations are in progress. See original paper for figures.