Gut Endocrine and Nutrient Sensing Systems: Post-print

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Abstract

Various nutrients and other chemical substances generated through digestive metabolism within the animal intestine can exert physiological effects via the intestinal endocrine and nutrient sensing system. As crucial components of this system, intestinal endocrine cells recognize and sense diverse intestinal nutrients through surface sensing receptors—including amino acid sensing receptors, fatty acid sensing receptors, and glucose sensing receptors—thereby regulating not only nutrient absorption and metabolism but also secreting gut-brain peptides such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK). These gut-brain peptides participate in regulating feeding behavior and other physiological functions through the gut-brain neural network comprising the central nervous system, autonomic nervous system, and enteric nervous system. This article reviews the research progress on animal intestinal endocrine systems, the gut-brain axis, and nutrient sensing receptors.

Full Text

Enteroendocrine and Nutrient Sensing System

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Abstract

Various nutrients and chemical substances produced through digestion and metabolism in the animal gastrointestinal tract exert physiological effects via the enteroendocrine and nutrient sensing system. As a crucial component of

this system, enteroendocrine cells detect luminal nutrients through specialized sensing receptors, including amino acid sensing receptors, fatty acid sensing receptors, and glucose sensing receptors. These cells not only regulate nutrient absorption and metabolism but also secrete gut-brain peptides such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK). Through the gut-brain neural network comprising the central nervous system, autonomic nervous system, and enteric nervous system, these gut-brain peptides participate in regulating feeding behavior and other physiological functions. This review summarizes recent research advances on the animal enteroendocrine system, gut-brain axis, and nutrient sensing receptors.

Key words: nutrient sensing; enteroendocrine system; gut-brain axis; sensing receptor

1. Enteroendocrine System

The animal enteroendocrine system recognizes nutrients through sensing receptors and mediates the secretion of various gut-brain peptides to regulate physiological functions, including appetite, feeding behavior, and nutrient absorption and metabolism [4]. This system consists of diverse enteroendocrine cells (EECs), including L cells, K cells, I cells, and enterochromaffin cells. Although EECs are dispersed among intestinal epithelial cells (IECs) and represent only 1% of the total IEC population, they can secrete over 20 types of gut-brain peptides through specific nutrient recognition, including GLP-1, PYY, CCK, glucose-dependent insulinotropic polypeptide (GIP), 5-hydroxytryptamine (5-HT), and ghrelin [1]. Gut-brain peptides secreted from the basolateral side of EECs can be recognized by specific receptors on vagal and spinal nerve fibers in the intestine, regulating physiological functions through neurosecretory pathways, or they can enter the vascular circulation to act on target organs in an endocrine manner. For example, GLP-1 reaches the pancreas through blood circulation, binds to GLP-1 receptors (GLP-1R) on pancreatic surfaces, and activates cells to secrete insulin [5]. Additionally, secreted gut-brain peptides can act in a paracrine fashion to activate surrounding IECs, promoting nutrient absorption or the release of metabolic products [4].

The types, distribution, and functions of EECs are closely related to the species of gut-brain peptides secreted and phylogenetic relationships. For instance, K cells secrete GIP, L cells secrete GLP-1 and PYY, I cells secrete CCK, and enterochromaffin cells secrete 5-HT [4]. EEC distribution varies among species: mouse intestinal L cells are primarily located in the distal ileum and colon, whereas pig intestinal L cells are mainly distributed in the duodenum [6]. Moreover, EEC distribution and function are regulated by diet. Recent studies have found that feeding mice a high-fat diet for two weeks significantly reduced the number of K cells in the small intestine and L cells in the colon, and after 16 weeks on a high-fat diet, expression of nutrient sensing-related transcription

factor genes in colonic L cells decreased significantly, accompanied by reduced GLP-1 secretion [7].

Recent advances in microscopy technology have deepened our understanding of EEC structure. Using serial block-face scanning electron microscopy, Bohórquez et al. [8] first discovered that mouse distal ileum EECs possess synapse-like structures, with secretory vesicles on the basolateral side guiding the exocytosis of gut-brain peptides. The study also revealed that EECs connect with enteric glia cells (EGCs), which primarily regulate the development of the enteric nervous system (ENS) and proliferation of IECs [9], suggesting that EGCs may regulate EEC function. These findings provide important scientific evidence for elucidating the interactive mechanisms through which the animal ENS participates in regulating gut-brain peptide secretion from EECs.

After sensing nutrients in the intestinal lumen, the enteroendocrine system acts on the central nervous system (CNS) through the gut-brain axis to regulate various physiological functions [10]. The gut-brain axis is a neural network composed of the CNS, autonomic nervous system, and ENS [2]. This network consists of numerous nerve fibers, including sympathetic and vagal fibers, that are widely distributed throughout the animal intestine. Vagal fibers account for 80% of total intestinal nerve fibers and can recognize gut-brain peptides such as GLP-1 and PYY through specific receptors [4]. Recent studies using subdiaphragmatic vagotomy have confirmed that vagal nerves primarily recognize luminal GLP-1 through GLP-1R distributed at their terminals [11]. Upon receptor activation, gut-brain peptides are converted into neural signals that are transmitted to the CNS via the vagus nerve, eliciting appropriate responses such as changes in appetite and feeding behavior [2]. Bogdanova et al. [12] found that activating opioid receptors (mu-opioid receptor) in the rat digestive tract transmitted appetite-suppressing signals through the vagus nerve to the CNS, reducing food intake and energy expenditure. The enteroendocrine system not only participates in regulating appetite and energy metabolism but also mediates various intestinal physiological functions through the gut-brain axis, including intestinal muscle reflexes, intestinal immunity, intestinal permeability, and endocrine regulation [2]. Studies using PYY knockout mice revealed that colonic L cells secrete PYY to activate PYY receptors (Y2R) distributed on vagal nerve terminals, and PYY signals are transmitted to the CNS through the gut-brain axis. The CNS then inhibits colonic smooth muscle contraction through nerve fibers distributed in the colon, slowing intestinal motility frequency and delaying colonic content emptying [13]. Therefore, the interaction between the animal enteroendocrine system and CNS plays a crucial role in regulating intestinal nutrient absorption, energy metabolism, and physiological functions.

3. Nutrient Sensing Receptors

Animal intestinal nutrient sensing primarily relies on various nutrient sensing receptors distributed on the surface of EECs, such as amino acid sensing receptors, fatty acid sensing receptors, and glucose sensing receptors [10]. These receptors specifically recognize proteins, lipids, and carbohydrates in the intestinal lumen, activate downstream signaling pathways, promote gut-brain peptide secretion, and thereby regulate nutrient absorption and metabolism to maintain energy homeostasis through the gut-brain axis [4].

3.1 Protein Sensing Receptors

Peptones, the products of initial protein digestion in the intestine, can be bound by various peptone sensing receptors distributed on the intestinal surface. Currently reported peptone sensing receptors include peptide transporter 1 (PepT1) and lysophosphatidic acid receptor 5 (LPAR5) [14]. PepT1 is widely distributed on the surface of small intestinal and colonic L cells and can recognize luminal peptones to promote GLP-1 secretion [14]. Similarly, LPAR5 can also sense peptones in the intestine and is mainly distributed on the surface of intestinal I cells [14]. Choi et al. [15] found in mouse EEC line STC-1 that peptones significantly increased LPAR5 expression, activated downstream extracellular regulated protein kinases 1/2 (ERK1/2) and protein kinase A (PKA) signaling pathways, and promoted CCK secretion. Additionally, research has found that the calcium sensing receptor (CaSR) on mouse intestinal L cell surfaces can also bind peptones, promoting GLP-1 secretion by activating transient receptor potential channels (TRPC) and voltage-dependent Ca2+ channels (VDCC), leading to increased intracellular calcium concentration [16]. Diakogiannaki et al. [14] discovered that peptones simultaneously activated both PepT1 and CaSR signaling pathways in mouse L cells to promote GLP-1 secretion, suggesting a synergistic mechanism between PepT1 and CaSR in peptone sensing that jointly regulates gut-brain peptide secretion from EECs.

After proteins are digested into amino acids in the intestine, they can be recognized by various amino acid sensing receptors distributed on the intestinal surface. CaSR can bind not only peptones [16] but also L-amino acids, particularly L-aromatic amino acids [4]. Mace et al. [17] found that rat small intestinal L cells and K cells could recognize L-amino acids through CaSR to regulate secretion of gut-brain peptides including GLP-1, PYY, and GIP. The study further revealed that CaSR-mediated gut-brain peptide secretion requires calcium ion participation. Zhou et al. [18] conducted more in-depth research on CaSR-mediated gut-brain peptide secretion mechanisms using mouse STC-1 cells. Their study showed that CaSR activates phospholipase C (PLC) and inositol triphosphate (IP3) signaling pathways, causing endoplasmic reticulum calcium release. Simultaneously, membrane TRPC and L-type VDCC are activated, guiding extracellular calcium influx. The resulting increase in intracellular calcium concentration promotes exocytosis of CCK and GLP-1 [18]. These studies demonstrate that L-amino acid binding to CaSR activates downstream

signaling pathways and ion channels, increasing intracellular calcium concentration and thereby regulating gut-brain peptide secretion.

The G protein-coupled receptor family C group 6 subtype a (GPRC6a) recognizes L-arginine, L-lysine, and L-ornithine in the intestinal lumen. Unlike CaSR, GPRC6a is not sensitive to L-aromatic amino acids, and its gene expression is highest in the animal jejunum and colon [19]. GPRC6a promotes gut-brain peptide expression and secretion by recognizing L-amino acids. Oya et al. [20] found in mouse L cell line GLUTag that L-ornithine significantly increased intracellular calcium concentration along with GLP-1 secretion. However, after blocking GPRC6a gene expression using small RNA interference, intracellular calcium concentration and GLP-1 secretion both decreased significantly. Therefore, the study speculated that calcium ions are required for GPRC6a amino acid sensing. Additionally, research has reported that GPRC6a can mediate energy metabolism. Clemmensen et al. [21] found that under high-fat diet feeding, GPRC6a knockout mice showed significantly increased food intake and body weight gain compared to normal mice, accompanied by disordered glucose metabolism. However, recent studies have found that intestinal GPRC6a does not mediate the regulation of food intake, satiety, and body weight gain in mice fed high-protein diets [22]. Therefore, the mechanism by which intestinal GPRC6a senses amino acids to mediate energy metabolism remains unclear and requires further investigation.

The umami receptor—type 1 taste receptor 1/3 (T1R1/T1R3)—recognizes L-aliphatic amino acids, particularly L-glutamine and L-asparagine, and is mainly distributed on the surface of intestinal I cells, K cells, and L cells [1]. Daly et al. [23] found in mouse STC-1 cells that L-phenylalanine, L-tryptophan, and L-lysine all significantly enhanced T1R1/T1R3 expression and promoted CCK secretion. Currently, the mechanism of amino acid sensing by T1R1/T1R3 in the intestine remains unclear, but more in-depth research exists on amino acid sensing in pancreatic cells. Wauson et al. [24] found that T1R1/T1R3 on pancreatic cells, upon binding L-amino acids, could mediate insulin secretion and maintain glucose homeostasis by activating downstream ERK1/2 and mammalian target of rapamycin complex 1 (mTORC1) signaling pathways. Additionally, research has found that T1R3 deletion induces autophagy (a cellular self-protective mechanism) in cells and promotes expression of other amino acid sensing transporters, suggesting the existence of compensatory mechanisms to cope with T1R1/T1R3 functional loss [25].

Based on the differential distribution of amino acid sensing receptors in the intestine and their varying sensitivities to amino acids, researchers speculate that interactions exist among intestinal amino acid sensing receptors that cooperatively recognize various amino acids [4]. However, current research on the synergistic mechanisms among these receptors is limited. Therefore, a deeper understanding of the signal transduction networks among various intestinal amino acid sensing receptors will help elucidate the mechanisms of amino acid sensing by EECs.

3.2 Lipid Sensing Receptors

Dietary fats produce medium-chain and long-chain fatty acids after hydrolysis in the intestine, which can be recognized by free fatty acid receptor (FFAR) 1 and FFAR4 on EEC surfaces [4]. Studies have shown that activating FFAR1 and FFAR4 on EECs promotes secretion of gut-brain peptides including GLP-1, PYY, and GIP. Hauge et al. [26] found that FFAR1 on intestinal L cells, upon binding -linolenic acid (ALA) and docosahexaenoic acid (DHA), promoted GLP-1 and GIP exocytosis through PLC and IP3 signaling pathways, causing endoplasmic reticulum calcium release and extracellular calcium influx via VDCC. Iwasaki et al. [27] discovered that activating mouse intestinal FFAR4 significantly increased GIP secretion from intestinal K cells, while inhibiting FFAR4 activation significantly decreased GIP expression. Furthermore, FFAR4 is involved in energy metabolism regulation. Under high-fat diet feeding, FFAR4 knockout mice showed significantly increased body weight gain and liver fat content, along with decreased insulin sensitivity and glucose tolerance compared to normal mice [28]. Tsukahara et al. [29] conducted in-depth research on the interaction between FFAR1 and FFAR4 using mouse L cells, finding that after FFAR1 activation, FFAR4 primarily inhibited FFAR1-mediated gut-brain peptide secretion through the cyclic adenosine monophosphate (cAMP)-PKA signaling pathway. Therefore, studies indicate that FFAR1 and FFAR4 receptors on intestinal L cells exhibit antagonistic effects in fatty acid sensing, jointly regulating long-chain fatty acid sensing in the intestine.

The animal intestine, particularly the large intestine, contains abundant short-chain fatty acids (SCFA) including acetate, propionate, and butyrate, which are primarily produced by microbial fermentation of indigestible carbohydrates (oligosaccharides, resistant starch, etc.) in the small intestine. SCFA can be recognized by FFAR2 and FFAR3 distributed on EEC surfaces in the small intestine and colon [4]. The binding affinity of FFAR2 and FFAR3 for SCFA depends on carbon chain length, with FFAR2 preferentially recognizing acetate and propionate, while FFAR3 primarily senses propionate, butyrate, and other SCFA [2]. Research has shown that activating FFAR2 and FFAR3 on EECs promotes gut-brain peptide secretion. Psichas et al. [30] found that mouse colonic L cell FFAR2 could effectively recognize propionate, significantly increasing PYY and GLP-1 secretion while causing increased food intake and body weight gain in mice. Additionally, propionate can be recognized by mouse intestinal FFAR3 receptors to regulate host gluconeogenesis and maintain glucose homeostasis via the gut-brain axis [31]. However, current research on the synergistic mechanisms between FFAR2 and FFAR3 in intestinal SCFA sensing is limited [1], requiring further investigation into the interactive mechanisms between these two receptor types.

G protein-coupled receptor 119 (GPR119) serves as another type of lipid sensing receptor, primarily recognizing fatty acid amides such as oleoylethanolamide (OEA), 2-oleoylglycerol (2-OG), and oleoyldopamine (ODA) to promote secretion of GLP-1, PYY, and GIP. GPR119 is mainly distributed on pancreatic

cells and intestinal K and L cells [4]. Moss et al. [32] found in GPR119 knockout mice that OEA- and 2-OG-induced GLP-1 secretion from colonic L cells was significantly reduced compared to normal mice. Further research revealed that GPR119 primarily activates cAMP and PKA signaling pathways after lipid sensing to promote GLP-1 exocytosis. Additionally, Patel et al. [33] found in obese mice that activating colonic GPR119 significantly improved glucose tolerance and regulated energy metabolism. Currently, several GPR119-specific agonists can significantly reduce animal food intake and body weight gain [4]. Therefore, GPR119 may serve as a potential therapeutic target for metabolic diseases such as type 2 diabetes and obesity, regulating lipid metabolism and energy intake.

3.3 Carbohydrate Sensing Receptors

The sweet taste receptor—type 1 taste receptor 2/3 (T1R2/T1R3)—is mainly distributed on intestinal K and L cell surfaces and can recognize polysaccharides and monosaccharides in the animal intestinal lumen, promoting secretion of GLP-1, CCK, and GIP [4]. Geraedts et al. [34] found that T1R2/T1R3 on mouse colonic EECs, upon binding carbohydrates, inhibited ATP-sensitive K+ (KATP) channels, causing increased intracellular potassium concentration and promoting GLP-1 secretion. Additionally, studies have shown that T1R2/T1R3 mediates glucose metabolism. Murovets et al. [35] discovered that T1R3 knockout mice exhibited significantly decreased insulin sensitivity and glucose tolerance, leading to glucose homeostasis disruption.

Intestinal glucose can also be recognized by sodium-glucose transporter 1 (SGLT1) and glucose transporter 2 (GLUT2) [2]. SGLT1 and GLUT2 in the animal small intestine, upon binding glucose, can promote secretion of PYY, GLP-1, and GIP, mediating glucose homeostasis [17]. Kuhre et al. [36] conducted in-depth research on glucose sensing mechanisms of SGLT1 and GLUT2 in rat small intestinal L cells, finding that SGLT1 and GLUT2 primarily promote GLP-1 secretion by inhibiting membrane KATP channels while activating L-type VDCC, causing increased intracellular potassium and calcium concentrations and cell depolarization. Meanwhile, SGLT1 can also activate membrane sodium channels to indirectly mediate GLP-1 exocytosis. These studies demonstrate that SGLT1 and GLUT2 jointly sense and transport glucose in the intestine, with SGLT1 playing a more important role than GLUT2 in mediating intestinal glucose sensing.

Furthermore, research has shown that when intestinal glucose concentration increases, the EEC sweet taste receptor T1R2/T1R3 can activate SGLT1 and GLUT2 expression through the PLC-protein kinase C signaling pathway to jointly sense intestinal glucose, further promoting glucose transport while mediating secretion of GLP-1, PYY, and other gut-brain peptides [37]. Therefore, studies indicate that interactive mechanisms exist among intestinal glucose sensing receptors T1R2/T1R3, SGLT1, and GLUT2, which cooperatively mediate intestinal glucose sensing and maintain glucose homeostasis.

4. Regulatory Role of the Enteroendocrine and Nutrient Sensing System

The enteroendocrine system, gut-brain axis, and nutrient sensing receptors work in concert to regulate food intake and feeding behavior [2]. Bogdanova et al. [12] found that peptides and amino acids could activate opioid receptors on rat digestive tract EECs, prompting the enteroendocrine system to secrete gut-brain peptides such as GLP-1 and PYY. These signals act on the CNS through the gut-brain axis, significantly inhibiting rat feeding behavior and reducing food intake. In high-fat diet-induced obese mice, intestinal amino acid sensing receptor GPRC6a can trigger the enteroendocrine system to produce gut-brain peptides, with negative feedback signals acting on the mouse hypothalamus via the gut-brain axis to regulate food intake and activity levels [21].

The enteroendocrine and nutrient sensing system also mediates nutrient absorption and transport to maintain energy homeostasis. Mellitzer et al. [3] found that mice with a deficient enteroendocrine system (Ngn3Δint mice) exhibited inhibited intestinal lipid absorption, impaired fat synthesis function, significantly reduced body weight, and disordered energy metabolism. Research indicates that the enteroendocrine and nutrient sensing system primarily regulates glucose metabolism balance. De Vadder et al. [31] discovered that after mouse intestinal fatty acid sensing receptor FFAR3 recognized SCFA, it promoted the enteroendocrine system to secrete GLP-1 and other gut-brain peptides, which acted on the CNS through the gut-brain axis to regulate glucose metabolism and maintain glucose homeostasis. Additionally, Clemmensen et al. [21] found that compared to high-fat diet-induced obese mice, GPRC6a knockout mice showed significantly elevated glucose and insulin levels, decreased glucose tolerance and insulin sensitivity, and disordered glucose metabolism.

Currently, research on the enteroendocrine and nutrient sensing system has focused primarily on rodents and in vitro EEC models, with limited studies in mammals such as humans and pigs. Therefore, the impact of this system on nutrient absorption and energy metabolism in mammalian intestines requires further investigation.

The animal intestine serves as a sensory organ, with EECs on the intestinal surface recognizing various nutrients—including proteins, lipids, and carbohydrates—through specific nutrient sensing receptors. This activates downstream signaling pathways and promotes secretion of gut-brain peptides such as GLP-1, PYY, and CCK. Through the gut-brain axis, these peptides not only regulate intestinal nutrient absorption and metabolism but also mediate feeding behavior, appetite, and other physiological functions. The enteroendocrine and nutrient sensing system plays a crucial role in regulating nutrient absorption and metabolic functions, yet the signaling pathways and synergistic mechanisms among nutrient sensing receptors remain unclear. Therefore, in-depth research

on the functions and mechanisms of the animal enteroendocrine and nutrient sensing system will help elucidate the mechanisms of nutrient absorption and metabolism, while providing scientific basis for improving dietary utilization and preventing and treating metabolic diseases.

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