

Glucose and amino acid in enterocyte: absorption, metabolism and maturation

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1. ABSTRACT

The main function of the porcine intestinal tract is nutrient digestion and absorption. This function is performed by the absorptive enterocytes, which are differentiated from the intestinal stem cells residing at the bottom of the crypt. Nutrients such as glucose and amino acids are transported, absorbed by various transporters embedded on the membranes of these enterocytes. Metabolism occurs in each cell along the crypt-villus axis (CVA). Because the intestinal epithelial cells are the most vigorous, self-renewing cells, regenerating from the crypt bottom to the villus tip in only three to five days, the CVA is an appealing organ for studying cell maturation. In this review, we examine the glucose and amino acid transporters expressed in the apical membrane, basolateral membrane, or the inside of the absorptive enterocytes. We also discuss glucose and amino acid metabolism in small epithelial cells, and show how these nutrients influence the proliferation and differentiation of an intestinal stem cell into one specialized cell type when they migrate from the bottom of the crypt to the tip of the villus.

2. INTRODUCTION

As the prime location of digestion in piglets, the small intestine is part of the most significant organ for nutrient absorption. The uptake function is performed by the intestinal epithelium, which is folded and arranged CVA. The epithelial cells are the most vigorous and self-renewing, regenerating from the crypt bottom to the villus tip in only three to five days (1). Cells at the bottom of the crypt that are mainly proliferating are called stem cells. After 2 days of division four to five times, they terminally differentiate into four specialized cell types: the crypt-sited Paneth cells and three types that cover the villus, i.e., the absorptive enterocytes, mucus-secreting goblet cells, and hormone-secreting enteroendocrine cells (2). More specific designations have now been established for those small intestinal cells, such as transit amplifying cells, +4 stem cells, leucine-rich repeat-containing G-protein coupled receptor 5+ cells, stem cells, Tuft cells, or motilin secreting cells (1-3). To provide a better description of their locations, researchers have labelled the cells that are sequentially isolated from the villus tip to the crypt bottom as F1 through F6, thereby yielding six "cell fractions" (4). Although cells can divide in several ways along the CVA, e.g., into 3, 5, 10, or 12 sections (4-6), the most common of these sort orders is from villi (F1) to crypt (Fn, n = number of sections).

Each of the four cell types occurs in a specific location. For example, the absorptive epithelial cells, or enterocytes, covered approximately 90% of the crypt and more than 95% of the villi, making them the most important for absorption, maturation, and growth along the CVA (1, 7, 8). In this review, we present the glucose

and amino acid transporters that are expressed in the small intestinal epithelial cells. We also provide a summary of how certain nutrients influence cell metabolism and some signaling pathways for cell maturation.

3. ABSORPTION OF CARBOHYDRATES AND AMINO ACIDS IN ENTEROCYTES

3.1. Hexose transporters

Over 50% of the energy needed for cell maintenance, growth, and production is supplied by dietary carbohydrates (9).

In piglets, hexose absorption within the intestine is achieved through either para-cellular or trans-cellular routes (10, 11). Hexose transporters are expressed on the membrane of small porcine enterocytes. They can be categorized as sodium-dependent glucose transporters (SGLTs) or facilitative glucose transporters (GLUTs), and include SGLT1, GLUT2, GLUT5, GLUT7, and GLUT12 (12, 13). In addition to their necessity for glucose absorption, these transporters have unique roles in glucose sensing (14, 15). Along the CVA, expression of intestinal glucose transporters is regulated by various factors, e.g., substrate concentration, food deprivation or feed restriction, disease, diurnal cycle, local or systemic hormone levels, and piglet developmental stage (16-18).

3.1.1. SGLT1 (*SLC5A1*)

In weaning piglets, SGLT1 protein is primarily found on the apical membrane of villus cells and is detected in only negligible amounts on the apical membrane of crypt cells (17). Because it has limited expression in other tissues, this protein is considered to be the only sodium-glucose co-transporter against the concentration gradient and the major route for absorption of dietary glucose in the enterocytes (Table 1)(12, 17). This protein has been cloned and characterized in pigs; its mature size in weanling animals is approximately 75 kilodaltons (17, 19). High activity by gut apical SGLT1 contributes to neonatal glucose homeostasis (20). Absorption of SGLT1 peaks along the CVA in the jejunum, and its mRNA abundance is lower in crypt cells than in villus cells (6). Its activity is governed by protein kinase C and mechanistic target of rapamycin (mTOR), which mediate intracellular signaling pathways (21, 22). Whereas the abundance of *Solute Carrier (SLC) 5A1* mRNA increases during the process of aging, the abundance of SGLT1 protein in the small intestine declines over time but always remains higher than that of *SLC5A1* mRNA (23). Expression of SGLT1 can be influenced by some amino acids, being inhibited, for example, throughout the small intestine of animals that are fed an isoleucine-deficient diet (24). As a glucose receptor, SGLT1 modulates diverse

Table 1. Hexose and amino acid transporters

Classification	Transport family	HUGO name	Specific transporter	Localization	Distribution proportion along CVA	Substance transported	References
Sugar transporter	SGLT	SLC5A1	SGLT1	AM	V > C	glucose	17
	GLUT	SLC2A2	GLUT2	BM	V > C	glucose, fructose, and galactose	11, 29
		SLC2A5	GLUT5	AM	V > C	Fructose	34, 36
		SLC2A7	GLUT7	AM	V > C	glucose and galactose	11, 39, UD
		SLC2A8	GLUT8	I	V > C	glucose and fructose	44, 45, UD
		SLC2A9	GLUT9	AM & BM		glucose and uric acid	46, 47, 49
		SLC2A12	GLUT12		V > C	D-glucose and 2-deoxy-D-glucose	53, UD
AA transporter	SLC1A	SLC1A1	EAAC1	AM	V > C	glutamic acid	63
		SLC1A2	GLT-1	AM	V < C	L-glutamic acid, L- and D-aspartic acid	65, 66, UD
		SLC1A3	GLAST	AM	V < C	glutamic acid	62, UD
		SLC1A5	ASCT2	AM & I		alanine, serine, threonine, and cysteine	62
	SLC6A	SLC6A19	B ⁰ AT1	AM	V > C	neutral AA	80, 76, 78
		SLC6A20	SIT1	AM	V < C	proline	85, UD
	SLC7A	SLC7A1	CAT1	AM & BM	V < C	arginine, lysine, ornithine, and histidine	87, 88, UD
		SLC7A6	y ⁺ LAT2	BM		cationic and neutral AA	92, 93
		SLC7A7	y ⁺ LAT1	BM	V > C	cationic and neutral AA	93, UD
		SLC7A8	LAT2	BM	V > C	aromatic neutral AA except proline	80, 95, UD
		SLC7A9	b ⁰ . ⁺ AT	AM & BM	V > C	cationic and neutral AA	60, 99, UD
		SLC7A10	Asc-1	BM	V < C	L-alanine, L-serine, L-cysteine, glycine, L-threonine	102, 103, UD
		SLC7A11	xCT	BM	V < C	glutamine, and L-Cystine	104, 105, UD
	SLC16A	SLC16A10	TAT1	AM & BM	V > C	tryptophan, tyrosine, and phenylalanine	109, UD
		SLC16A14	B ⁰ , +	AM	V < C	neutral and cationic AA	111, UD
	SLC38A	SLC38A2	ATA2	BM	V < C	serine, proline, glutamine, and alanine	114, UD
		SLC38A5	SN2	AM or BM	V < C	glutamine, asparagine, and histidine	115, 116, UD
	Other	SLC36A1	PAT1	AM	V > C	proline, glycine, and alanine	118, UD
		SLC15A1	PepT1	AM	V > C	di- and tripeptides	125, UD

AM: apical membrane, BM: basolateral membrane, I: intracellular, V: villi, C: crypt, UD: Unpublished Data

cellular functions (14). Not only does it act as a sugar transporter to sustain energy production in the cells, but it also functions as a receptor for sensing extracellular glucose concentrations to control food intake (15). Via a signaling process: stimulation of the T1R2 and T1R3 taste receptor by sugars activates gustducin(25, 26).

3.1.2. Facilitative glucose transporters

Among the 14 currently identified members of the facilitative glucose transporter family, only GLUT2, GLUT5, GLUT7, GLUT9, and GLUT12 are known to exist within the small intestine. Conclusions about their

involvement in hexose transport across the apical or basolateral membrane of the enterocytes are still controversial. Only two of those recognized members -- GLUT2 and GLUT5-- are fructose transporters (27, 28).

3.1.2.1. GLUT2 (*SLC2A2*)

The GLUT2 protein transports intracellular hexoses across the basolateral membrane(table1) (29). Predominantly expressed on that membrane, it has large capacity for three kinds of substrate: glucose, fructose, and galactose(table1)(11). The sequence of porcine GLUT2 shares 87.0.% and 79.4.% identity with GLUT2 in humans and mice, respectively (30). This protein mediates basolateral transport of fructose from the enterocyte to the blood. In adult rats, it is expressed only in enterocytes, and is detected at the tip and on the side of the villi but not at the base of the villi or in the crypts (31). It is required for glucose sensing in the cells of central nervous system and the small intestinal cells(32, 33). Animals fed an isoleucine-deficient diet show suppressed expression of GLUT2 in the duodenum and jejunum (24).

3.1.2.2. GLUT5 (*SLC2A5*)

As a member of the solute carrier (SLC) family 2, GLUT5 is principally expressed on the apical membrane of enterocytes(table1) (34). Fructose intake results in the upregulation of intestinal *SLC2A5* mRNA and production of this protein (35). Research on the small intestine in adult rats and humans has demonstrated that *SLC2A5* mRNA is mainly localized in the mid-villus region(table1)(36). Based on fructose-feeding experiments, this mRNA is abundant in the upper three-fourths of the villus cells but is virtually non-existent in the crypts (37). Furthermore, the mRNA abundance of *SLC5A1*, *SLC2A2*, and *SLC2A5* mRNA in the chicken small intestine increases linearly with aging (38).

3.1.2.3. GLUT7 (*SLC2A7*)

GLUT7 is a probable transporter of glucose and galactose, and recognizes D-glucose as a substrate(table1)(11). It shares 53% similarity with the sequence of GLUT5 and is primarily expressed on the apical membrane of small intestinal epithelial cells (table1)(39). Although GLUT7 has not yet been cloned and characterized in pigs, *SLC2A7* mRNA has been detected in the porcine small intestine (40).

3.1.2.4. GLUT8 (*SLC2A8*)

The GLUT8 protein is expressed in both the small and large intestines of rodents and human(41-44), as well as in pigs (UD)(table1). Investigations with immuno-histochemistry have demonstrated its intracellular localization in the enterocytes and

crypt cells(table1)(44). Our research group has also determined that its distribution is greater in the villi than in the crypt cells (UD)(table1). Immunofluorescence and confocal microscopy results have shown that activity by this fructose/glucose transporter is down-regulated in Caco2 cultures (45).

3.1.2.5. GLUT9 (*SLC2A9*)

In mice, expression of GLUT9 is low in the duodenum but higher in the jejunum and ileum (table1) (46, 47). This protein acts as a glucose transporter in several cell types, e.g., hepatocellular G2 cells, albeit to a lesser extent when compared with the major transporter GLUT1 (48). Approximately 30 to 40% of circulating uric acid is cleared in the enterocytes (table1)(49), and GLUT9 has been identified as a high-capacity urate transporter, rather than as a glucose transporter, in humans and rodents (50, 51).

3.1.2.6. GLUT12 (*SLC2A12*)

Homologous to the insulin-regulatable glucose transporter GLUT4, GLUT12 has been detected in human breast adenocarcinoma cell line MCF-7, and immuno-blotting has been used to demonstrate that it is expressed in skeletal muscle, adipose tissue, and the small intestine (52). Among the hexoses, D-glucose and 2-deoxy-D-glucose are the main substrates transported by this glucose transporter (table1)(53). In transgenic mice, increased expression of GLUT12 results in improved whole-body insulin sensitivity, which leads to an increased rate of glucose clearance in insulin-responsive tissues under insulin-stimulated conditions (54).

3.2. Amino acid transporters

As an essential element primarily contained in amino acids (AA), nucleosides, polyamines, and polymers, nitrogen (N) is the most generously supplemented nutrient in pig fodder (55). During the suckling period, efficiency of N-utilization by the entire body is maintained at approximately 83% (56). In humans, optimal growth and regulation of body weight necessitates AA uptake through the epithelium (57). Although most AA transport systems are denoted based on substrate pREFERENCES, e.g., anionic, cationic, or neutral, and on whether the sodium ion must be activated or co-transported, i.e., sodium-dependent or requiring an exchanger (58), a new genomic and molecular nomenclature system has been introduced for describing the SLC family system in humans (59, 60). Serving as carriers and sensors, AA transporters interact with intracellular nutrient-signaling pathways to regulate metabolism (61). The transporters that are expressed in the small intestine are generally members of the SLC1A, SLC6A, SLC7A, SLC16A, and SLC38A families.

3.2.1. SLC1A family

The seven members of the SLC1A family that are expressed in the intestine include five high-affinity glutamate transporters -- EAAC1, GLT-1, GLAST, EAAT4, and EAAT5 (SLC1A1, SLC1A2, SLC1A3, SLC1A6, and SLC1A7, respectively) -- plus two neutral-AA transporters, ASCT1 and ASCT2 (SLC1A4 and SLC1A5, respectively) (62).

3.2.1.1. EAAC1 (SLC1A1), GLT-1 (SLC1A2), and GLAST (SLC1A3)

Also known as Excitatory AA Transporter 3 (EAAT3) and Excitatory AA Carrier (EAAC1), SLC1A1 belongs to System X-AG, a Na⁺-dependent high-affinity transport system (62). The latter protein is the predominant isoform in that system, and is the primary Na⁺-dependent glutamate (Glu) transporter expressed in the epithelial cells of neonatal piglets(63). That system is also the main transporter of luminal L-Glu across the apical membrane of enterocytes(table1) (63). Whereas expression of EAAC-1 increases during the phase of cell differentiation and is regulated at the transcription and translation levels from the crypt to the upper villus cells, the activity of transporters in the X-AG system is high during the proliferation and differentiation of mid-villus epithelial cells but low in differentiated upper villus cells(table1)(63). However, the level of *SLC1A1* mRNA collected from the middle villus cells is lower when compared with the protein content (63). In *Xenopus oocytes*, mTOR enhances the abundance of EAAT3 protein by stimulating carrier insertion into the cell membrane (64).

Several terms are used when referring to SLC1A2, e.g., EAAT2 or glutamate transporter 1 (GLT-1) (62). This protein transports L-Glu, as well as L- and D-Asp, and is present in the apical membranes of some polarized cell types, including enterocyte (table1)(65, 66). Both mTOR and β -Klotho kinases up-regulate EAAT1 and EAAT2 whereas the kinases SPAK and OSR1 down-regulate them (67-69).

As part of the X-AG system, SLC1A3 has two synonyms: Glutamate Aspartate Transporter (GLAST) and Excitatory AA Transporter 1 (EAAT1), and is located on the apical membranes (table1)(62). This protein is expressed by the crypt-like cell line IEC-17 (70). Both SPAK and OSR1 down-regulate the activity of EAAT3 (71).

3.2.1.2. ASCT2 (SLC1A5)

Known as ASCT2, SLC1A5 is a member of the ubiquitous alanine-serine-cysteine preferring (ASC) system, which mediates Na⁺-dependent transport of small neutral AAs and has high affinity for Ala, Ser, Thr, and Cys (62). As a neutral-AA transporter, ASCT2 also accepts Glu and Asn with high affinity, but Met,

Leu, and Gly with low affinity (table1)(62). This protein is identical to ATB0 on the apical membrane of the rabbit small intestine, and the tissue and intracellular distribution of ASCT2/ATB0 parallels that of system B0 activity (72). As an essential AA antiporter, ASCT2/ATB0 cannot mediate net AA absorption and is expressed outside the apical membrane of epithelial cells (57, 73). Treatment with 2% L-Glu increases the mRNA expression of *SLC1A5* in the jejunal mucosa (74).

3.2.2. SLC6A family

3.2.2.1. B0AT1 (SLC6A19)

Encoded by *SLC6A19*, B0AT1 absorbs the bulk of neutral AA in the intestine (table1)(75, 76). This transporter is part of a Na⁺-dependent, chloride-independent system that drives the uptake of major neutral AAs across the apical membrane into enterocytes and kidney proximal tubular cells (77). Through unique control mechanisms, B0AT1 is co-expressed with angiotensin-converting enzyme 2 along the entire small intestinal CVA in young animals(76). As shown in studies of a heterologous system in mice, B0AT1 accepts all neutral AAs but prefers large neutral AAs such as branched-chain AAs and Met (table1)(78, 79). This transporter is expressed on the apical membrane in all parts of the small intestine but does not exist in the colon (table1)(80), and increases from the duodenum to the ileum (81, 82). Expression of B0AT1 protein in the brush-border membrane requires co-expression of collectrin (83, 84). The signal for B0AT1 is more intense at the tips of the villi (75). Co-transport activity of apical Na⁺-Gln is much higher in the upper villus cells than in other parts of the CVA whereas Na⁺-Gln co-transport affinity is lower in the upper villus cells than in the middle villus and the crypt cells(76). Furthermore, *SLC6A19* mRNA abundance is lower in the crypt than in the villus cells(76). Although they contain large amounts of B0AT1 protein, the intestinal vesicles show very low transport activity (57). B0AT1-specific Na⁺-neutral AA co-uptake activity is highest in the jejunal upper villus cells when compared with cells in the middle villus and the crypt, and Na⁺-Gln co-transport activity is very high along the entire CVA in young pigs (76).

3.2.2.2. SIT1 (SLC6A20)

Sodium/Imino-acid Transporter 1 (SIT1) belongs to the IMINO system, which mediates the Na⁺-dependent transport of AAs such as proline (Pro) and hydroxyproline in a variety of intact tissues and membrane vesicle preparations, including the intestine and kidney (Table1)(85). This system has been characterized in some detail in membrane vesicles from the jejunum of rabbit, rat, and mouse (85, 86). The luminal brush-border SIT1 is localized to the kidney and intestine in the mouse (82).

3.2.3. SLC7A family

3.2.3.1. CAT1 (SLC7A1)

As a major member of System y⁺, CAT-1 is a Na⁺-independent transporter for cationic AAs such as Arg, Lys, Orn, and His, and is positively charged under physiological conditions (60). It is located on both the apical and basolateral membranes of the intestine (table1) (87, 88). In pigs, CAT-1 has been cloned and characterized from pulmonary artery endothelial cells (89). Dietary Arg supplementation improves the expression of ileal *SLC7A1* (90). Its mRNA abundance is similar in the jejunum and the ileum (91).

3.2.3.2. y⁺LAT1 (SLC7A7) and y⁺LAT2 (SLC7A6)

Both *SLC7A7* and *SLC7A6* belong to System y⁺L. Whereas the transport of basic AAs by this system is Na⁺-independent, that of neutral AAs may be dependent on Na⁺ (table1)(92). These AA transporters consist of a light chain (y⁺LAT1 or y⁺LAT2) and a heavy chain (4F2hc) through a disulfide linkage, thereby making them heterodimeric (60). Both proteins are functional on the basolateral membrane of the small intestine (table1)(93). Feeding with dietary Arg improves the expression of jejunal *SLC7A7* in swine (90), and cysteamine supplementation increases the mRNA levels of *SLC7A7* in the jejunum of finishing pigs (94).

3.2.3.3. LAT2 (SLC7A8)

This AA transporter is responsible for the Na⁺-independent movement of large branched and aromatic neutral AAs except Pro (table1)(80, 95). One isoform, LAT2, is a heterodimer formed by the 4F2 (SLC3A2) heavy chain and light chain LAT2 (80). The 4F2hc/LAT2 complex is expressed primarily on the basolateral membrane of the small intestine and kidney (96), but is most highly expressed in the jejunum and ileum (97). However, LAT2 has not been identified and characterized at the molecular and functional levels in pigs (93).

3.2.3.4. b⁰,⁺AT (SLC7A9)

Another member of the SLC7A family is a Na⁺-independent transport transporter that exchanges intracellular cationic and neutral AAs and is located in the brush border of the proximal tubule and the small intestine (table1)(60). This heterodimeric AA transporter consists of a light chain (b⁰,⁺AT) and a heavy chain (rBAT) through a disulfide linkage (60). The light chain is a catalytic subunit and the heavy chain is required for trafficking AA to the cell membrane (98). The b⁰,⁺AT/rBAT protein complex induces Na⁺-independent, high-affinity transport of L-Cystine (CSSC) and cationic AAs, and is a lower-affinity

transporter for neutral AAs that is achieved through by an obligatory exchange mechanism (table1)(99, 100). While 4F2-hc6 also encodes a protein capable of b⁰,⁺ activity, it associates with 4F2-hc rather than with rBAT (101). Cysteamine supplementation improves the mRNA levels of *SLC7A9* in the jejunum mucosa (94).

3.2.3.5. Asc-1 (SLC7A10)

Belonging to the ASC system, Asc-1 is a Na⁺-independent, high-affinity transporter that moves small neutral AAs such as L-Ala, L-Ser, L-Cys, Gly, L-Thr, and 2-aminoisobutyric acid (table1)(102, 103). Functional expression of Asc-1 transporters requires the linkage of 4F2 heavy chain (hc) via a disulfide bond. One Type-II membrane glycoprotein, 4F2hc, is expressed on the basolateral membrane of small intestinal epithelial cells (103).

3.2.3.6. 4F2hc (SLC3A2)-xCT(SLC7A11)

System X-C is a Na⁺-independent anionic-AA transport system highly specific for CSSC and glutamine (Gln)(table1). It is presents on the basolateral membrane of various tissues, including the small intestine. This transporter activity directly controls intracellular glutathione levels because the uptake and reduction of Cys are rate-limiting for GSH synthesis (60, 104, 105). Another heterodimer, X-C, consists of 4F2hc as the heavy chain and xCT (X-C transporter, *SLC7A11*) as the light chain (106). In contrast to other transporters, e.g., L, y⁺L, and b⁰,⁺, Xct is unique to System X-C. Transport activity is thought to be mediated by Xct, a protein that has been characterized at the molecular and functional levels in humans and mice, but not in pigs(93, 105, 106).

3.2.4. SLC16A family

3.2.4.1. TAT1 (SLC16A10) and B⁰,⁺(SLC16A14)

The SLC16A family is also known as the monocarboxylate transporter (MCT) family (107, 108). It includes TAT1, which functions in the trans-epithelial transport of aromatic AAs such as Try, Tyr, and Phe (109). As a Na⁺ and Cl⁻-independent and low-affinity transporter, it mediates electroneutral-facilitated diffusion (109). The *SLC16A10* mRNA is highly expressed in the intestines and various other tissues, and is an epithelial basolateral transporter that acts as a net efflux pathway (109, 110). Located on the apical membrane of intestinal epithelia, this protein has the highest affinity for hydrophobic AAs but low affinity for Pro (table1)(109). The orphan transporter MCT14 (*SLC16A14*) is a neuronal aromatic-amino-acid transporter in mouse (107).

It transports neutral and cationic AAs in the apical membrane, showing the highest affinity for hydrophobic AAs and the lowest affinity for Pro (table1)

(111). Expression of its mRNA is highest in the cecum and colon, low in the distal ileum, and undetectable in the duodenum and jejunum. Research is still needed to determine whether ATB0,+ contributes significantly to the absorption of AAs in the small intestine, or if another ATB0,+ isoform is responsible for system B0,+ activity (93).

3.2.5. SLC38A family

3.2.5.1. ATA2 (*SLC38A2*) and SN2 (*SLC38A5*)

Sodium-coupled AA transporters (SNATs) can belong to either System A or System N (112). Both types share many functions and are characterized by a distinct sensitivity to low pH (113). One type, ATA2 (or SNAT2), is a strong transporter of short-chain neutral AAs such as Ser, Pro, and especially Gln and Ala (table1)(114). Unlike System N, System A is adaptively regulated by hormones and growth factors, and it does not mediate proton exchanges (113, 115). The SN2 protein mediates Na⁺-dependent transport of neutral AAs, in particular, Gln, Asn, and His (table1)(116). In addition to the small intestine, *SLC38A5* expression is detected in multiple brain regions, as well as the colon and spleen (115). Whereas ATA2 is distributed only on the basolateral membrane, SN2 is also located on the apical membrane (table1)(114, 115).

3.2.6. Other transporters

3.2.6.1. PAT1 (*SLC36A1*) and PEPT1 (*SLC15A1*)

Both PAT1 and PEPT1 are curtain H⁺-coupled co-transporters for which their optimal intestinal absorptive capacity depends upon the functioning of the brush-border Na⁺-H⁺ exchanger NHE3 (117). The PAT1 protein is the molecular correlate of the rat intestinal AA carrier and is targeted to the apical membrane of enterocytes in the mouse small intestine (table1)(118, 119). It was initially identified as a lysosomal AA transporter (120). In oocytes, PAT1 transports Pro, Gly, Ala, betaine, sarcosine (N-methylglycine), MeAIB, and GABA. This transporter has low affinity for all of its substrates, with transport affinity (*K_m* values) ranging from 3 to 7 mM (121).

The high-capacity/low-affinity PEPT1 is responsible for the absorption of more than 8,000 different di- and tripeptides (122). A humanized PEP1 mouse model has been used to show that this protein is substantially expressed in the duodenum, jejunum, and ileum (123). Furthermore, this proton-coupled peptide transporter contributes to the permeability of 5-aminolevulinic acid in the intestine (124). Located on the apical membrane, it is an important intestinal drug transporter (table1)(125).

4. GLUCOSE AND AA METABOLISM ALONG CVA

4.1. Glucose metabolism

Glucose metabolism within enterocytes is complex because it is closely tied to the activity of glucose transporters, their dynamic expression, and the capacity to sense carbohydrate concentrations. In young cells in the intestinal crypts of mice and sheep, metabolism of SGLT1 is irreversibly programmed by the level of dietary carbohydrates, and is not subsequently re-programmed as they migrate up the villus. In contrast, diet supplements can help regulate de novo synthesis of *SLC2A5* mRNA and GLUT5 protein in cells lining the villus (126). Glucose metabolism, especially in the citrate cycle, is greater in the villi tips than in the crypt cells (4). Other proteins expressed during glycolysis are down-regulated, including fructose-1,6-bisphosphatase, fructose-bisphosphate aldolase, and glyceraldehyde-3-phosphate dehydrogenase (Figure 1)(4). In early-weaned piglets, proteins involved in the tricarboxylic acid cycle, β -oxidation, and the glycolysis pathway are significantly down-regulated in the villus while glycolytic proteins are significantly up-regulated in the jejunal crypt cells (127).

4.2. AA metabolism

Although numerous studies have examined AA metabolism inside differentiated tissues and cells, only a few investigations have explored dynamic metabolism along the CVA. In piglets, energy metabolism, and especially protein expression, in the intestinal epithelial cells increases from the bottom of the crypt to the tips of the villi as those cells mature (figure1)(4).

As a non-essential AA, Gln is produced in the gut mucosa and transported from the enterocyte apical membrane (63). It has many important functions in nutrition, metabolism, and signaling. For example, it can be synthesized in two ways: a. changed from α -ketoglutarate, synthesized endogenously, by either glutamate dehydrogenase or by some aminotransferases; b. changed from other amino acids comprise glutamine, arginine, proline and histidine(128). Its metabolism is associated with an increase in *SLC1A1* mRNA and it enhances cell viability, transepithelial electrical resistance, and membrane integrity in the intestinal porcine enterocyte cell-1, or IPEC-1 (129).

The expression of proteins related to Gln metabolism is decreased from the crypt to the villus tip (4), and Gln is required for the N-related proliferation of intestinal epithelial cells (130). When the diet of the channel catfish *Ictalurus punctatus* is supplemented with Gln, the heights of the enterocytes

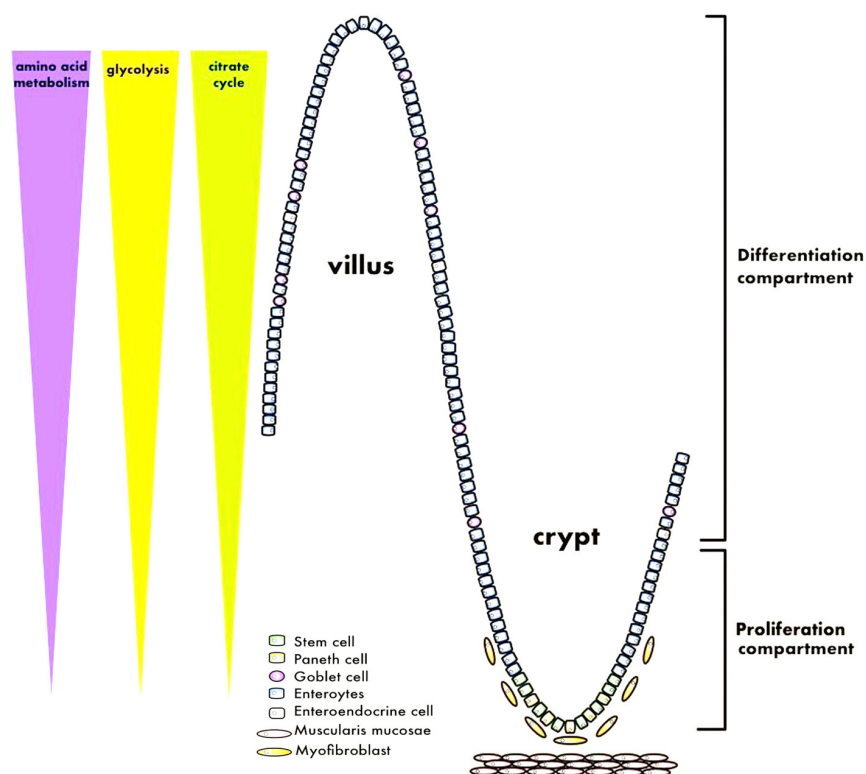


Figure 1. Glucose and amino acids metabolism along crypt-villus axis.

and microvilli are significantly increased and the rate of enterocyte migration is accelerated in the intestine (131). Moreover, mRNA expression of AA transporter genes in the piglet jejunum and ileum is significantly increased in response to supplementation with Gln or its replacement AKG, thereby leading to improved Gln metabolism in the enterocytes and greater utilization of AAs (132). The addition of Asn also elevates the activity of key enzymes involved in the tricarboxylic acid cycle, including citrate synthase, isocitrate dehydrogenase, and α -ketoglutarate dehydrogenase complex (133). Finally, Arg is a semi-essential AA that becomes essential during periods of rapid lean tissue deposition. It is synthesized only from citrulline, a non-dietary AA produced mainly in the gut. Therefore, the gut is a critical site for arginine and citrulline metabolism, which can be affected by the resident microbiota (134).

5. EFFECTS OF GLUCOSE AND AMINO ACIDS ON THE GROWTH AND MATURATION OF ENTEROCYTES

The maturation of enterocytes in the small intestine along the CVA is a dynamic process controlled by gene expression via sensing, regulation, and adaptation to the nutrient environment. In addition to classical methods of analysis, e.g., immuno-histochemical staining and ELISA, more modern technologies are being applied to investigate expression

and the signal pathways involved in this process, such as microarrays, proteomics, transcriptomics, 2D-DIGE, and MALDI-MS (5, 135). Taking such new approaches has also revealed that a nutrient-sensing mechanism within the crypt modulates the size and activity of the intestinal stem cell pool (136).

Oligosaccharide treatment of human milk can reduce proliferation and increase differentiation in HT-29 and post-confluent Caco-2Bbe cells, eventually influencing the maturation of enterocytes *in vitro* (137). Furthermore, Arg stimulates the proliferation of IPEC-1 by activating the mTOR signal pathway, which then increases protein synthesis and decreases protein degradation. In particular, dietary supplementation with Arg improves relative protein expression for phosphorylated mTOR and phosphorylated ribosomal protein S6 kinase-1, while also reducing the production of TLR4 and phosphorylated levels of nuclear factor- κ B (138). This AA stimulates cell migration in conjunction with focal adhesion kinase signaling and NO-dependent pathways (139). It also activates the immediately downstream mTOR target, p70 S6 kinase, in the enterocytes (140).

When nitric acid is available, Leu increases the migration of intestinal cells (141) and can regulate the mTOR signaling pathway through the activation of p70 S6 kinase and phosphorylation of 4E-BP1 (142).

When broiler hens receive dietary Leu supplementation, the villus height and the ratio of villus height to crypt depth in the jejunum and in ileum are increased, and the expression of Mtor S6K1 rises when the level of Leu increases from 1.3.7.% to 2.1.7.% (143).

Under Gln deprivation, the PI3-Kinase/Akt pathway is controlled as the expression of PI3K and p-Akt increases in Caco-2 cells. However, the optimal dose of Gln enhances the expression of phosphorylated AMPK and activates the AMPK pathway within IPEC-1 (144, 145).

Theoretical mechanisms for signalling pathways and transport regulators have also been suggested. For example, hedgehog signals from the developing epithelium are thought to direct embryonic villus formation and specify the site of crypt development at the villus base (146). In the mouse intestine, established markers for absorptive and goblet cell differentiation are up-regulated in villus cells while Paneth cell markers are maximally expressed in the crypt cells (135). The Wnt pathway is the dominant force behind stem cell proliferation while the Notch pathway reduces such proliferation (135, 147). As a Wnt target gene, the transcription factor *Ascl2* acts as a master regulator of intestinal stem cells, cooperating with b-catenin/Tcf to activate fundamental genes. In particular, suppression of Wnt/ β -catenin signaling, rather than clonogenic capacity, affects the asymmetric division of those cells (148, 149). The greater contents of eukaryotic protein translational pathway initiation factors 4E (eIF4E) protein and its binding protein 1 γ -isoform to phosphorylated (Pi) eukaryotic elongation factor 2 (eEF2) protein in crypt than upper villi suggest that the crypt cells have higher translational efficiency than upper villus cells (6). By feeding a ketogenic diet, differentiation is increased in the enterocyte, goblet, and Paneth cell lineages (150).

Higher abundances ($P < 0.0.5.$) of total eukaryotic initiation factor 4E (eIF4E) protein and eIF4E-binding protein 1 γ -isoform in contrast to a lower ($P < 0.0.5.$) abundance of phosphorylated (Pi) eukaryotic elongation factor 2 (eEF2) protein and the eEF2-Pi to total eEF2 abundance ratio suggest higher global protein translational efficiency in the crypt cells than in the upper villus cells

6. PROSPECTS

Although glucose and AA transporters have been investigated for more than 40 years, only a limited number of viable hypotheses have been presented to explain the underlying molecular mechanisms and metabolic interactions. For example, AA transporters are widely used as an index when studying cancers or designing medical technologies (151, 152). Therefore, researchers need more information related to intrinsic

quality if these AAs are to serve as potential regulated sites/targets in cancer therapies or when developing new drugs. With regard to small intestinal cells, nutrients have a clear influence on the metabolism of substances and energy. Nevertheless, the relationships, crosstalk, and reactions between or even across the key proteins within each enterocyte require further examination. Now that evidence for the regulators of related genes and pathways has been aggregated, their practical utilization can be explored in the manufacture of medicines and animal feed.

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Abbreviations: AA, amino acid; CVA, crypt-villus axis; EAAC1, Excitatory AA Carrier 1; EAAT, excitatory AA transporter; GLT-1, glutamate transporter 1; GLUT, facilitative glucose transporter; MCT, monocarboxylate transporter; mTOR, mechanistic target of rapamycin; SGLT, sodium-dependent glucose transporter; SIT1, sodium/imino-acid transporter 1; SLC, solute carrier; SNAT, sodium-coupled AA transporters; T1R2 and T1R3, taste receptor type 1 member 2 and taste receptor type 1 member 3; MCF-7, michigan cancer foundation-7; N, nitrogen; ASCT1, neutral amino acid transporter A; SPAK, ste20-related proline-alanine-rich kinase; OSR1, protein odd-skipped-related 1; GLAST, glutamate aspartate transporter; ASC system, alanine-serine-cysteine preferring system; B(0)AT1, system B(0) neutral amino acid transporter AT1; IMINO system, Na⁺ and Cl⁻ dependent profile IMINO transporter; CAT-1, cationic amino-acid transporter-1; 4F2hc, 4F2 cell-surface antigen

heavy chain; LAT1, L-type large neutral amino acid transporter 1; LAT2, L-type large neutral amino acids transporter 2; y+LAT2, Na⁺ dependent cationic and Na⁺ dependent neutral amino acid transporter 2; b^{0,+}AT, Na⁺ dependent cationic and zwitterionic amino acid transporter; rBAT, heavy chain corresponding to the b^{0,+} system; CSSC, L-Cystine; 4F2-Ic6, 4F2 cell-surface antigen light chain 6; GSH, glutathione; X-C, The cystine/glutamate antiporter; xCT, subunit of system xc⁻; MCT, monocarboxylate transporter; TAT1, T-type amino acid transporter 1; PAT-1, proton-coupled amino acid transporter 1; PEPT1, peptide transporter 1; NHE3, sodium–hydrogen antiporter 3; MeAIB, methylaminoisobutyric acid; GABA, γ-aminobutyric acid; IPEC-1, porcine small intestinal epithelial cell line-1; AKG, alpha-Ketoglutaric acid; ELISA, enzyme linked immunosorbent assay; 2D-DIGE, two dimension difference gel electrophoresis; MALDI-MS, matrix-assisted laser desorption/ionization mass spectrometry; TLR4, toll-like receptor 4; PI3-kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase; Akt, protein kinase B (PKB); AMPK, 5' adenosine monophosphate-activated protein kinase; eEF2, eukaryotic elongation factor 2; eIF4E, eukaryotic initiation factor 4E.

Key Words: Intestinal epithelial cell, Amino acid transporter, Glucose absorption, Metabolism, Maturation, Crypt-villus axis, Review

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