Animal Nutrition 9 (2022) 1–6

Contents lists available at ScienceDirect

Animal Nutrition

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

Review Article

Role of dietary amino acids and microbial metabolites in the regulation of pig intestinal health

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ARTICLE INFO

Article history:
Received 17 May 2021
Received in revised form
17 September 2021
Accepted 10 October 2021
Available online 23 October 2021

Keywords:
Pig
Amino acid
Intestinal microbe
Metabolite

ABSTRACT

With the rapid development of sequencing technology, research on pigs has focused on intestinal microbes. Accumulating evidence suggests that the metabolites of intestinal microbes are the key medium for interactions between microbes and the host. Amino acid metabolism is involved in the growth and immune processes of pigs. The gut microbes of pigs are heavily involved in the metabolism of amino acids in their hosts. Here, we review the latest relevant literature. Research findings show that microbial metabolites, such as indoles, short-chain fatty acids, and ammonia, play a key role in gut health. Moreover, we summarize the effects of amino acids on the structure of the gut microbial community and the metabolism of amino acids by pig gut microbes. Evidence shows that microbial amino acid metabolites act as signal molecules in the intestine and play an important role in the intestinal health of pigs.

1. Introduction

With the prohibition of antibiotics in the pig breeding industry, functional supplementary products such as amino acids are more widely used to improve growth performance and immunity. Intestinal microbes play crucial roles in the metabolism of amino acids in pigs and in their growth-promoting and immune functions (Xiang et al., 2020; Yin et al., 2017). Gut microbes can regulate the host's nutrition and metabolism, immune response, and even brain activity, among many physiological functions (Agus et al., 2018). The complex microbial community structure in the intestine is inextricably linked to the host's metabolism. Accumulating evidence shows that improving the dietary structure and supplementing certain nutrients can regulate intestinal microbes (Tremaroli and Bäckhed, 2012). Amino acids act as supplementary nutrients to pig diet. Through the mediation of proteins, the small intestine absorbs amino acids and transports them to various tissues. In the case of plasma amino acids, the small intestine's main role is to maintain homeostasis, whereas the main responsibility for amino acid transport lies with microbes and their metabolites in the large intestine (Bröer and Fairweather, 2018).

The dynamic changes in the metabolic products of amino acids and related microorganisms have not been sufficiently investigated. Recent studies have shown that amino acid catabolism products produced by intestinal flora are an important factor for intestinal homeostasis. Here, we review the metabolic processes of amino acids in pigs and the role of gut microbes in these processes. We discuss the role of microbial metabolism in the host and the effect of microbial metabolites' modulation mechanisms on the host's intestinal immunity (Fig. 1).

2. Bacteriala amino acid catabolism in pig intestines

The gastrointestinal tract of pigs is a complex host of diverse microbial communities. The metabolic processes of these microorganisms can improve host functions, enhance intestinal immunity, and improve intestinal nutrient absorption and health. Research has shown that intestinal microbes can metabolize and utilize amino acids. After amino acids are absorbed by the small intestine, many endogenous and exogenous nitrogen-containing

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

Production and Hosting by Elsevier on behalf of KeAi

https://doi.org/10.1016/j.aninu.2021.10.004

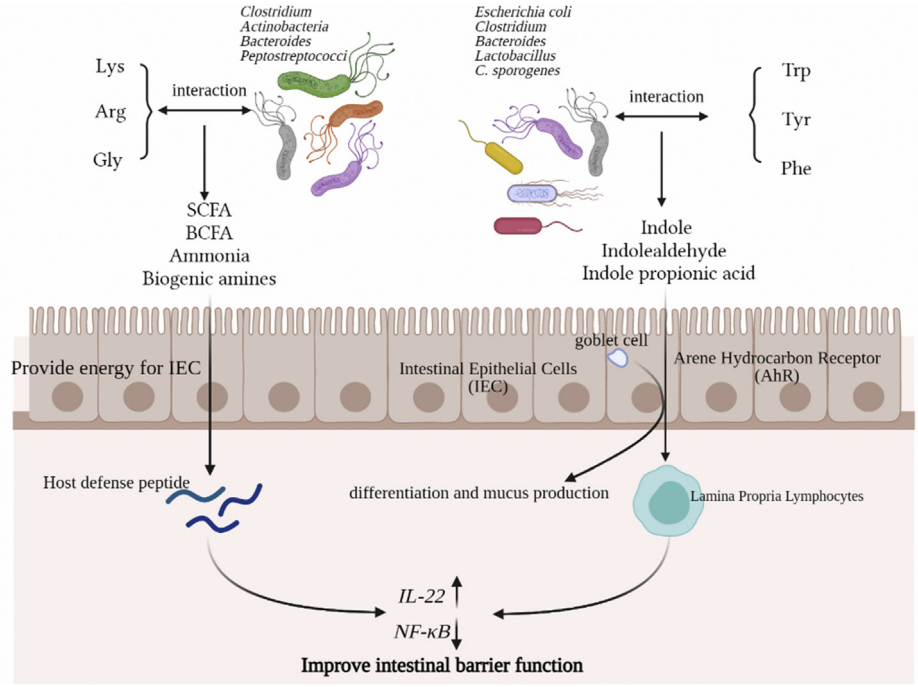

Fig. 1. The beneficial effects of amino acids on pig intestinal health through the action of intestinal microbes. Metabolites of various types of amino acids fermented by intestinal microorganisms acting on epithelial cells to reinforce the intestinal immune barrier. SCFA = short-chain fatty acids; BCFA = branched-chain fatty acids; *IL-22* = interleukin-22; *NF-κB* = nuclear factor-κB.

compounds enter the large intestine through the cecum, where they are used by colonic microbes to produce metabolites through fermentation (Abdallah et al., 2020).

2.1. Microbial catabolism of nonaromatic amino acids in pig intestines

Amino acids are absorbed and first metabolized by porcine small intestinal epithelial cells. Mucosal cells of the small intestine play a major role in metabolizing lysine. Research has shown that lysine can also be metabolized by the intestinal microbiota of piglets (Stoll et al., 1998). Moreover, growing evidence shows that other amino acids, such as methionine and phenylalanine, can also be used by small intestine microorganisms (Davila et al., 2013). Most intestinal microorganisms preferentially use amino acids and ammonia as high-quality nitrogen sources. To some extent, some amino acids are absorbed by intestinal microorganisms as substrates and transported to bacterial cells as protein structures for catabolism (Neis et al., 2015). *Clostridium* clusters, Proteobacteria, and *Bacillus*, *Lactobacillus*, and *Streptococcus* are the most common strains known to participate in amino acid fermentation in the small intestine (Dai et al., 2011). In vitro experiments have shown that lysine, arginine, threonine, and glutamic acid are the amino acids most commonly used by small intestine microorganisms. The metabolism of these amino acids depends on the type of microorganism and the gut compartment (Dai et al., 2010, 2012). The main microorganisms involved in amino acid metabolism in the large intestine are *Clostridium* and *Peptostreptococcus* (Davila et al., 2013). These bacteria can metabolize lysine, arginine, glycine, and other amino acids into complex mixtures of ammonia, short-chain fatty acids (SCFA), and branched-chain fatty acids (BCFA) (Dai et al., 2011). Metabolites such as SCFA can promote the production of aryl hydrocarbon receptors and hypoxia-inducible factor-1α (HIF-1α), increasing the expression of interleukin-22 (*IL-22*) and ultimately improving intestinal immunity (Yang et al., 2020). Biogenic amines are other substances produced by microorganisms through amino acid decarboxylation. Biogenic amines derived from animal intestinal metabolism mainly include cadaverine, a decarboxylation product of lysine, and agmatine, a product of arginine (Sánchez-Jiménez et al., 2013). *Lactobacillus rhamnosus* can ferment histidine as a substrate and decarboxylate it to produce histamine, a microbial metabolite (Frei et al., 2013). Biogenic amines in appropriate amounts are crucial for intestinal health, as they can maintain intestinal function stability and improve intestinal immunity (Fan et al., 2017). However, excessive amounts can cause poisoning, headaches, and digestive disorders (Özogul and Hamed, 2018). Fusobacteria in the intestine can use cysteine to produce hydrogen sulfide through the action of intestinal epithelial cells. Although hydrogen sulfide is known to be a toxic gas, recent studies have shown that low concentrations of hydrogen sulfide produced by endogenous metabolism can maintain the integrity of the intestinal mucus layer and reduce inflammation of the intestinal mucosa (Blachier et al., 2019).

2.2. Microbial catabolism of aromatic amino acids in pig intestines

Many studies have examined the metabolic processes of aromatic amino acids. As early as the 18th century, it was discovered that tryptophan could be metabolized into indole by *Escherichia coli* and *Vibrio cholera*. Consequently, indole was once used as a metabolite marker to distinguish *E. coli* from other intestinal microorganisms (Lee and Lee, 2010). The metabolism of tryptophan to indole is mediated by tryptophanase, which is found in the expression of many intestinal microorganisms, including *E. coli*, *Clostridium*, and *Bacteroides* (Devlin et al., 2016; Smith and Macfarlane, 1996). It has also been found that tryptophan can be used by other microorganisms to produce indole derivatives through various metabolic pathways. For example, *Lactobacillus* spp. can use aromatic amino acid aminotransferase and indolelactic acid dehydrogenase to metabolize tryptophan into indole-3-

aldehyde and indolelactic acid (Zelante et al., 2013). Moreover, tryptophan can be metabolized into indole propionic acid by various intestinal microorganisms, such as *Clostridium sporogenes* and *Clostridium botulinum* (Wikoff et al., 2009). Indole propionic acid can improve the intestinal barrier function through pregnane X receptor and Toll-like receptor protein (Venkatesh et al., 2014). The metabolic pathways of other aromatic amino acids have also been extensively studied. Through the action of *Streptomyces maritimus*, phenylalanine can be converted to cinnamic acid and ammonia through nonoxidative deamination by phenylalanine ammonia lyase (Xiang and Moore, 2005). Studies have shown that these processes of amino acid metabolism are determined by key genes of the involved microorganisms. The *fldH, fldC,* and *acdA* genes play an essential role in the reduction metabolism of threonine, phenylalanine, and tyrosine, whereas *porA* is involved in the reduction metabolism of phenylalanine and tyrosine.

3. Role of dietary amino acids in the regulation of intestinal microbes in pigs

Intestinal microbes have received increasing attention and have shown intricate relationships with animal growth, development, and health. The intestinal flora exhibits considerable plasticity and can undergo structural changes under the influence of the environment (such as diet changes and acute stress) (Conlon and Bird, 2014). Proteins and decomposed amino acids in the diet are important substrate sources of intestinal microbial fermentation in pigs. Amino acids can also be used as a source of nitrogen, promoting the growth of gut microbiota and the host's growth and development (Wu et al., 2011). The addition of amino acids to pigs' diet can significantly adjust the structure and functional characteristics of the intestinal microbial community.

Several mechanisms through which amino acids act on gut microbes have been recognized. The intake of amino acids promotes the secretion of intestinal β-defensin, endogenous cationic peptides, and other antibacterial substances in the intestines, effectively inhibiting the growth of harmful bacteria (Sherman et al., 2006). Amino acids can also promote the contraction of the gallbladder, affecting the production of cholecystokinin and changing the metabolic processes of intestinal microbes (Steinert et al., 2015). Furthermore, porcine gut microbes can catabolize amino acids to produce metabolites, such as kynurenine and indole, which contribute to the host's feedback regulation (Sun et al., 2020). In the following subsections, we discuss the interactions between pig gut microbes and amino acids. Table 1 describes the regulatory relationship between amino acids and gut microbes.

Table 1
The regulatory relationship between amino acids and gut microbes.

Amino acids	Gut microbiota	Relation	References
Glycine	*Clostridium*	↑	
Tyrosine	*Lactobacillus algidus*	↑	Säde et al. (2020)
	Rikenellaceae	↑	Zhang et al. (2019)
Aspartic	*Clostridium*	↑	Li et al. (2019)
	Intestinibacter	↑	
	Prevotella	↑	Zhou et al. (2016)
Lysine	*Streptococcu*	↑	Yin et al. (2018)
	Bacteroides	↑	
	Bacillus	↑	
	Clostridium	↑	
	Actinobacteria	↑	Yin et al. (2017)
	Saccharibacteria	↑	
	Synergistetes	↑	
Tryptophan	*Lactobacillus*	↑	Liang et al. (2018)
	Clostridium	↑	
	Streptococcus	↓	
	Escherichia coli	↓	Messori et al. (2013)
Methionine	*Phascolarctobacterium*	↑	Azad et al. (2018)
	Bacteroides	↑	
Threonine	*Escherichia coli*	↓	Trevisi et al. (2015)

3.1. Interactions between nonessential amino acids and pig gut microbes

Nonessential amino acids can be synthesized by pigs themselves or obtained through the ingestion and transformation of other amino acids. However, the body content also affects the growth and immune functions of pigs and exerts a profound regulatory effect on the structure of the intestinal microbial community (Dai et al., 2013). Low glycine levels can lead to disorders of the metabolic system. Rom et al. found that this phenomenon can significantly increase the abundance of *Clostridium* spp. (Rom et al., 2020). Another study found that the serum tyrosine content of obese pigs was significantly higher than that of lean pigs, leading to changes in microbial metabolites (trimethylamine-N-oxide) related to obesity (He et al., 2012). Furthermore, an experiment conducted to investigate the growth performance of pigs showed that sufficient aspartic acid intake can increase daily weight gain, reduce the abundance of *Actinobacteria* and *Bacteroides* in the intestinal tract, and increase the levels of *Clostridium* and *Intestinibacter*. The levels of these nonessential amino acids in the body are mainly related to the growth and metabolism of pigs. They are mostly involved in the regulation of the microbial community involved in membrane transport and metabolism (Li et al., 2019).

3.2. Interactions between essential amino acids and pig gut microbes

The 11 essential amino acids for pigs are lysine, tryptophan, methionine, cystine, arginine, histidine, leucine, isoleucine, threonine, phenylalanine, and valine. Pigs either cannot synthesize them or cannot synthesize them in sufficient amounts to meet their needs. Therefore, these amino acids must be added to pigs' diet to maintain their nitrogen balance, meet their growth needs, and promote immunity (Chen et al., 2009). Lysine supplements have been found to increase the feed intake of piglets and reduce the abundance of *Streptococcus*, *Bacteroides*, *Bacillus*, *Pasteurella*, *Clostridium sensu stricto*, *Faecalibacterium, Paucisalibacillus*, and *Lachnoclostridium*. Most of these microbial communities are related to host metabolism, especially amino acid metabolism (Yin et al., 2018). Tryptophan is mostly added to diets for weaned piglets. It can reduce the abundance of *Clostridium sensu stricto* and *Streptococcus* and increase the abundance of *Lactobacillus* and *Clostridium* XI, which are related to tryptophan metabolism in the jejunum, ultimately improving the intestinal barrier function (Liang et al., 2018). Tryptophan can boost the resistance of weaned piglets to F4 enterotoxigenic *E. coli* colonization and increase the diversity of intestinal microbes (Messori et al., 2013). Furthermore, trials have shown that adding 0.48% methionine to lactating sows' diet can significantly increase their antioxidant capacity and increase the abundance of *Phascolarctobacterium* and *Bacteroides*, contributing to maintaining piglet health (Azad et al., 2018). The addition of arginine to feed can alleviate the effects of weaning stress in piglets and counteract stress-induced metabolic disturbances. However, it cannot restore disturbed intestinal flora (He et al., 2011). Threonine can produce mucin and immunoglobulin, protecting weaned piglets from *E. coli K88ac* infection, which can affect their growth performance (Trevisi et al., 2015). Most of these essential amino acids are related to piglets' growth performance and immunity. Therefore, they are used in the swine industry to increase productivity and reduce stress and disease during growth.

4. Microbial amino acid metabolites as signaling molecules

Most research on amino acid microbial metabolites as signal molecules has focused on aromatic amino acids, whereas the role of other amino acids has not been extensively explored. Indole, the main metabolite of tryptophan, is well known as an intercellular molecular signal (Roager and Licht, 2018). *E. coli* has been shown to produce 600 μmol/L of indole in suspension culture species (Domka et al., 2006), and the concentration of indole detected in human feces ranges from 250 to 1,100 μmol/L (Bansal et al., 2010). Indole can inhibit the production of spores and biofilms, compromise the stability of plasmids, and produce virulence factors, thereby regulating the structure of intestinal microbes (Lee and Lee, 2010). Indole derivatives in the intestine can also affect the integrity of the intestinal barrier through the aryl hydrocarbon receptor (AhR)/IL-22 axis. Indole-3-aldehyde can use AhR to activate lamina propria lymphocytes and produce IL-22, which further promotes the proliferation of intestinal epithelial cells and ensures the integrity of the intestinal barrier structure (Hou et al., 2018). Moreover, indole-3-aldehyde and indolelactic acid can activate AhR in $CD4^+$ T cells through *Lactobacillus reuteri* and program them into immune regulatory T cells (Cervantes-Barragan et al., 2017). It seems that the microbial metabolites of aromatic amino acids and their ligand AhR play a decisive role in intestinal barrier immunity. In vitro experiments have shown that tryptophan metabolites indole-3-ethanol, indole-3-pyruvate, and indole-3-aldehyde inhibit *tumor necrosis factor-α* (*TNF-α*)-induced increased epithelial permeability in human Caco-2 IEC cell lines (Hou et al., 2018). Indolepropionic acid (IPA), another microbial-derived metabolite of indole, can also inhibit the expression of TNF-α in intestinal epithelial cells and at the same time enhance intestinal immunity through the mediation of *TLR4* (Venkatesh et al., 2014) and *IL-10R1* (Alexeev et al., 2018). Arginine can increase the expression of *pBD2* and *pBD3* in ileum tissue, promote the secretion of host defense peptides, and protect the integrity of the intestinal barrier function (Osei-Boadi et al., 2013). Nitric oxide, the microbial metabolite of arginine, is also essential in this process, as it can prevent intestinal mucosal damage and inhibit inflammation (Leitão et al., 2011). Isoleucine, leucine, and valine seem to increase the expression of β-defensin in porcine intestinal epithelial cells by activating the sirtuin-1-ERK-90-kDa ribosomal S6 kinase pathway, thereby enhancing intestinal immunity (Ren et al., 2016).

5. Effects of microbial amino acid metabolites on intestinal health

Metabolites of amino acids produced through intestinal microbial fermentation are closely related to intestinal health (Lallès, 2016). Indole, the most abundant microbial metabolite of aromatic amino acids, exerts strong intestinal anti-inflammatory activity, and its anti-inflammatory mechanism has been thoroughly studied (Jansson et al., 2009; Santoru et al., 2017). Indole exhibits an immune-enhancing effect on the colon. It can inhibit the activation of nuclear factor-κB (*NF-κB*), increase intestinal transmembrane resistance, and improve the intestinal barrier function (Bansal et al., 2010). Moreover, experiments have demonstrated that indoleacrylic acid can mediate goblet cell differentiation and mucus production through AhR, thereby improving intestinal immunity and repairing intestinal epithelial barrier damage (Wlodarska et al., 2017). The content of indole derivatives in the intestine, including indole-3-aldehyde and indole acetic acid, is significantly reduced under intestinal inflammation. This metabolic disorder in the intestine leads to damage to the intestinal barrier and increases the risk of infection and inflammation (Lamas et al., 2016). Indole metabolized by intestinal microbes can affect the time of action potentials fired by colonic L cells and promote the production of glucagon-like peptide-1 (Chimerel et al., 2014), which participates in the regulation of appetite and plays an important role in fat loss and metabolic regulation (de Mello et al., 2017).

Although most SCFA in the intestine are produced through the fermentation of dietary fibers, less than 1% of intestinal microbes can use amino acids for fermentation to form propionic acid and butyric acid (Dai et al., 2011). For example, *Intestinimonas* AF211 can ferment lysine to form butyric acid in several ways (Bui et al., 2015). *Clostridium* can enter the pyruvate cycle through coenzyme B12-dependent glutamate mutase. Pyruvate is disproportionated to butyric acid, acetic acid, and propionic acid (Buckel, 2001). Short-chain fatty acids can mediate the expression of host defense peptides in pig intestines (Wu et al., 2020). Due to the metabolism of intestinal microorganisms, the SCFA content in the colon is the highest. In addition to providing energy to intestinal epithelial cells, they can also promote the secretion of host defense peptides (Hamer et al., 2008). Many experiments have shown that butyrate can promote the expression of anti-inflammatory factors in intestinal epithelial cells while stabilizing the structure of the intestinal microbial community, increasing metabolic activity, stabilizing intestinal development, and improving immunity (Chung et al., 2012; Kamada et al., 2013; Lee and Mazmanian, 2010). Specifically, butyrate can downregulate the expression of the *NF-κB* and histone deacetylase 1 (*HDAC1*) genes in colonic epithelial cells to reduce inflammation (Xu et al., 2016). Propionate has been shown to change the microbial structure, increase the abundance of probiotics, and affect the expression of pro-inflammatory cytokines, thereby regulating colon health in fistula pig models (Li et al., 2020).

6. Conclusion

This review of recent research provides a thorough understanding of the effects of amino acids on the growth and immune processes of pigs. Extensive evidence demonstrates the effects of various amino acids on changes in the structure of pig intestinal microbial communities, as well as the processes of microbial metabolism and decomposition of amino acids. The growing understanding of these processes has led to investigations of the role of microbial amino acid metabolites as signaling molecules in the intestine. The findings have demonstrated the importance of microbial amino acid metabolites for intestinal health. This provides a solid research basis for more efficient pig breeding and new options for antibiotic-free production. However, many aspects remain underexplored. For example, most studies on microbial amino acid metabolites have focused on functional amino acids (arginine and tryptophan), whereas few studies have examined other types of microbial amino acid metabolites. Therefore, further research is needed to gain a deeper understanding of the microbial metabolism of other amino acids and its effects on pig intestinal health.

Author contributions

Yong Ma: Writing – original draft preparation, revision, and investigation. **Xuebing Han**: Revision. **Jun Fang**: Supervision – oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team. **Hongmei Jang**: Validation.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately

influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

Acknowledgements

This research was supported by National Natural Science Foundation of China (No. 31772642, 31672457, 41807135), Hunan Provincial Science and Technology Department (2019TP2004, 2020NK2004, 2020ZL2004), China Postdoctoral Science Foundation (2018M632963, 2019T120705), Scientific Research Fund of Hunan Provincial Education Department (2020JGYB112, 18B107), Double First-class Construction Project of Hunan Agricultural University (SYL201802003, YB2018007, CX20190497), Natural Science Foundation of Hunan province, China (No. 2019JJ50220), and Undergraduate on Innovation and Entrepreneurship Training Program (No. S202010537084).

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