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REVIEW ARTICLE

Roles of amino acids in preventing and treating intestinal diseases: recent studies with pig models

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Abstract Animal models are needed to study and understand a human complex disease. Because of their similarities in anatomy, structure, physiology, and pathophysiology, the pig has proven its usefulness in studying human gastrointestinal diseases, such as inflammatory bowel disease, ischemia/reperfusion injury, diarrhea, and cancer. To understand the pathogenesis of these diseases, a number of experimental models generated in pigs are available, for example, through surgical manipulation, chemical induction, microbial infection, and genetic engineering. Our interests have been using amino acids as therapeutics in pig and human disease models. Amino acids not only play an important role in protein biosynthesis, but also exert significant physiological effects in regulating immunity, anti-oxidation, redox regulation, energy metabolism, signal transduction, and animal behavior. Recent studies in pigs have shown that specific dietary amino acids can improve intestinal integrity and function under normal and pathological conditions that protect the host from different diseases. In this review, we summarize several pig models in intestinal diseases and how amino acids can be used as therapeutics in treating pig and human diseases.

Keywords Pig models · Intestinal disease · Amino acids · Therapeutics

Abbreviations

Akt	Protein kinase B
AMPK	AMP-activated protein kinase
APC	Adenomatous polyposis coli
BCAA	Branched-chain amino acids
CRC	Colorectal cancer
CRH	Corticotropin-releasing hormone
DAO	Diamine oxidase
DSS	Dextran sodium sulphate
ERK	Extracellular signal-regulated kinase
FAP	Familial adenomatous polyposis
I/R	Ischemia/reperfusion
IBD	Inflammatory bowel disease
IL	Interleukin
LPS	Lipopolysaccharide
mTOR	Mammalian target of rapamycin
NAC	*N*-Acetylcysteine
NOD	Nucleotide-binding oligomerization domain protein
OAT	Ornithine-δ-aminotransferase
PI3K	Phosphatidylinositol 3-kinase
P5C	Δ^1-Pyrroline-5-carboxylate

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ROS	Reactive oxygen species
TLR	Toll-like receptor
TNBS	Trinitrobenzene sulfonic acid
TNF	Tumor necrosis factor
ZO	Zonula occludens

Introduction

Rodents have been widely used as models of human nutrition, physiology and pathophysiology in health and in disease. However, in numerous cases rodents cannot accurately replicate the human conditions. Compared to rodents, the pig has a closer match of human biochemistry, cell biology, anatomy, physiology, and pathophysiology. The pig shows a high homology in DNA sequence and chromosomal structure with those of humans (Verma et al. 2011), and there are considerable anatomical and physiological similarities of the organ systems, for example, the intestine, between pigs and humans (Clouard et al. 2012; Heinritz et al. 2013). Furthermore, pigs are monogastric omnivores, and their dietary requirements and physiology in digestion and nutrient absorption are closely resembled to those of humans (Clouard et al. 2012). Moreover, pigs have an ability to ferment nutrients in the colon, and possess similar intestinal microbial ecosystem and microbiota to those of humans (Heinritz et al. 2013; Gonzalez et al. 2015). Taken together, these characteristics have made the pig an ideal model for investigating human intestinal diseases, such as inflammatory bowel disease (IBD) (Pouillart et al. 2010), ischemia/reperfusion (I/R) injury (Spanos et al. 2007), diarrhea (Kocher et al. 2014), necrotizing enterocolitis (Jiang and Sangild 2014), short bowel syndrome (Jiang and Sangild 2014; Gonzalez et al. 2015), stress-induced intestinal dysfunction (Gonzalez et al. 2015; Wu et al. 1996b), and cancer (Flisikowska et al. 2012).

In general, amino acids are absorbed and used by the host to synthesize proteins and other important substances, and are oxidized as a source of energy (Wu 2013b). Recent studies indicated that amino acids possess additional, novel functions in growth, health, and disease. For example, some amino acids can attenuate intestinal damage, maintain barrier function and intestinal integrity, restore mucosal immune homeostasis, reduce oxidative stress and inflammatory cytokine production, and increase the level of immune regulatory cytokines (Li et al. 2016; Ruth and Field 2013; Wu et al. 2015; Yi et al. 2016). Based on our and other's findings in pig models, amino acids, such as arginine (Liu et al. 2008), glutamine (Ewaschuk et al. 2011), glycine (Wu 2015), cysteine (Song et al. 2016), *N*-acetylcysteine (NAC) (Hou et al. 2012; Yi et al. 2016), and proline (Kang et al. 2014), are beneficial to gut health and hold great promise in treating a wide array of gut-related disorders in both pigs and humans. In this article, we highlight several intestinal diseases, pig models, and the potential therapeutic roles of amino acids in diseases of the gut.

Intestinal diseases and models

Due to the multifactorial etiology of disease, many different experimental strategies (such as surgical manipulation, and feeding or injection with chemicals or microorganisms) have been used to induce intestinal lesions in pig models for the study of molecular changes, histopathology, mechanisms, and treatment strategies (Table 1).

IBD

IBD, a chronic, remitting and relapsing intestinal inflammatory response, harbors two diseases, ulcerative colitis and Crohn's disease (Randhawa et al. 2014). IBD can affect the entire gastrointestinal tract and mucosal layer, which may increase the risk of colorectal cancer (CRC) (Clevers 2004; Kaser et al. 2010). Clinically, severe diarrhea, bleeding, abdominal pain, loss of fluid and electrolytes are the characteristics of IBD (Randhawa et al. 2014). Though the etiology of IBD remains undetermined, several factors, including immunologic abnormalities, loss of tolerance to commensal bacteria, disruption of mucosal barrier, and increase in inflammatory mediators and oxidative stress, are related to the pathogenesis of IBD (Goyal et al. 2014).

To date, multiple models, such as spontaneous, chemical-induced, bacteria-induced, genetically engineered, transgenic, mutation knock-in and gene knock-out have been established to study IBD and their related complications (Goyal et al. 2014). Among the various models, chemical [for example, trinitrobenzene sulfonic acid (TNBS), dextran sodium sulphate (DSS) and acetic acid]-induced and bacteria (for example, *Salmonella*)-induced colitis models in the pig are extensively used: (1) Crohn's disease can be induced by rectal instillation of TNBS (15 mg/kg in 5 mL 50% ethanol solution) (Pouillart et al. 2010). The pathologic changes include extensive ulceration, inflammation, and bloody stools (Pouillart et al. 2010). (2) Ulcerative colitis can be induced by injection of DSS at 1.25 g/kg BW/day for 5 days (Kim et al. 2010) or 0.75 g/kg BW/day for 7 days (O'Shea et al. 2016). The signs of DSS-induced ulcerative colitis include severe and bloody diarrhea, elevated gut permeability and concentrations of cytokines [for example, interleukin (IL)-6 and tumor necrosis factor (TNF)-α] (Kim et al. 2010), increased proximal colon pathology score and colonic Enterobacteriaceae (O'Shea et al. 2016). The distorted crypt architecture, infiltration of inflammatory cells into the mucosa and

Table 1 Examples of pig models of intestinal diseases

Pig models	Procedure	Features	References
IBD			
TNBS	Rectal instillation of TNBS (15 mg/kg in 5 mL 50% ethanol solution)	↑Ulceration, inflammation and bloody stools	Pouillart et al. (2010)
DSS	Injection of DSS at 1.25 g/kg BW/day for 5 days	↑Bloody diarrhea, gut permeability, concentrations of cytokines, distorted crypt architecture, infiltration of inflammatory cells into the mucosa and submucosa, crypt abscesses and cryptitis	Kim et al. (2010)
	Injection of DSS at 0.75 g/kg BW/day for 7 days	↑Proximal colon pathology score and colonic Enterobacteriaceae	O'Shea et al. (2016)
Acetic acid	Intrarectal administration of 10 mL of 10% acetic acid	↑Histopathology scores, intraepithelial lymphocyte number and density of colon, myeloperoxidase activity, concentrations of malondialdehyde and pro-inflammatory mediators of plasma and colon ↓Goblet cell number of colonic mucosa	Wang et al. (2013a)
Bacteria	Infected intragastrically with a highly virulent, penta-resistant strain of *Salmonella typhimurium* DT104 (10^{11} cells per animal)	↑DAO activity ↓Transepithelial ion conductance, histamine fluxes and histamine *N*-methyltransferase activity	Aschenbach et al. (2007)
I/R injury	Clamping the superior mesenteric artery at its origin and is sustained for 2 h, and duration of reperfusion is 2 h after release of the clamp	↑Oxygen-derived free radicals and pro-inflammatory cytokines (TNF-α, IL-1, and IL-6)	Spanos et al. (2007)
Diarrhea			
Norovirus	Oral inoculation with human norovirus genogroup II.4 (HS66 strain)	Related to systemic and intestinal antibody, antibody-secreting cells, cytokine and cytokine-secreting cells responses	Souza et al. (2007)
Rotavirus	Orally infused with 4 mL of porcine rotavirus dissolved in the essential medium	↑Diarrhea rate, serum rotavirus antibody concentration and intestinal crypt depth ↓Villus height: crypt depth, mucin 1 and 2 concentrations, goblet cell number and phosphorylated mTOR level	Mao et al. (2015)
Escherichia coli	Challenged with *Escherichia coli* K88	↑Crypts depth, urinary lactulose:mannitol and plasma endotoxin concentration ↓Villus height and expression of tight junction protein ZO-1 and occludin	Yang et al. (2014)
CRC	Produced gene-targeted cloned pigs with mutations in the APC gene	↑Aberrant crypt foci and low- and high-grade dysplastic adenomas	Flisikowska et al. (2012)

APC adenomatous polyposis coli, *CRC* colorectal cancer, *DAO* diamine oxidase, *DSS* dextran sodium sulphate, *I/R* ischemia/reperfusion, *IBD* inflammatory bowel disease, *IL* interleukin, *mTOR* mammalian target of rapamycin, *TNBS* trinitrobenzene sulfonic acid, *TNF* tumor necrosis factor, *ZO* zonula occludens

submucosa, crypt abscesses and cryptitis are observed in the hematoxylin and eosin-stained colon sections in DSS-treated pigs (Kim et al. 2010). (3) Colitis can be induced by intrarectal administration of 10 mL of 10% acetic acid to the pig (Wang et al. 2013a). It was found that acetic acid administration caused increase in the histopathology score, intraepithelial lymphocyte number and density of colon, myeloperoxidase activity, concentrations of malondialdehyde and pro-inflammatory mediators in the plasma and colon, and reduction in goblet cell number in colonic mucosa (Wang et al. 2013a). (4) Ulcerative colitis can be induced by *Salmonella typhimurium* (Cho and Chae 2004). *Salmonella typhimurium* DT104 infection (10^{11} cells per animal) decreases transepithelial ion conductance, histamine flux and histamine *N*-methyltransferase activity, and increases diamine oxidase (DAO) activity (Aschenbach et al. 2007). The pathophysiologic processes of this disease may be association with the expression of cyclooxygenase-2 and nitric oxide synthase 2 (Cho and Chae 2004).

I/R injury

I/R injury, a crucial research field for studying small bowel transplantation, is known to cause allograft rejection, tissue injury, and organ dysfunction (Yandza et al. 2012; Lenaerts et al. 2013). I/R injury is characterized by altered permeability of vascellum and epithelium, and dramatical damage of villus (Spanos et al. 2007). The pig model of I/R injury is commonly used to capture the disease process in humans. A surgical model in pigs showed that ischemia can be established by clamping the superior mesenteric artery at its origin and is sustained for 2 h, and duration of reperfusion is 2 h after release of the clamp (Spanos et al. 2007). The related studies found that I/R induces inflammation and tissue injury by producing reactive oxygen species (ROS) and pro-inflammatory cytokines (Spanos et al. 2007). Similarly, Kostopanagiotou et al. (2011) reported that I/R affected the function and structure of small bowel transplantation and induced inflammatory cascades by the production of cytokines (e.g., TNF-α, IL-8), hyaluronic acid, and reactive nitrogen species (e.g., nitric oxide).

Diarrhea

Diarrhea is one of the most concerning and important public health problems that cause considerable morbidity and mortality among children. In particular, viral pathogens, such as norovirus and rotavirus, can cause outbreaks of gastroenteritis and diarrhea (Heinritz et al. 2013; Zhang et al. 2016). Thus, norovirus (or rotavirus)-infected pig models have been used to study the mechanisms of diarrhea, dehydration, and intestinal lesions in humans (Souza et al. 2007; Meurens et al. 2012; Kocher et al. 2014; Mao et al. 2015). For example, the gnotobiotic pig is suitable for the investigation of pathogenesis, host immunity, and vaccine development of viral diarrhea (Meurens et al. 2012; Kocher et al. 2014), as the gnotobiotic pig model is deficient in maternal antibodies and is pathogen free. Souza et al. (2007) found that the diarrhea caused by human norovirus genogroup II.4 (HS66 strain) in gnotobiotic pigs was related to systemic and intestinal antibody, antibody-secreting cells, cytokine and cytokine-secreting cells. Mao et al. (2015) reported that in the rotavirus-infected pigs, frequency of diarrhea, serum rotavirus antibody concentration, and intestinal crypt depth were increased. On the other hand, ratios of villus height and crypt depth, concentrations of mucin 1 and 2, numbers of goblet cells, and levels of phosphorylated mammalian target of rapamycin (mTOR) of intestinal mucosa were decreased (Mao et al. 2015). In another trial, the rotavirus infection also altered both gut microbial diversity and composition of the microbial community (Li et al. 2014). These may reflect the pathobiological mechanism of viral diarrhea in infected children. In addition, studies using pigs have found that not only viruses but also *Escherichia coli* is associated with diarrhea and the release of toxic materials to impair intestinal barrier function (Heinritz et al. 2013; Yang et al. 2014). In addition, it has been reported that pigs challenged with *E. coli* K88 showed intestinal barrier damage, increased urinary lactulose:mannitol ratio, plasma endotoxin concentration, and intestinal mucosal injury, such as shorter villi, deeper crypts and the decreased expression of tight junction protein zonula occludens (ZO)-1 and occludin (Yang et al. 2014). Furthermore, the early weaning of piglets provides a natural model for the occurrence of diarrhea and its prevention by dietary supplementation with glutamine (Wang et al. 2015b; Wu et al. 1996b).

Colorectal cancer (CRC)

This year over 600,000 people worldwide will die of CRC. It is the third most frequently diagnosed and third most deadly cancer in the United States. Standard treatment for CRC showed some efficacy but fall short in terms of increasing long-term survival. CRC is a malignant disease, and its etiology includes genetic background and environmental risk factors (Gao et al. 2017). Recent studies indicate that gut microbiota may be an important contributor factor in the initiation and development of CRC (Gao et al. 2017). In addition, the familial adenomatous polyposis (FAP), a genetic disorder resulting from mutations in the adenomatous polyposis coli (APC) gene, is one of the major sources of hereditary

CRC (Bong et al. 2016). The vast majority of FAP patients will develop CRC if they cannot be treated at an early stage (Bong et al. 2016). FAP is classically characterized by hundreds of adenomatous polyps in the rectum and colon, which, if not removed, ultimately progress to tumor (Croner et al. 2005). The pig has its advantages in human cancer research because of its size, easy handling, and drug delivery in the same way as in human patients, and for follow-up blood and imaging work over time, as well as its genetic, biochemical, and physiological similarities to humans. In addition, high-throughput genome sequencing and a collection of precision-genetic tools combined with bioinformatics analysis, and profiling of transcriptomics/proteomics/metabolomics/secretomics/interactomics can be applied in the pig. The ability to modify pig genomes through targeted nucleases combined with the development of novel reproductive technologies including cloning allows researchers to create complex and unique models of cancer in pigs that are more applicable to human disease. Previously, Flisikowska et al. (2012) produced gene-targeted cloned pigs carrying mutations in the APC gene (*APC1061* and *APC1311*), which are orthologous to human FAP mutations (*APC1061* and *APC1309*), to model the symptoms of FAP patients and to develop diagnostics and therapeutics for CRC. These pigs showed classic features of aberrant crypt foci and low- and high-grade dysplastic adenomas in the large bowel (Flisikowska et al. 2012). Without a doubt, pig models in cancer help us understand the molecular bases of tumorigenesis and to develop immunotherapeutic, pharmaceutical, endoscopic, and surgical interventions.

The impact of amino acids on intestinal diseases

Amino acids are necessary not only for the biosynthesis of various proteins, but also for the regulation of key metabolic pathways (Hou et al. 2015a, b; Li et al. 2007). Despite these beneficial effects, studies in animals and humans with intestinal diseases have demonstrated that dietary supplementation with amino acids sustains intestinal integrity and normal immunocompetence, reduces oxidative stress, and protects the host from different diseases, thereby decreasing morbidity and mortality (Ruth and Field 2013; Li et al. 2007). In this section, we consider their roles in pathological states and display their treatment outcomes in intestinal diseases in pig models (Table 2). The possible mechanisms responsible for the beneficial effects of amino acids in intestine are shown in Fig. 1.

Arginine

Arginine is the nitrogenous precursor for synthesizing nitric oxide. Arginine activates mTOR signaling in enterocytes to promote protein synthesis and prevent lipopolysaccharide (LPS)-induced cell death (Tan et al. 2010). This amino acid also enhances angiogenesis in the small intestine to augment nutrient absorption (Yao et al. 2011), as well as immune status in early-weaned piglets (Tan et al. 2009). Interestingly, a recent finding indicated that arginine played important roles in pig nutrition partially via modulating amino acids utilization and metabolism in the small-intestinal microbiota (Dai et al. 2012). Numerous experiments have shown that arginine and nitric oxide play a modulatory role in physiology of gastrointestinal tract. We previously demonstrated that 0.5 or 1.0% arginine ameliorated the adverse effects of *E. coli* LPS on the pig intestine, including improving intestinal morphology (villus height and crypt depth), regulating cell proliferation and apoptosis, and also decreasing the expression of pro-inflammatory cytokines (IL-6 and TNF-α) via activating peroxisome proliferator-activated receptor γ (Liu et al. 2008). Zhu et al. (2013) reported that arginine increased the numbers of IgA-secreting cells, $CD8^+$ and $CD4^+$ T cells, and decreased mast cell number and lymphocyte apoptosis of Peyer's patches in piglets challenged by LPS. In addition to reducing intestinal injury induced by LPS, supplementation with arginine has also been reported to augment intestinal protein synthesis in part by p70S6k stimulation in piglet rotavirus enteritis (Corl et al. 2008). Besides, Spanos et al. (2007) observed amelioration of intestinal I/R injury with administration of arginine. Further, studies in humans with CRC have found that oral 30 g of arginine once a day can inhibit the formation and development of colorectal tumors (Ma et al. 2007). Thus, arginine supplementation can ameliorate intestinal diseases.

Glutamate and glutamine

Glutamine and glutamate, along with aspartate, are the major energy substrates for enterocytes (Wu 1998). A number of animal studies indicated that glutamate and glutamine play versatile roles in the metabolism and function of gut. As a specific precursor for the synthesis of glutathione and other amino acids (alanine, aspartate, ornithine, and proline) (Ruth and Field 2013), glutamate shows positive effect in improving intestinal mucosa morphology (Wu et al. 2012), reducing intestinal hyperpermeability (Vermeulen et al. 2011) and enhancing

Table 2 Summary of studies investigating the functions of amino acids on intestinal diseases in pig models

Amino acids	Functions	Models	References
Arginine	↑Villus height, the numbers of IgA-secreting cells, CD8+ and CD4+ T cells, PPARγ ↓Crypt depth, mast cell number, lymphocyte apoptosis of Peyer's patches, IL-6 and TNF-α	*Escherichia coli* lipopolysaccharide	Liu et al. (2008) and Zhu et al. (2013)
	↓Histological changes, TNF-α, IL-1, and IL-6	I/R injury	Spanos et al. (2007)
	↑Intestinal protein synthesis	Rotavirus	Corl et al. (2008)
Glutamate	↑Intestinal barrier function, mTOR ↓TNF-α, CRH/CRHR1, TLR4 and NOD	*Escherichia coli* lipopolysaccharide	Wang (2015) and Ren (2015)
Glutamine	↓Villous atrophy, intestinal morphology impairment, diarrhea and damage to tight junction proteins and intestinal electrolyte movement	*Escherichia coli* K88	Yi et al. (2005) and Ewaschuk et al. (2011)
	↑Mucosal architecture (e.g., recovery of villous surface area), ERK	Ischemic-injured	Blikslager et al. (1999)
	↑Sodium and chloride absorption	Rotavirus	Rhoads et al. (1991)
Glycine	↓Protein degradation (by regulation of AMPK and mTOR signaling) and inflammatory response (by regulation of TLR4 and NOD signaling)	*Escherichia coli* lipopolysaccharide	Wu (2015)
Proline	↑SOD, DAO	*Escherichia coli* lipopolysaccharide	Kang et al. (2014)
Sulfur-containing amino acids	↑Apoptosis initiator caspase-8 ↓Intestinal permeability, pro-inflammatory cytokines (TNF-α, IL-6, IL-12p40, IL-1β), pro-survival genes cFLIP and Bcl-xL	DSS	Kim et al. (2009)
	↑D-Xylose in plasma, DAO in intestinal mucosa, tight junction proteins occludin and claudin-1, villus height to crypt depth, RNA/DNA, protein/DNA, proliferating cell nuclear antigen, epidermal growth factor, Nrf2 signaling pathway ↓DAO in plasma, caspase-3, HSP70 and TLR4 signaling	*Escherichia coli* lipopolysaccharide	Hou et al. (2012, 2013) and Song et al. (2016)
	↑Goblet cell number, protein/DNA ratio, epidermal growth factor and claudin-1 ↓Intraepithelial lymphocyte number and density, myeloperoxidase, malondialdehyde, TNF-α and caspase-3	Acetic acid	Wang et al. (2013a)
	↑Nitric oxide ↓Hyaluronic acid, TNF-α and IL-8	I/R injury	Kostopanagiotou et al. (2011)
Threonine	↑IgG and IgA concentration	*Escherichia coli* K88	Wang (2006)
Tryptophan	↑Apoptosis initiators ↓Pro-inflammatory cytokines and intracellular adhesion molecule-1	DSS	Kim et al. (2010)
	↑Feed intake and growth performance	*Escherichia coli* K88	Trevisi et al. (2009)

Table 2 continued

Amino acids	Functions	Models	References
Aspartate and asparagine	↑Intestinal morphology, development, digestive and barrier function, and intestinal mucosal energy status ↓Pro-inflammatory cytokine (via TLR4, NODs and p38), enterocyte apoptosis (via p38 and ERK1/2) and AMPK	*Escherichia coli* lipopolysaccharide	Pi et al. (2014), Wang et al. (2015d, 2016) and Chen et al. (2016)
Branched-chain amino acids	↑Villus height, villus height: crypt depth, number of goblet cells, mucin 1 and 2, and phosphorylated mTOR level ↓Feed efficiency (g feed/g gain) and mean cumulative score of diarrhea	Rotavirus	Mao et al. (2015)
Other amino acids	–	–	–

AMPK AMP-activated protein kinase, *CRH* corticotropin-releasing hormone, *CRHR* CRH receptor, *DAO* diamine oxidase, *DSS* dextran sodium sulphate, *ERK* extracellular signal-regulated kinase, *I/R* ischemia/reperfusion, *IL* interleukin, *mTOR* mammalian target of rapamycin, *NOD* nucleotide-binding oligomerization domain protein, *Nrf2* NF erythroid 2-related factor 2, *PPAR* peroxisome proliferator-activated receptor, *SOD* superoxide dismutase, *TLR* toll-like receptor, *TNF* tumor necrosis factor

mucosal barrier and anti-oxidative functions (Jiao et al. 2015). Moreover, in our previous work, dietary supplementation of 1.0 or 2.0% glutamate appears to be therapeutic in intestine during inflammatory states via (1) improving intestinal barrier function by suppression of corticotropin-releasing hormone (CRH)/CRH receptor 1 signalling pathway; (2) decreasing pro-inflammatory cytokine production by regulation of toll-like receptor (TLR4) and nucleotide-binding oligomerization domain protein (NOD) signaling pathways; (3) inhibiting protein degradation by maintenance of mTOR signaling (Ren 2015; Wang 2015). Dietary supplementation of glutamate has been reported to enhance anti-oxidative capacity in the small intestine of weanling piglets and reduce the incidence of diarrhea in these neonates (Rezaei et al. 2013a).

Glutamine exerts key role in the maintenance of intestinal structure and function, regulates amino acid utilization by intestinal bacteria, and beneficially alters endogenous gut microbiota (Dai et al. 2013; Zhang et al. 2017). Compared to glutamate, much more research on the therapeutic effect of glutamine in gastrointestinal diseases has been documented (e.g., Haynes et al. 2009; Wu et al. 1996b; Yi et al. 2015). Yi et al. (2005) reported that 2% glutamine mitigated villous atrophy, intestinal morphology impairment, and diarrhea in weaned pigs challenged with *E. coli* $K88^+$. Similarly, Ewaschuk et al. (2011) found that supplementing the weaning diet of piglets with 4.4% glutamine regulated the mucosal cytokine response, and decreased damage to tight junction proteins and intestinal electrolyte movement after *E. coli* (K88AC or K88 wild-type) challenge. In addition, glutamine plus transforming growth factor-alpha treatment can synergistically restore mucosal architecture (e.g., recovery of villous surface area) via increasing the activity of extracellular signal-regulated kinase (ERK) in porcine ischemic-injured intestine (Blikslager et al. 1999). Glutamine also stimulates jejunal sodium and chloride absorption in pig rotavirus enteritis (Rhoads et al. 1991). Furthermore, based on the previous results in mouse model, glutamine establishes a protective role in colitis-associated CRC (Tian et al. 2016). As noted above, glutamine is recognized as an important dietary component in maintaining intestinal health.

Glycine

Glycine, the simplest amino acid, is the most abundant amino acid in the plasma of postnatal pigs (Wang et al. 2013b). This amino acid is remarkably deficient in sow's milk (Wu and Knabe 1994) and in plant-based diets for postweaning pigs (Wu et al. 2014). There is evidence that endogenous synthesis of glycine is inadequate to

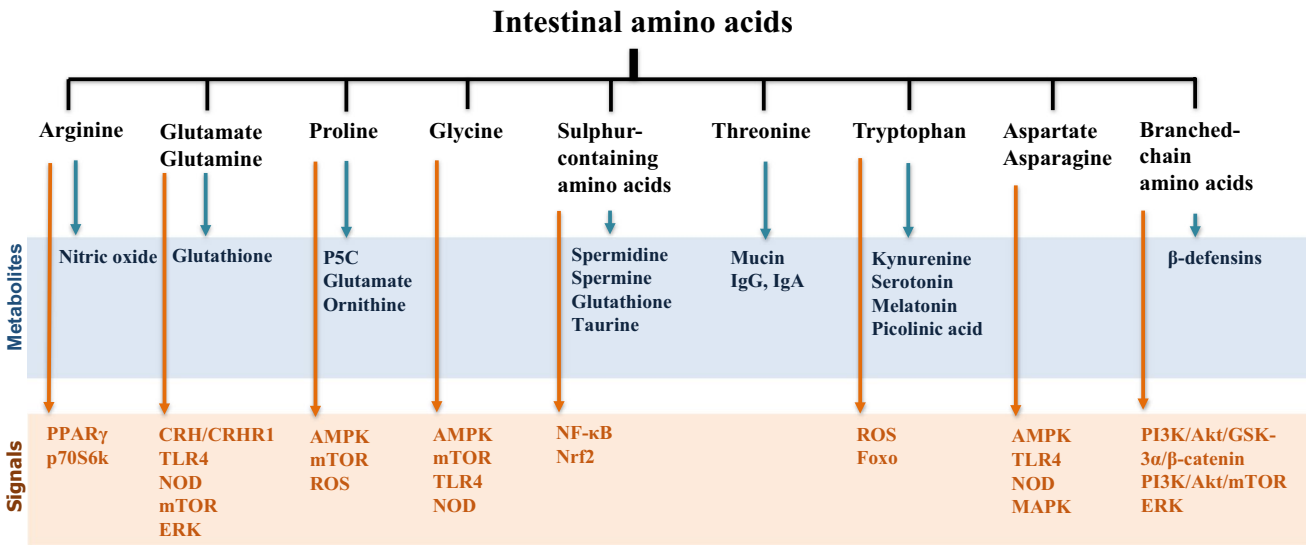

Fig. 1 Possible mechanisms responsible for the beneficial effects of amino acids in intestine. *Akt* protein kinase B, *AMPK* AMP-activated protein kinase, *CRH* corticotropin-releasing hormone, *CRHR* CRH receptor, *ERK* extracellular signal-regulated kinase, *Foxo* forkhead box o, *GSK* glycogen-synthase kinase, *MAPK* mitogen-activated protein kinase, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor-κB, *NOD* nucleotide-binding oligomerization domain protein, *Nrf2* NF erythroid 2-related factor 2, *PI3K* phosphatidylinositol 3-kinase, *PPAR* peroxisome proliferator-activated receptor, *P5C* Δ^1-pyrroline-5-carboxylate, *ROS* reactive oxygen species, *TLR* toll-like receptor

support optimal intestinal health or maximum growth of the whole-body (including the small intestine) in young pigs (Wang et al. 2014a). Of note, glycine has been proved to be an anti-inflammatory, immunomodulatory, and cytoprotective agent (Zhong et al. 2003). In vitro studies using intestinal porcine epithelial cells showed that glycine inhibits oxidative stress (Wang et al. 2014b) and improves intestinal mucosal barrier by regulating the expression and distribution of claudin-7 and ZO-3 (Li et al. 2016). In recent years, mounting evidence has documented the protective effect of glycine in intestinal diseases in animals and humans. We reported that supplementing the weaning diet of piglets with 1.0 or 2.0% glycine was beneficial in attenuating LPS-induced protein degradation [by regulation of AMP-activated protein kinase (AMPK) and mTOR signaling] and inflammatory response (by regulation of TLR4 and NOD signaling) (Wu 2015). During LPS-induced sepsis, less intestinal hemorrhage is observed in the rats supplemented with glycine (Effenberger-Neidnicht et al. 2014). Glycine appears to exert great protective effects in preventing I/R injury to intestine, which is clearly suggested by a large body of researches with experimental animals (Zhong et al. 2003; Petrat et al. 2012). Moreover, dietary glycine prevents hypoxia–reoxygenation-induced necrotizing enterocolitis (Meyer et al. 2006) and chemical-induced colitis (Tsune et al. 2003) in rats. However, the research is mainly focused on the rat models, evidence from the pig models is limited. Nevertheless, based on the reported findings, dietary glycine supplementation may provide an effective strategy in keeping intestinal health.

Proline

Proline is an indispensable amino acid in young mammals, due to a limited ability to synthesize proline from glutamine, glutamate or arginine in the small intestine of young pigs (Wu et al. 1994, 1996a). Proline is a major precursor for the synthesis of polyamines (Wu et al. 2000a, b) and arginine (Wu 1997) in enterocytes of pigs to support intestinal cell growth and migration. It has been well demonstrated that dietary proline supplementation plays an important role in the gut of the weaned piglets regulating cell differentiation and de novo synthesis of arginine and polyamines (Wu et al. 2011). Recently, we showed that proline supplementation can increase immunostimulatory effects on inactivated *Pasteurella multocida* vaccine-immunized mice (Ren et al. 2013) and improve growth performance, increase superoxide dismutase activities, and has a positive effect on the gastrointestinal tract digestibility in early-weaned pigs (Kang et al. 2014). In addition, the villus height, percentage of proliferating cell nuclear antigen-positive cells, alkaline phosphatase activity, the protein expressions of tight junction proteins (ZO-1, occludin and claudin-3) and voltage-gated K^+ channel (Kv) 1.1 protein are increased in the intestine of proline-treated piglets (Wang et al. 2015c). Metabolism of proline in mammals

involves four other amino acids, glutamate, glutamine, ornithine, and arginine, and seven proximal enzymatic activities, Δ^1-pyrroline-5-carboxylate (P5C), reductase, proline oxidase/proline dehydrogenase, P5C dehydrogenase, P5C synthase, glutamine synthetase, glutaminase, and ornithine-δ-aminotransferase (OAT) (Hu et al. 2008; Hu and Hou 2014). With the exception of OAT, which catalyzes a reversible reaction, the other four enzymes are unidirectional (Hu et al. 2008; Hu and Hou 2014). In addition, proline metabolism also links with three other pivotal metabolic systems, namely the TCA cycle, the urea cycle, and the pentose phosphate pathway (Hu et al. 2008; Hu and Hou 2014). Thus, proline metabolism involves in $NADP^+$, NAD^+, ROS, and ATP production, redox balance, and ammonia detoxification in intestinal epithelial cells (Hu et al. 2008; Hu and Hou 2014; Phang et al. 2015; Wu 1998).

Sulfur-containing amino acids

Methionine and cysteine are involved in the biosynthesis of proteins of the immune system (Li et al. 2007). A sufficient intake of dietary methionine is important for mucosal integrity (Chen et al. 2014), morphological development (Shen et al. 2014; Zhong et al. 2016), and intestinal antioxidant capacity (Shen et al. 2014; Zhong et al. 2016). *S*-Adenosylmethionine, the activated form of methionine, participates in plenty of essential metabolic processes, such as the methylation of DNA and proteins and the synthesis of spermidine and spermine (Li et al. 2007). In addition, dietary methionine intake may be related to reduce the risk of CRC (de Vogel et al. 2008; Zhou et al. 2013). Moreover, Tang et al. (2015) reported that methionine deficiency inhibited autophagic response and accelerated death in IPEC-1 cells infected with enterotoxigenic *E. coli*. However, in the methionine restriction experiments in rats, reduction in dietary intake of methionine results in improved colon tight junction barrier function (Ramalingam et al. 2010) and inhibited colon carcinogenesis (Komninou et al. 2006).

Cysteine is important for normal intestinal function, including the immune surveillance of the intestinal epithelial layer and regulation of the mucosal response to foreign antigens (Fang et al. 2010). Cysteine also involves in the biosynthesis of glutathione and taurine, both of which possess potent anti-oxidative activity and can suppress oxidative stress during IBD (Kim et al. 2009). Kim et al. (2009) reported that cysteine supplementation (0.144 g/kg BW/day) improved intestinal permeability, local chemokine expression, neutrophil influx and colon histology, and regulated the expression of pro-inflammatory cytokines, apoptosis initiator, and pro-survival genes in a porcine model of colitis, supporting the importance of cysteine in attenuating local inflammation and restoring gut homeostasis. Moreover, cysteine in diet (0.25 or 0.5%) protected intestinal integrity, as demonstrated by increased proliferating cell nuclear antigen, occludin and claudin-1 expression, and down-regulated caspase-3 activity in weaned piglets after LPS challenge (Song et al. 2016). This beneficial effect of cysteine is resulted from its anti-inflammation, anti-oxidation, and regulatory effect on suppressing nuclear factor-κB (p65) nuclear translocation and enhancing NF erythroid 2-related factor 2 translocation (Song et al. 2016). However, excessive cysteine (5–10 mmol/L) may induce vacuole-like cell death by activating endoplasmic reticulum stress and mitogen-activated protein kinase signaling in intestinal porcine epithelial cells (Ji et al. 2016).

Because cysteine is detrimental at a high concentration, NAC (the precursor of cysteine) is commonly used to deliver cysteine. NAC can be rapidly metabolized by the small intestine and restore intestinal function (Wang et al. 2013a). Xu et al. (2014) reported that NAC can improve intestinal bacteria in piglets by enhancing *Lactobacillus* and *Bifidobacterium* counts and reducing *E. coli* counts. In the acetic acid-induced colitis model, dietary supplementation with 500 mg/kg NAC regulates anti-oxidative responses, apoptosis, and epidermal growth factor expression in colonic mucosa, and thus partially ameliorates the adverse effects of acetic acid in pigs (Wang et al. 2013a). In addition, NAC preconditioning also attenuates ischemia–reperfusion injury in piglet small bowel transplantation (Kostopanagiotou et al. 2011). Moreover, results from recent studies indicated that NAC alleviates LPS-induced intestinal alterations, such as DAO activity (a marker of intestinal injury), D-xylose concentration (a marker of intestinal absorption) in the circulation, levels of tight junction proteins, and ratios of villus height to crypt depth, RNA/DNA and protein/DNA (Hou et al. 2012; Yi et al. 2017). Further examination revealed that NAC attenuates LPS-induced intestinal inflammation through multiple signaling pathways, such as redox, epidermal growth factor, TLR4, PI3K/Akt/mTOR, and AMPK signaling (Hou et al. 2013; Yi et al. 2017).

Threonine

Threonine is of great importance in intestinal health needed especially for synthesis of mucin (Mao et al. 2011). Increasing dietary threonine intake can increase serum IgG concentration and promote a healthy microbiota (Trevisi et al. 2015; Wang et al. 2006). Trevisi et al. (2015) reported that the diet with 9.0 g threonine/kg reduced *E. coli* counts in feces of pigs and led to favorable impact on average daily feed intake in the first week after weaning, as compared

to 8.5 g threonine/kg diet. However, either an excess or a deficiency of dietary threonine is deleterious to the intestinal mucosal integrity and barrier function (Wang et al. 2010). Some of the negative consequences include villus atrophy, increased apoptosis, and decreased mucin concentration (Wang et al. 2010). Consistent with these, Hamard et al. (2010) reported that paracellular permeability and the expression of genes associated with immune and inflammatory responses (e.g., the complement C1s subcomponent, the MHC class I antigen, the T cell differentiation antigen CD6, the C–C motif chemokine 16, and chemokine receptors) were increased in piglets given to a 30% reduced threonine diet for 2 weeks. Further, threonine requirement may be increased under pathological conditions, such as ileitis and sepsis (Mao et al. 2011). Baird et al. (2013) showed that threonine increased heat-shock protein expression and decreased apoptosis in heat-stressed intestinal epithelial cells. Wang (2006) also reported that dietary threonine increased concentrations of IgG and IgA in jejunal mucosa and improved intestinal morphological features in piglets after *E. coli* $K88^+$ challenge. Interestingly, however, very little research has been done to investigate the therapeutic potential of threonine on intestinal diseases.

Tryptophan

As the precursor of multiple bioactive compounds (e.g., kynurenine, serotonin, melatonin, and picolinic acid) (Wu 2013b), tryptophan is important to regulate physiological function in the intestine, such as intestinal permeability, motility, and secretion (Wang et al. 2015a; Tossou et al. 2016). Dietary tryptophan also has a role in microbiota diversity in the gut of pigs (Messori et al. 2013). Kim et al. (2010) showed that tryptophan (0.115 g/kg BW day) given to pigs after DSS-induced colitis improved colitis symptoms and histological parameters. Furthermore, the expression of the pro-inflammatory cytokines (for example, TNF-α, IL-6, interferon-γ, IL-12p40, IL-1β, and IL-17) and intracellular adhesion molecule-1 was reduced, and the expression of apoptosis initiators (caspase-8 and Bax) was increased in tryptophan-supplemented pigs (Kim et al. 2010). Moreover, Trevisi et al. (2009) found that a tryptophan-enriched diet (1 g of tryptophan/kg to the basal diet) was beneficial in attenuating the changes of feed intake and growth performance in susceptible weaned piglets orally challenged with *E. coli* K88. However, Koopmans et al. (2012) compared the basal diet group (apparent ileal digestible tryptophan = 1.9 g/kg) with a tryptophan-enriched basal diet group (+5 g of free tryptophan/kg), and found that there was limited effect of surplus dietary tryptophan on stress and immunology in a pig model of systemic endotoxemia. Nevertheless, a recent study conducted by Tossou et al. (2016) concluded that dietary tryptophan at a high level (0.75%) could negatively influence intestinal epithelial morphology and tight junction proteins. Taken together, the efficacy and functions of tryptophan on intestinal diseases are controversial, and thus further research is warranted to determine the dosage and molecular bases of tryptophan functioning in human and animal health and disease.

Aspartate and asparagine

Like glutamine and glutamate, aspartate and asparagine are abundant in sow's milk (Rezaei et al. 2016). Aspartate is also one of the major metabolic fuels in mammalian enterocytes and metabolize through mitochondrial oxidation (Wu 2013a). Asparagine, with a similar chemical structure to glutamine, can stimulate cell proliferation in intestinal epithelial cells via increasing ornithine decarboxylase activity and cellular polyamine levels. Both aspartate and asparagine contribute to mounting a successful immune response and attenuating intestinal injury (Li et al. 2007; Pi et al. 2014; Wang et al. 2015d, 2016; Chen et al. 2016). However, the evident from pig is limiting. We recently demonstrated that a supplementation of aspartate or asparagine (0.5 or 1.0%) improved intestinal morphological features, development, digestion, and barrier function under pathological conditions (Pi et al. 2014; Wang et al. 2015d, 2016; Chen et al. 2016). Our previous research showed that aspartate or asparagine supplementation improved intestinal mucosal energy status and enhanced activities of tricarboxylic acid cycle key enzymes through inhibiting the AMPK signaling pathway in weaned piglets challenged with LPS (Pi et al. 2014; Wang et al. 2015d). We also found that these beneficial effects are associated with the decrease of intestinal pro-inflammatory cytokine (via TLR4, NODs, and p38 pathways) and of enterocyte apoptosis (via p38 and ERK 1/2 pathways) (Chen et al. 2016; Wang et al. 2016).

Branched-chain amino acids (BCAA)

BCAA, including valine, leucine, and isoleucine, are essential amino acids and important regulators of protein metabolism and autophagy (Rezaei et al. 2013b). The growth performance, intestinal development, and expression of amino acid transporters in weaned piglets are elevated by BCAA supplementation to a low-protein diet (17.1% crude protein) (Zhang et al. 2013). In addition, feeding a diet with BCAA is found to enhance intestinal immune defense system via the improvement of morphological integrity and of immunoglobulin production in the intestine (Ren et al. 2015). Furthermore, dietary leucine supplementation promotes

intestinal development in young pigs (Sun et al. 2015). Some studies indicate that isoleucine induces the expressions of β-defensins in human (Konno et al. 2012) and porcine (Mao et al. 2013) intestinal epithelial cells, which are essential for the mammalian innate immunity. Moreover, BCAA possess therapeutic effects on diseases. For example, Alam et al. (2011) reported that adding isoleucine in oral rehydration salts solution showed some beneficial effects on decreasing stool output of non-cholera acute watery diarrhea in children. Other studies in pigs have also shown that 1% leucine supplementation attenuated the effects of porcine rotavirus infusion on feed efficiency, diarrhea, mucin production, and goblet cell numbers in the jejunal mucosa (Mao et al. 2015). Of note, these amino acids can activate some signaling pathways in intestinal cells. Taking leucine as an example, researches in pigs and humans have demonstrated that leucine can reduce mucosal proteasome activity (Coëffier et al. 2011), enhance cell proliferation via phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/glycogen-synthase kinase-3α/β-catenin pathway (Coëffier et al. 2011), and up-regulate amino acid transporter expression by PI3K/Akt/mTOR and ERK signaling pathways (Zhang et al. 2014) in the intestine. Thus, BACC play an important role in intestinal growth, integrity, and function.

Other amino acids

Lysine, histidine, phenylalanine, tyrosine, serine, and alanine are required for protein synthesis and important for immune function (Li et al. 2007). These amino acids have also been demonstrated to exert beneficial effects in intestine. Studies in pigs have shown that lysine in the diet influences apparent nutrient digestibility and expression of cationic amino acid transporter in the small intestine (Wang et al. 2012). Peterson et al. (1998) reported that histidine protected the mouse intestinal tissue from *Salmonella*-induced injury. In addition, Dietary supply with specific amino acids (containing threonine, serine, proline, and cysteine) can promote mucin synthesis and improve the gut microbiota in DSS-treated rats (Faure et al. 2006). However, the effects of these amino acids on intestinal disease are still rarely studied compared to other amino acids. Thus, future studies including the information about the molecular mechanisms that regulate the actions of amino acids on intestine are needed.

Conclusions

Amino acids serve as the building blocks of protein and also regulate metabolic pathways to improve the survival, growth, and development of amino acids (Hou et al. 2015b). They are called functional amino acids (Wu 2010). Emerging evidence shows that pigs fed conventional diets cannot synthesize many amino acids that are required for optimal intestinal health and growth (Hou et al. 2016). Aside from the importance of generating pig models for the understanding and treating pig diseases, considering the similarities in anatomy, nutritional needs, immunology and physiology of the gut, the pig offers an attractive model to exploit the mechanisms of human intestinal diseases. In addition, the size and ease in handling piglets allows for drugs to be administered in the same way as in human patients and for follow-up blood work over time. The pig is also ideal for screening and developing new therapeutics. Furthermore, with the new development and insights into nutritional research, amino acids show great promises in maintaining or improving intestinal integrity and functions under pathological events. Recent studies in pigs indicate that specific dietary amino acids, in particular, arginine, glutamine, glycine, cysteine, NAC, and proline can regulate the intestinal microbial milieu and host immune system by fine-tuning inflammatory cytokine secretion and the redox status of intestinal cells, and thus exert protective effects on cells. Of note, arginine, glutamine, glycine, and proline can be synthesized de novo in pigs via interorgan metabolism of amino acids (Wu 2013b). Although they were traditionally considered as "nutritionally nonessential amino acids", this term has now been recognized as a misnomer in nutritional sciences (Hou and Wu 2017). Supplementation with peptides (Hou et al. 2017) or crystalline amino acids (Wu 2013b) is effective in improving intestinal health and alleviating intestinal dysfunction under diseased conditions. More research endeavors are warranted in terms of using functional amino acids to their full potentials in improving health and treating diseases in humans and animals.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. Hence, no informed consent was required for any part of this review.

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