Animal Nutrition 2 (2016) 69–73

Contents lists available at ScienceDirect

Animal Nutrition

journal homepage: http://www.keaipublishing.com/en/journals/aninu/

Review article

Amino acid sensing in the gut and its mediation in gut-brain signal transduction

Jing Liu, Kaifan Yu, Weiyun Zhu*

Laboratory of Gastrointestinal Microbiology, Jiangsu Key Laboratory of Gastrointestinal Nutrition and Animal Health, College of Animal Science and Technology, Nanjing Agricultural University, Nanjing 210095, China

ARTICLE INFO

Article history:
Received 25 February 2016
Received in revised form
24 March 2016
Accepted 25 March 2016
Available online 1 April 2016

Keywords:
Amino acid sensing
Gut hormones
Sensing receptor
Amino acid transporter
Gut-brain signaling

ABSTRACT

Animal gastrointestinal tract is not only a digestive organ, but also a nutrient sensing organ which detects luminal nutrient and thus can regulate food intake. There are many amino acid sensing receptors and transporters in the gut. Amino acids sensing by these receptors and transporters can stimulate the intestinal endocrine cells to release a variety of gut hormones. These hormones trigger a series of physiological effects via the nerve system. This review summarized the recent advance on the amino acid sensing receptors and transporters in the gastrointestinal tract, the gut hormones released from the intestinal endocrine cells and the hormones-induced signal transduction between the gut and brain. A better understanding of these processes may help to gain further insight into the specific role of amino acids in digestion and provide guidelines in developing strategy for the better use of amino acids in the diet.

1. Introduction

Animal gastrointestinal (GI) tract is the largest digestive and immune organ in the body. In addition, as a nutrient sensor, the GI tract is also involved in regulating glucose and energy homeostasis. Gastrointestinal tract serves as a sensing organ, which was confirmed by Bayliss and Starling (1902) when they discovered the first gut-derived hormone secretin. Recent advances highlighted that intestinal luminal nutrients (such as carbohydrate, fat and protein) are sensed by specific 'taste' receptors or transporters located in the membrane of cells in the intestinal epithelium. Among the receptors, G-protein-coupled receptor family C group 6 member A (GPRC6A), the taste receptor 1 family (T1Rs), calcium-sensing receptor (CaSR) can sense luminal protein and amino acids. Gut hormones are produced due to sensing the amino acids by endocrine cells. After secreted, the hormones enter into lamina propria and recognize respective receptors on the vagal afferent nerve, which signals to the brain. This process establishes the basis for regulating appetite and energy balance by the gut-brain axis. The progress in nutrient sensing indicates a promising approach to treating obesity and diabetes by targeting nutrient-induced hormone production.

2. Amino acids sensing receptor and transporter

2.1. Amino acids sensing receptor

Amino acids are signaling ligands for sensory receptors. Some of G-protein-coupled receptors (GPCRs) expressed on the enteroendocrine cells (EECs) or brush cells participate in the luminal amino acids sensing. Moreover, the specific amino acids transporters on the cell membrane also play an important role in the amino acids sensing.

G-protein-coupled receptors, including T1Rs, GPRC6A and CaSR, are the major amino acids sensing receptors.

The T1R family consists of three different subtypes (T1R1, T1R2 and T1R3) which were originally found in oral epithelial cells. Subsequent research demonstrates that they are also expressed on

* Corresponding author.
E-mail address: zhuweiyun@njau.edu.cn (W. Zhu).

Peer review under responsibility of Chinese Association of Animal Science and Veterinary Medicine.

Production and Hosting by Elsevier on behalf of KeAi

http://dx.doi.org/10.1016/j.aninu.2016.03.007

the intestinal brush cells and enteric endocrine cells of different species (Shirazi-Beechey et al., 2014). The T1R1 and T1R3 form a heterodimer to recognize most of the L-type amino acids except tryptophan. The responses are strictly dependent on the combined presence of T1R1 and T1R3, and are highly selective for *L*-amino acids; *D*-amino acids do not activate the T1R1/T1R3 heterodimer. The T1R1/T1R3 can also detect umami tastants such as monosodium glutamate (MSG), *L*-2-amino-4-phosphono-butyric acid (*L*-AP4), but the signal mediated by the transduction pathway involving T1R1/T1R3 may be different from that involving metabotropic glutamate receptor (mGluRs) (Temussi, 2009). As a typical G-protein-coupled receptor, T1R1/T1R3 is activated only when α-Gustducin (a G protein) exists.

The CaSR is a class C G-protein-coupled receptor which was firstly found in bovine parathyroid gland and is involved in extracellular calcium homeostasis in mammals. Lately, CaSR has been identified in the GI endocrine G, I and D cells where it acts as an amino acids sensor. Calcium-sensing receptor is not only activated by extracellular calcium but is also activated by *L*-aromatic amino acids (such as *L*-phenylalanine, *L*-tryptophan). The CaSR senses aromatic *L*-amino acids only when intracellular calcium concentration is higher than 1 mmol/L. Oral administration of *L*-phenylalanine (*L*-Phe) stimulated gastrin secretion in wild type but not in CaSR knockout mice. However, when CaSR knockout mice were treated with cinacalcet (an agonist of CaSR), the effect of gastrin secretion would occur (Feng et al., 2010), suggesting that *L*-Phe stimulated cholecystokinin (CCK) release via CaSR. In addition, some small peptides are also the ligands of CaSR. Several γ-glutamyl peptides, such as γ-Glu-Cys-Gly (GSH) and γ-Glu-Val-Gly, are involved in CaSR activation (Ohsu et al., 2010). Calcium-sensing receptor was involved in the CCK secretion induced by various protein hydrolysate; CCK secretions induced by protein hydrolysate were significantly decreased by the presence of CaSR antagonist compared with vehicle (Nakajima et al., 2012). This study indicated the significant role of CaSR in mediating CCK secretion by peptides stimulation in enteroendocrine cells.

The GPRC6A is a member of G protein-coupled receptor and expresses in gastric G cells, small intestinal and colonic L cells (Oya et al., 2013). It can sense many kinds of amino acids, especially basic amino acids (such as *L*-lysine, *L*-arginine and *L*-ornithine) and small neutral amino acids (such as *L*-alanine, *L*-glycine and *L*-serine), but the affinities of these amino acids are different: *L*-arginine > *L*-ornithine ≥ *L*-lysine = *L*-alanine ≥ glycine > serine (Wellendorph et al., 2005). G-protein-coupled receptor family C group 6 has a high homology with CaSR and its activation requires the presence of extracellular calcium. In HEK293 cells GPRC6A could be activated by an extracellular calcium concentrations of 5 mmol/L (Pi and Quarles, 2012). Interestingly, the CaSR agonist NPSR-568 can also activate GPRC6A (Pi et al., 2005).

2.2. Amino acid transporters

Amino acid transporters are widely expressed on the cell membranes, monitoring the amino acids concentration and mediating extra- and intra-cellular amino acids exchange. Amino acids transport may be coupled to movements of ions, including Na^+, H^+, K^+, and/or Cl^-, as well as movement of other amino acids by antiport. However, the mechanisms of different amino acid transporters are almost different. Bröer (2008) summarized the amino acids transporters in the apical and basolateral membrane (Table 1).

Several lines of evidence have shown that some of the amino acid transporters themselves can function as an amino acid sensor and are essential for amino acids sensing. Sodium dependent neural amino acids transporter 2 (SNAT2), a major amino acid transporter, is one of the best characterized amino acid transceptor. Amino acids uptake via SNAT2 are coupled with the inward movement of Na^+, which helps down its electrochemical gradient. It has been proved that this transport mechanism is involved in the stimulation of gut hormone release through consequential increases in intracellular Ca^{2+} (Young et al., 2010), and specifically in glutamine stimulated GLP-1 release from intestinal L cells (Tolhurst et al., 2011). In addition, studies have shown that like SNAT2, the B^0AT1 is also related to trigger GLP-1 release from GLUTgs cells in presence of glutamine (Reimann et al., 2004). Some other transporters, like EAAT3, y+LAT1 and CAT-1, may act by initiating downstream signaling and modulating gene expression in response to amino acids availability. However, whether they are involved in gut hormone release is remain unclear.

3. Amino acid sensing mediated GI hormone release

The EECs are derived from multipotent stem cells, located towards the base of the intestinal crypts. Although they represent less than 1% of the epithelial population, they constitute the largest endocrine organ of the human body. It is thought that EECs are the primary chemosensory cells. There are at least 15 subtypes of enteroendocrine cells that react to changes in gut contents by releasing peptide hormones, which then enter blood vessels and activate extrinsic or intrinsic afferent nerves or other nearby target cells. Sensing of amino acids will stimulate EECs to release glucagon-like peptide-1(GLP-1), cholecystokinin (CCK) and peptide tyrosine–tyrosine (PYY).

Table 1
Part of the amino acid transport system in mammalian intestinal epithelial cells.

System	cDNA	Gene	AA substrate	Mechanism	Iron	Expression
ASC	ASCT2	*SLC1A5*	A,S,C,T,Q	A	Na^+	AM
B^0	B^0AT1	*SLC6A19*	AA^0	S	Na^+	AM
$B^{0,+}$	$ATB^{0,+}$	*SLC6A14*	AA^0, AA^+, β-Ala	S	Na^+, Cl^-	AM
$b^{0,+}$	$rBAT/b^{0,+}AT$	*SLC3A1/SLC7A9*	R,K,O	A	–	AM
IMINO	IMINO	*SLC6A20*	P,HO-P	S	Na^+, Cl^-	AM
L	4F2hc/LAT2	*SLC3A2/SLC7A8*	AA^0 except P	A	–	BM
PAT	PAT1	*SLC36A1*	P,G,A,β-Ala	S	H^+	BM
T	TAT1	*SLC16A10*	F,Y,W	U	–	BM
X^-_{AG}	EAAT3	*SLC1A1*	E,D	S	Na^+, H^+, K^+	AM
y^+L	$4F2hc/y^+LAT1$	*SLC3A2/SLC7A7*	K,R,Q,H,M,L	A	Na^+	BM
y^+L	$4F2hc/y^+LAT2$	*SLC3A2/SLC7A6*	K,R,Q,H,M,L,A,C	A	Na^+	BM
A	SNAT2	*SLC38A2*	G,P,A,S,C,Q,N,H	S	Na^+	AM, BM
X^-c	4F2 hc/xCT	*SLC3A2/SLC7A11*	E	A	–	AM, BM
y^+	CAT-1	*SLC7A1*	R, K、O, H	U	–	AM, BM

A = anti-port; AM = apical membrane; AA^0 = neutral amino acids; S = symport; AA^+ = cationic amino acids; BM = basolateral membrane; U = uni-port.