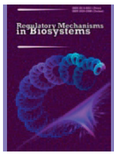

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Biological impact and importance of functional amino acids in pig nutrition

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Increasing pig productivity and maintaining animal health without the use of antibiotics and other growth stimulants are key challenges in modern pig farming. In addition to the long-standing ban on the use of antibiotics in livestock farming, in 2022, the EU also introduced a ban on the use of zinc oxide in piglet feeding due to the environmental contamination risks. In order to overcome the food deficit and improve the overall productivity of the industry, selective breeding is being carried out in pig farming to enhance the litter size of sows. However, this often leads to the birth of a large number of small piglets that require special care to ensure adequate nutrition to support their growth and development. One such approach is the use of functional amino acids in animal feeding, as recent studies have shown the impact of amino acids on metabolism and the body as a whole, their utilization, exchange, and application to improve productivity, health, and animal well-being. The correct selection and use of functional amino acids in pig feeding can contribute not only to increased productivity but also to improved product quality and reproductive performance. The aim of this review was to summarize data from the last 10–15 years regarding the use of functional amino acids in the feeding of pigs from various groups. An analysis of the literature showed that the use of functional amino acids in pig feeding can enhance their productivity and serve as an alternative to banned substances, especially during critical periods of life, as well as for stimulating growth and productivity in animals.

Keywords: functional amino acids; nutrition; metabolism; well-being; productivity; health; arginine family amino acids; branched-chain amino acids.

Introduction

Amino acids, depending on whether they can be synthesized a new in animal body cells and support nitrogen balance or body growth, are classified into essential (EAAs) and non-essential (NEAAs) amino acids (Mou et al., 2019; Zhang et al., 2021). Those amino acids that cannot be synthesized anew must be included in the diet and supplied to the body to support the vital functions, growth, and development of animals (Hou & Wu, 2018a; Mou et al., 2019). With the development of modern analytical methods and biochemical studies, scientists have discovered that the utilization rate of some non-essential amino acids (NEAAs) exceeds the rate of their synthesis under certain conditions, such as early weaning, lactation, pregnancy, injuries, infections, heat, and cold stress (Zhang et al., 2021; Yi et al., 2018; França I. et al., 2024). The growing body of data in the literature has led to the development of a new concept – functional amino acids (FAAs) in animal nutrition, which are defined as amino acids that are used not only for protein synthesis but also for regulating key metabolic pathways, improving survival, growth, development, reproduction, lactation, and animal health (Liang et al., 2018a, 2018b). Functional amino acids include both essential (EAAs) and non-essential (NEAAs) amino acids (Zhang et al., 2021).

The significance of functional amino acids (FAAs) for the animal body lies in the following: providing substrates for the synthesis of tissue proteins and regulating their degradation; influencing the synthesis and secretion of hormones; serving as a source of energy when oxidized; regulating the protective function of the endothelium, vasodilation, and blood flow; regulating nutrient metabolism (including oxidative stress), maintaining acid-base balance, and homeostasis in the body (Le Floc'h et al., 2018; Prates et al., 2021; Zhang et al., 2021).

New knowledge about the metabolism and functions of amino acids in pigs has prompted a review of the numerous functions of amino acids in nutrition, health, and productivity at various stages of their growth and development (reproduction, lactation) (Zhang et al., 2021; França et al., 2024).

For example, in recent decades, the focus in pig farming has been on the breeding and use of multiparous sows, as an increase in the number of live-born and weaned piglets per production cycle means greater economic efficiency for producers. Optimizing feeding is considered a very important element in achieving these high productivity standards while maintaining the health of the sows. One of the ways to address these issues is the use of functional amino acids (Prates et al., 2021; Hodkovicova et al., 2023).

In recent decades, a pressing issue that has been constantly discussed worldwide is the use of antibiotics and the development of antibiotic-resistant strains of microorganisms, leading to the search for alternative approaches to address this problem (Beaumont et al., 2022). Additionally, zinc oxide, which had been used for many years to reduce diarrhea in weaned piglets, was banned for use in the EU in 2022 due to the potential risk of increasing environmental contamination and enhancing resistance to it in certain types of bacteria (Pejsak et al., 2023). In both cases, the use of functional amino acids (FAAs) could become one of the solu-tions to this problem.

According to existing data, functional amino acids include the arginine family, which consists of: glutamine, glutamate, arginine, proline, aspartate, asparagine, ornithine, and citrulline; branched-chain amino acids (leucine, isoleucine, and valine); tryptophan and glycine (Zhang et al., 2021; Ji et al., 2022; Hodkovicova et al., 2023).

The limited systematic knowledge about the metabolism and functions of some functional amino acids in pigs hinders their widespread use in modern pork production systems. To achieve this goal, this article highlights the effects of functional amino acids on pigs of different ages and productivity types, and provides a scientific basis for revising recommendations regarding the potential application of these amino acids in animal nutrition.

Arginine

As is well known, arginine is considered an essential amino acid. Indeed, the U.S. National Research Council has recognized arginine as a conditionally essential amino acid for pigs, influencing their growth, development, reproduction, and lactation. The synthesis of arginine in the body should be considered in the context of the arginine family, which includes arginine, glutamine, glutamate, proline, aspartate, asparagine, ornithine, and citrulline. Typically, interconversion between these amino acids often occurs through complex interorgan metabolism, which plays a significant physiological role in the life processes of pigs (Fig. 1).

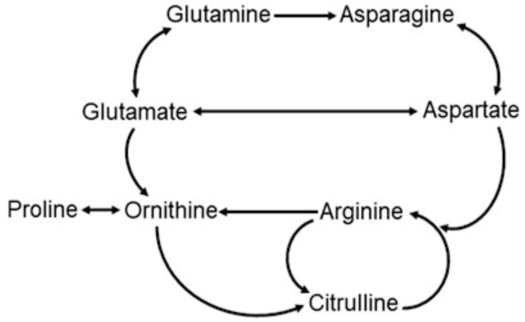

Fig. 1. Interconversion of amino acids in the arginine family (group) in pigs

The immediate precursor of arginine in the body is citrulline, which is synthesized in all tissues (primarily in the kidneys) with the involvement of aspartate. Arginine is metabolized to ornithine by arginases (type I and type II) and L-arginine: glycin amidinotransferase through a cell-specific pathway, and is also oxidized by nitric oxide synthase to nitric oxide and citrulline in cells of all types. Citrulline, synthesized from arginine, is converted back to arginine by L-arginine: glycin amidinotransferase and lyase (Zhang et al., 2021).

Approximately 40% of dietary arginine undergoes metabolic breakdown in the small intestine during its first pass through the portal vein. The limited absorption of arginine by the liver, around 8%, is due to the small number of cationic amino acid transporters in hepatocytes (Wu, 2021).

In the liver, arginine is used by arginase, L-arginine: glycin amidinotransferase, argindecarboxylase, and nitric oxide synthase (NOS) to produce ornithine, creatine, agmatine, and NO (Wu et al., 2018). Additionally, arginine is used by the liver to synthesize homoarginine and lysine via argininosuccinate synthetase (Hou et al., 2016). Furthermore, arginine is an allosteric activator of N-acetylglutamate synthetase, which catalyzes the formation of N-acetylglutamate (an allosteric activator of carbamoylphosphate synthetase-I) from glutamate and acetyl-CoA. Thus, arginine is essential for maintaining the urea cycle in the liver in an active state for ammonia detoxification, which is vital for pigs.

An interesting fact is that the activity of arginase is absent in the placenta of pigs, where the breakdown of arginine occurs via NOS to stimulate NO synthesis, which is crucial for fetal survival and growth. The activity of NOS in the placenta is very low, and thus a large amount of arginine is transferred from the mother to the fetus, explaining the high levels of arginine in the allantoic fluid of pigs to support embryo growth and development in the early and mid-stages of pregnancy (Watford & Wu, 2018).

Arginine supports DNA synthesis and mitochondrial activity in the epithelial cells of the intestine, thus promoting the development and regeneration of the intestinal mucosa (Nuntapaitoon et al., 2018). Furthermore, arginine is essential as a substrate for the formation of creatine and polyamines (Modina et al., 2019), which support proper intestinal function; they promote cell proliferation and migration, which are important for the morphology and function of the mucosa, and they also participate in the prevention of intestinal dysfunctions (Liu et al., 2019b; Blavi et al., 2021; Perez-Palencia et al., 2024). However, research (Hagen et al., 2024) indicates that increasing the level of arginine increased the final body mass of animals and poultry (Sychov et al., 2022), but did not have a clear impact on gut health.

Arginine is a necessary element for the nutrition of newborn piglets, as its synthesis in the body does not meet the metabolic needs, and its deficiency is a major factor limiting the maximum growth of suckling piglets. Milk provides no more than 40% of the total daily arginine requirement in 7-day-old piglets (Wu, 2021). Supplementing with 0.2% and 0.4% L-arginine in piglets aged 7 to 21 days, which were fed milk replacers, increased plasma arginine concentration by 30% and 61%, respectively, and increased body weight gains by 28% and 66% (Kim & Wu, 2004), while also increasing protein content in skeletal muscles (Kim et al., 2007).

There are many studies on the effects of various doses of arginine on the body. Existing studies do not indicate any negative effects of diets containing up to 2% arginine (Hu et al., 2015). In stressful or unfavorable conditions, such as weaning, the need for this amino acid may increase, making endogenous synthesis and even intake from the diet insufficient to meet the body's needs, thus requiring additional supplementation of the amino acid (Chalvon-Demersay et al., 2021).

Experimental studies have demonstrated that supplementing piglets' feed with 0.2–1.0% arginine before weaning enhances their growth and development (Blavi et al., 2021). Adding 0.4–0.8% arginine to the diet aids in DNA synthesis, stimulates the development of the intestinal mucosa, and boosts the number of goblet cells in the mucosa. Similar results were obtained when 1% arginine was added to the diet, which also increased the overall mass of the intestines (Prates et al., 2021), thus improving pig performance by increasing feed intake, average daily weight gains, and stimulating protein synthesis. The mechanism of arginine's positive effect is that it is metabolized in the body to nitric oxide, proline, glutamine, and polyamines, and the physiological levels of these metabolites alleviate stress responses and regulate protein synthesis.

Research on the addition of 0.7% L-arginine to the diet demonstrated improved intestinal integrity and increased growth performance in animals (Greiner et al., 2023). This can also be a useful method for improving the development of microvessels in the small intestine of weaned piglets, as it increases the height of intestinal villi and the expression of vascular endothelial growth factor in the submucosal and mucosal layers of the intestine.

According to a study Bao et al. (2021), the addition of 1% arginine reduces moisture loss in muscle tissue, increases intramuscular fat content, and enhances antioxidant capacity and glutathione peroxidase activity in serum, which improves the antioxidant ability of skeletal muscles.

Similar effects were demonstrated in a study on pigs that were supplemented with 1% arginine, where the percentage of lean meat increased by 15.0%, and the fat content decreased by 34.6%. This also affects the marbling of pork (Hu et al., 2017).

A 60-day study with the addition of 1.0% L-arginine to the diet during the fattening of pigs (Tan et al., 2009) found that it increased body weight gain by 6.5%, muscle content in the carcass by 5.5%, while fat content in the carcass decreased by 11% compared to the control.

L-arginine, one of the most essential functional amino acids (FAA) for sows, still requires further investigation regarding the duration of supplementation and the most suitable time for amino acid administration. Arginine stimulates the secretion of insulin, growth hormone, prolactin, glucagon, and placental lactogen in pregnant sows (Blachier et al., 2013). According to studies Kim et al. (2007), the addition of 1% L-arginine to sows from day 30 of pregnancy until farrowing improved the viability of piglets by 23% and unincreased their live weight by 28%. It was also found that higher doses of L-arginine in the early stages of pregnancy positively affect the development of the ovaries, support lactation, increase fertility, and promote fetal growth (Mou et al., 2019). Arginine undergoes metabolic changes in the body, being converted into nitric oxide, creatinine, and polyamines. These compounds are crucial during the early stages of pregnancy for proper fetal development, growth, angiogenesis, and placental formation. Notably, administering 0.5–1% L-arginine to pregnant sows from day 85 of pregnancy until farrowing positively affected the number of live-born piglets. An increase in oxygen saturation and birth weight of piglets was also observed (Nuntapaitoon et al., 2018).

The mammary glands of lactating sows utilize both arginase and NOS for the active breakdown of arginine, producing proline, ornithine, and urea, and to a lesser extent, polyamines and NO (Liang et al., 2018c). Adding 1.0% arginine-HCl to the diet of lactating sows increased milk production, fat content, and piglet growth due to enhanced angiogenesis in the mammary glands and increased blood flow to the mammary glands (Zhu et al., 2017).

Glutamate

Glutamate is one of the most common amino acids in both plant and animal-based feeds (Hou et al., 2019; Li & Wu, 2020), as well as in tissue proteins of the body. Since 95–97% of dietary glutamate is catabolized in the small intestine of pigs during its first passage into the portal vein, glutamate is metabolized to CO_2, glutathione, alanine, and aspartate in this process. Essentially, all glutamate in the body is produced from other amino acids through several metabolic pathways. Glutamate can be synthesized in virtually all cell types in pigs' bodies. The nitrogen (N) and carbon (C) skeletons for glutamate synthesis mainly come from amino acids such as glutamine, leucine, isoleucine, valine, alanine, aspartate, and glucose (the primary source of α-ketoglutarate (α-KG)) (Wu, 2021).

The contribution of metabolic pathways to glutamate synthesis varies across different tissues. The liver absorbs a small amount of glutamate from the portal vein, so endogenous synthesis is the primary source of glutamate in this organ for release into the bloodstream in the post-absorptive state (Wu, 2017). It is unlikely that under physiological conditions, the liver in pigs synthesizes glutamate from glutamine through an intra-organ cycle of glutamate formation from glutamine or significant formation of glutamate from branched-chain amino acids (leucine, isoleucine, and valine) due to the low activity of branched-chain amino acid transaminase (BCAT) (Li et al., 2009). Instead, alanine, proline, phenylalanine, and asparagine are the main substrates for glutamate synthesis in the liver (Wu, 2017). Transamination of glutamate via pyruvate and oxaloacetate also occurs in the liver, skeletal muscles, and mammary glands of pigs, leading to the formation of alanine and aspartate from glutamate (Ytrebo et al., 2006; Li et al., 2009; Wu, 2021). Other tissues such as skeletal muscles, the small intestine, and the kidneys catabolize both branched-chain amino acids (leucine, isoleucine, and valine) and glutamine to regulate amino acid homeostasis and inter-organ metabolism in the body (Hou and Wu, 2018b). Branched-chain amino acids also undergo intense transamination in both the mammary gland and placenta of pigs to provide the formation of glutamate, glutamine, alanine, and aspartate for milk protein synthesis and the tissue formation of the fetus and placenta, respectively (Li et al., 2009).

According to its role in protein synthesis, amino acids are essential for maintaining the integrity of the intestinal mucosal barrier and thus play a key role in intestinal homeostasis (Yang et al., 2015). Tight junctions are widely distributed in the intestinal epithelium as the primary physical barrier for selectively regulating the passage of molecules and ions through the paracellular pathway. Glutamate increases the number of tight junction proteins in the small intestine, thereby improving the barrier function of the intestinal mucosa (Zheng et al., 2018; Tan et al., 2019). Additionally, glutamate regulates inflammatory and oxidative responses to pro-inflammatory cytokines or reactive oxygen species to mitigate increased intestinal permeability by enhancing the expression of tight junction proteins (Wang et al., 2014a). The barrier function of the intestinal mucosa and its absorptive functions depend on a continuous supply of a large amount of ATP, and glutamate is one of the main substrates metabolized in the epithelial cells of pigs' intestines to form ATP (He et al., 2019b). Thus, glutamate is indispensable for the optimal functioning and health of the small intestine.

Adequate glutamate supplementation is necessary for maximum and efficient growth in suckling piglets. The milk of sows is rich in glutamate; however, its quantity is insufficient for the maximal growth of piglets, as the oral administration of sodium glutamate to piglets raised by sows (0.5 and 1.0 g/kg body weight per day) for 21 days increased the expression of glutamate receptors and glutamate transporters in their stomach and small intestine (Zhang et al., 2021). Research results highlight the important role of glutamate in maintaining the physiology and function of the intestine in weaned piglets. For instance, adding 1–4% sodium glutamate (Rezaei et al., 2013a) or 2% glutamate to the diet of weaned piglets also increased the concentration of glutathione, antioxidant capacity, and the integrity of the small intestine, as well as its digestive and absorptive functions. These results further emphasize the crucial role of glutamate in intestinal development, as well as in the growth and well-being of suckling and weaned piglets.

In pigs, excessive deposition of subcutaneous fat is a significant issue for market-weight pigs fed typical finishing diets. Glutamate supplementation in the diet promotes skeletal muscle growth in pigs (Hou & Wu, 2018b). For example, the addition of 1% glutamate reduced the average thickness of the backbone fat and increased intramuscular fat deposition in pigs during grow-out and finishing (Hu et al., 2017). Furthermore, adding 3% sodium glutamate to a diet based on corn and soybean meal positively altered lipid content and fatty acid profiles in the skeletal muscles of pigs by regulating the expression of genes related to lipid metabolism, lipid component composition, and muscle fiber types (Kong et al., 2015). Additionally, supplementing the diet with a mixture of glutamate and arginine led to a decrease in the average thickness of backbone fat and subcutaneous fat percentage, but increased the intramuscular fat content in the long back muscles and the biceps femoris, while supplementation with a glutamate and leucine mixture increased the mass of the biceps femoris and the concentration of glutamate and carnosine in the biceps femoris (Hu et al., 2017; Hu et al., 2019).

Many studies have shown that adding 0.15–4% glutamate or 0.5–4.0% sodium glutamate to the diet is safe for pigs (Hou & Wu, 2018b). Based on these studies, Hou & Wu (2018b) stated that feed additives containing at least 2% glutamate are safe for pigs of any age. Since 95–97% of glutamate is broken down in the small intestine of pigs (Wu, 2021), exogenous additives and endogenous synthesis of glutamate in extra-intestinal tissues are necessary to maintain normal intestinal physiology and support optimal growth in weaned piglets and pigs in finishing.

Glutamine

One of the most common amino acids in the pig's body and the third most abundant free amino acid in the plasma of pregnant and lactating sows, as well as piglets, is glutamine (Table 1) (Wu, 2017).

Table 1
Content of functional amino acids in the plasma, tissues, and body of 42-day-old pigs

Amino acid	Free amino acids in plasma, nmol/mL	Amino acid content, µg/g of raw tissue	
		musculus gastrocnemius	whole body
Glutamine	536 ± 12	10900 ± 400	6750 ± 290
Glutamate	103 ± 6	18600 ± 800	12100 ± 480
Arginine	124 ± 8	14100 ± 500	9710 ± 420
Proline	242 ± 10	8020 ± 370	1220 ± 590
Aspartate	30 ± 2	10700 ± 400	5150 ± 190
Asparagine	112 ± 7	8540 ± 300	6140 ± 260
Ornithine	72 ± 4	–	–
Citrulline	76 ± 2	–	–
Leucine	162 ± 9	16500 ± 600	9810 ± 390
Isoleucine	131 ± 8	10600 ± 500	5070 ± 450
Valine	170 ± 10	12000 ± 500	6040 ± 250
Tryptophan	70 ± 3	2730 ± 140	1590 ± 70
Glycine	1072 ± 31	7500 ± 320	16800 ± 620

70% of the glutamine in feed is metabolized in the small intestine of pigs during the first pass through the portal vein, so most of the circulating glutamine in the body is formed through endogenous synthesis. The only enzyme capable of synthesizing glutamine in animal cells is glutamine synthetase (GS) (Wu, 2021). This ATP-dependent enzymatic reaction uses glutamate and ammonia (produced by the breakdown of essential amino acids) as substrates and occurs in various tissues of the body (lungs, adipose tissue, mammary glands during lactation, small intestine), but the primary site of glutamine synthesis is skeletal muscle (Li et al., 2009). The breakdown of glutamine in the body primarily involves its hydrolysis to glutamate and ammonia (via phosphate-activated glutaminase), with glutamate further metabolized to glutathione, glucose, and other amino acids (alanine, ornithine, proline, and arginine) or oxidized to CO_2. Ammonia obtained from glutamine is used for urea synthesis, which helps maintain low ammonia concentrations in the blood. In the kidneys, ammonia derived from glutamine is vital for regulating acid-base balance (Wu, 2021). However, in pigs, glutaminase activity is absent in the mammary glands during lactation and in the placenta (Self et al., 2004), which maximizes the amount of glutamine available for milk formation and rapid growth and development of fetal and placental tissues. Interestingly, glutamine increases the amount of tight junction proteins in the small intestine of pigs, thereby improving the barrier function of the intestinal mucosa (Zheng et al., 2018). Additionally, glutamine is one of the main substrates metabolized in the epithelial cells of the pig intestine to form ATP, and more ATP is produced from it in enterocytes than from glucose and fatty acids (He et al., 2019b).

It has been proven that the intestinal microbiota has a broad biological impact on the health and growth of both humans and animals (Sommer et al., 2017). Amino acids can influence the composition and diversity of the intestinal microbiota in pigs, thereby improving gut function. For example, adding 1% glutamine to the diet increased the number of beneficial gut microbiota (Bacteroidetes and Actinobacteria) while reducing the numbers of harmful bacteria (Oscillospira and Treponema), which contributed to a reduction in constipation in sows during late pregnancy (Zhang et al., 2017). Thus, glutamine is essential for the optimal functioning and health of the small intestine.

Glutamine, an amino acid, undergoes intense catabolism in the small intestine, with only a portion entering the portal circulation of pregnant sows (Wu, 2021). The amount of amino acids from the arginine family is particularly high in the allantoic fluid of pigs during early pregnancy, suggesting that they play a crucial role in the growth and development of embryos. Increasing evidence supports this idea. For instance, adding 1% glutamine to the diet of sows between the 90th and 114th days of pregnancy increased the birth weight of piglets, while simultaneously reducing birth weight variability and mortality by 33% and 46%, respectively (Wu et al., 2011). Furthermore, adding 1% glutamine to the diets of multiparous sows from day 85 of pregnancy to farrowing increased the average birth weight of piglets, as well as the development of their intestines and tight junction protein content, while reducing weight variability in the piglets at birth (Zhu et al., 2018).

The use of combinations of amino acids from the arginine family in pig feeding has also improved their reproductive function. For instance, supplementing a corn and soybean meal-based diet with a mixture of arginine and glutamine (0.4% arginine + 0.6% glutamine) increased the number of live-born piglets by 1.4 per litter and boosted the birth weight of piglets (+10% for all piglets born and +15% for live-born piglets) (Wu et al., 2011). Additionally, glutamine may also promote fetal growth and development (Wang et al., 2018).

Glutamine is the most abundant free amino acid in sow milk, with its secretion in milk being 125% greater than its absorption by the mammary gland from arterial blood (Haynes et al., 2009). This is explained by the formation of glutamine in the mammary glands of pigs from branched-chain amino acids (BCAAs), as the absorption of these amino acids by the mammary glands greatly exceeds their excretion in milk (Li et al., 2009). Adding 1% glutamine to the diet of lactating sows increased glutamine concentration in milk, plasma, and skeletal muscles of sows, as well as increasing milk production and improving piglet growth (Wu et al., 2011). Similarly, adding glutamine to the diet of lactating sows increased lipid concentrations in colostrum and milk (Santos de Aquino et al., 2014).

Sow milk is rich in glutamine, but its amount is still insufficient for optimal piglet growth (Wu et al., 2011; Hou & Wu, 2018a). For instance, Haynes et al. (2009) reported that increasing glutamine intake, beyond that provided in milk, improved the growth rates of suckling piglets by 12%. Piglets suffer from stress caused by weaning, which leads to reduced feed intake and gut dysfunction. Studies highlight the essential role of glutamine in maintaining gut physiological functions, but the amount of glutamine derived from the diet and synthesized from glucose + branched-chain amino acids (BCAAs) and other amino acids is insufficient for optimal growth in weaned piglets (Wang et al., 2008). Therefore, adding glutamine to the diet is crucial for maximizing growth rates in weaned piglets. This is supported by experimental data, such as adding 1.0% glutamine to the diet, which enhanced weight gain in piglets aged 21–28 days, as well as the integrity and villus height of the intestinal epithelium (Wang et al., 2008; Wang et al., 2015b). These results further emphasize the critical role of functional amino acids in gut development and the growth of weaned piglets.

Glutamine itself is not toxic to cells, as large quantities (8–10 times greater than physiological concentrations in plasma) are typically present in culture media for all cell types. Supplementation with up to 1% glutamine (on a feed basis) for at least 34 days does not reduce feed intake nor lead to disease or death in newborn or weaned piglets, pregnant or lactating sows. However, as with any other amino acid, a high dose of added glutamine (2% glutamine in the diet) can reduce feed intake in weaned piglets and should be avoided in pig farming (Wu et al., 2011). Overall, glutamine is now recognized as an essential nutrient that positively impacts the small intestine, as well as the growth and health of the entire organism. Therefore, an adequate amount of dietary glutamine is crucial for the survival, growth, development, lactation, and reproduction of pigs (Wu, 2021).

Proline

In the past ten years, interest in researching the metabolism and use of proline in animal husbandry has increased. Proline was first discovered in 1901 as a component of the acidic hydrolysates of casein. In addition to its structural functions in collagens, proline plays important metabolic and physiological roles in cell differentiation and numerous biochemical processes in cells (Kang et al., 2014), as well as in fetal growth and development, playing a crucial role in angiogenesis and vascular remodeling. Proline is the second most abundant amino acid in the pig body after glycine (Wu, 2021).

As one of the most abundant amino acids in sow colostrum and milk, proline plays an extremely important role in cellular energy perception, cell differentiation, and may help reduce the redox status of cells (Kang et al., 2014). However, piglets weighing up to 5 kg cannot produce enough proline to satisfy their needs. Therefore, introducing L-arginine as a precursor can be considered a safe and effective way to boost the synthesis of nitric oxide and proline in piglets, with proline potentially reducing some of the arginine requirements (Wu, 2021).

In adult animals, proline is formed from arginine via the involvement of P5C synthetase and ornithine aminotransferase (OAT). The formation of proline from arginine actively occurs in mammary gland tissues, the small intestine, liver, and kidneys (Watford & Wu, 2018), but the rate of synthesis is insufficient to support optimal growth and tissue repair in young and adult animals under stress (Li & Wu, 2018). In experiments with parenteral nutrition, piglets cannot synthesize enough proline to maintain its concentration in plasma, and the concentration of arginine synthesized from proline also decreases due to intestinal atrophy (Wu, 2021).

In the small intestine of pigs, glutamate and glutamine from feed and blood can be converted into proline, but this synthesis pathway is absent in other animal tissues due to the lack of P5C synthetase (Wu, 2021; Li & Wu, 2018). Endogenous proline synthesis is very active in the body (Wu, 2021), as pigs are typically fed plant-based feeds that contain low concentrations of proline (Hou et al., 2019).

In the mammary gland tissues of pigs, proline is synthesized from arginine and ornithine with the involvement of arginase. This mechanism explains the high content of glutamate, glutamine, and proline in the milk of sows, along with a significant deficiency of arginine. The concentration of proline is high in sow milk because lactating sows' mammary glands use arginase and NOS to actively break down arginine, producing proline, ornithine, and urea, with a lesser amount of polyamines and NO (Liang et al., 2018c). Mitochondrial proline oxidase (POX) is the only known enzyme that initiates proline degradation in animal cells. Almost all cell types that contain mitochondria express POX, except for mammary gland tissues. In pigs, POX activity is highest in the small intestine, followed by the liver, kidneys, and placenta. Polyamines derived from proline are particularly important for the development of the placenta and the small intestine of newborn pigs, which lack arginase activity. Therefore, proline can serve as the main amino acid for polyamine synthesis in the small intestine. Since polyamines are required for DNA and protein synthesis, proline metabolism plays a crucial role in supporting the growth and development of embryos in pigs. As embryos and newborn piglets grow rapidly, dietary and endogenously synthesized proline plays an important role in their growth and development (Wu, 2021). The inability of mammals to endogenously synthesize proline from arginine and glutamate makes proline an essential amino acid for this group (Wu, 2021), and an adequate amount of proline in the diet is crucial for the productivity and growth of animals (Hou et al., 2016).

Several studies have been conducted to investigate the dose and impact of proline on the organism. For instance, adding 0.35–2.1% L-proline to a chemically formulated proline-free diet containing 0.48% arginine and 2% glutamate, depending on the dose, improved daily growth rate of piglets by up to 20% and feed efficiency by up to 19%, while also reducing plasma urea concentration by half. Notably, increasing the L-proline content in the diet from 0.0% to 2.1% raised the daily nitrogen content from 1.27 to 1.53 g/kg of metabolic body mass, further indicating that piglets cannot synthesize proline in sufficient quantities on their own (Rezaei et al., 2013b).

Aspartate

Aspartate is a natural, endogenous amino acid that is widely present in the body and demonstrates various physiological functions: nutrition, regulation of reproductive function, and plays an important role in the functioning of the endocrine and nervous systems. In animal nutrition, D- and L-forms of aspartate are used. However, there are very few studies in the literature on the effect of D- and L-aspartate on growth intensity and biological processes in pigs. Aspartate, together with glutamine and glutamate, is one of the main substrates metabolized in the epithelial cells of the intestines of pigs, leading to the formation of ATP (He et al., 2019b).

Li et al. (2019) investigated the effects of D- and L-aspartate supplementation on growth and gut microbiota in young pigs. In their study, piglets were fed 1% D-aspartate, L-aspartate, and DL-aspartate for 35 days. The results showed that the addition of D-aspartate to the diet significantly suppressed average daily feed intake and average daily weight gain, through the effect of amino acids on the microbial populations in the intestines. Similar results were obtained by Pi et al. (2014), who found that adding 0.5% and 1.0% aspartate to the diet reduced growth suppression and intestinal damage caused by lipopolysaccharide load in weaned piglets.

Li et al. (2018) conducted a 21-day experiment to evaluate the effects of glutamate and aspartate. The control group was given a diet with 2.9% glutamate and 1.5% aspartate, while the experimental group received diets containing 2.6%, 3.2%, or 3.5% glutamate and 1.3% or 1.7% aspartate. The results indicated that higher doses of aspartate and glutamate negatively impacted growth performance, whereas lower doses of aspartate, as well as smaller amounts of glutamate and aspartate, were more advantageous for growth and feed efficiency. These results once again emphasize the crucial role of functional amino acids in gut development, as well as in the growth and development of weaned piglets.

Asparagine

The intestine requires a large amount of energy for normal functioning; therefore, an energy deficit in the intestinal mucosa can lead to damage. Asparagine is a precursor to many amino acids, such as aspartate, glutamine, and glutamate, which can be used to supply energy to enterocytes (Wu, 2021).

The addition of 0.5% and 1.0% asparagine to the diet of weaned piglets exposed to bacterial lipopolysaccharides (LPS) improved intestinal morphology, as indicated by increased villus height and villus-to-crypt depth ratio, as well as reduced crypt depth. The addition of asparagine also increased the RNA:DNA and protein:DNA ratios, as well as disaccharidase activity in the intestinal mucosa. Furthermore, the supplementation of asparagine reduced the energy deficit in the intestine caused by bacterial LPS, as indicated by elevated levels of ATP and adenylate energy charge, as well as a decrease in the adenosine monophosphate : adenosine triphosphate (AMP:ATP) ratio. Additionally, the introduction of asparagine increased the activity of key enzymes in the citric acid cycle, including citrate synthase, isocitrate dehydrogenase, and the α-ketoglutarate dehydrogenase complex. Together, these results suggest that asparagine supplementation minimizes intestinal damage caused by bacterial lipopolysaccharides through modulation of the AMPK signaling pathway and improves the energy status of intestinal enterocytes (Wang et al., 2015a).

Ornithine

Ornithine is a non-proteinogenic, dispensable amino acid in mammalian nutrition that is not part of proteins. It plays an important role in the biosynthesis of urea. In the body, ornithine is synthesized through the hydrolysis of arginine in the urea cycle and is a key substrate for the synthesis of proline and polyamines. Proline positively affects reproductive processes. Studies have shown that proline supplementation during pregnancy increases embryonic survival and placental development, and short-term proline administration can increase litter size and birth weight in piglets (Gonzalez-Añover & Gonzalez-Bulnes, 2017). In addition to modulating placental angiogenesis through the synthesis of polyamines, which are essential for cell growth, proline plays important roles in biological processes, including protein synthesis and angiogenesis (Tan et al., 2022). These results suggest that ornithine supplementation in pregnant females can enhance placental angiogenesis through the synthesis of proline and polyamines. Confirmation of this was provided by the results of Yang et al. (2024), which showed that adding 0.15% ornithine to the diet of pregnant sows stimulates placental angiogenesis and promotes intestinal development in suckling piglets, as colostrum and milk from sows contain small amounts of ornithine.

Citrulline

Citrulline is a non-essential amino acid produced by enterocytes in the small intestine and serves as a precursor for arginine synthesis (Bahri et al., 2013). Additional citrulline supplementation in the diet increases arginine levels, sometimes more effectively than adding arginine itself, mainly because dietary arginine is metabolized in the intestine and liver (Agarwal et al., 2017). Since enterocytes of the small intestine are the main site of citrulline production, both citrulline and arginine can become limiting under conditions that threaten normal intestinal function. Citrulline and arginine are also important precursors for the synthesis and regulation of nitric oxide (NO), which becomes critical during immune activation and conditions requiring vasodilation (e.g., heat stress). Furthermore, additional citrulline supplementation improves intestinal integrity markers in various gastrointestinal damage models (Kvidera et al., 2024), potentially due to its ability to restore NO function and visceral microcirculation (Wijnands et al., 2012). It has been shown that during heat stress, citrulline supplementation reduces body temperature and affects antioxidant status and the heat shock response in poultry (Chowdhury et al., 2021; Uyanga et al., 2021). Additionally, citrulline supplementation reduced the respiratory rate in lactating sows and decreased piglet mortality before weaning during the summer (Liu et al., 2019a). Research results (Du et al., 2023) showed that adding 1% L-citrulline to the diet of finishing pigs for 52 days significantly increased final live weight, average daily gain, carcass weight, and average backfat thickness. Thus, citrulline is a promising functional amino acid in pig nutrition.

Leucine, isoleucine, and valine

Leucine, isoleucine, and valine are known as branched-chain amino acids (BCAAs), due to the similarity in their structures, and they have a similar mechanism of catabolism. In addition to being important for protein synthesis, BCAAs play a vital role in regulating energy homeostasis, intestinal barrier function, metabolic processes, gut health, immunity, and body resistance, nutrient absorption, and stimulate the activity of digestive enzymes, the expression of intestinal nutrient transporters, and the development of the intestinal microbiota (Shimomura et al., 2015; Mou et al., 2019). As the most abundant essential amino acids, BCAAs are not only substrates for the synthesis of nitrogenous compounds but also act as signaling molecules that regulate glucose metabolism, lipid metabolism, and protein synthesis (Nie et al., 2018), improve pork quality, promote muscle tissue growth, and accelerate gut development (Zhang et al., 2017).

While most amino acids are metabolized in the liver, BCAAs are transported to skeletal muscles for breakdown, where they are quantitatively the most important site for transamination (Wilkinson et al., 2013). Due to the action of branched-chain aminotransferase (BCAT), BCAAs are reversibly converted into α-keto acids. The α-keto acids of isoleucine, leucine, and valine are α-keto-β-methylvalerate, α-ketoisocaproate, and α-ketoisovalerate, respectively. Next, α-ketoisocaproate enters the bloodstream and is absorbed by various tissues, where it undergoes irreversible oxidative decarboxylation to isovaleryl-CoA, leading to the formation of acetoacetate (a ketone body) and acetyl-CoA (precursors of ketone bodies and fatty acids). This reaction is catalyzed by the branched-chain α-keto acid dehydrogenase (BCKD) complex located in the mitochondria. This process occurs most actively in the liver, moderately in the heart and kidneys, and with relatively low activity in skeletal muscles. The end products of this reaction are ketogenic for α-ketoisocaproate, glucogenic for α-ketoisovalerate, or both for α-keto-β-methylvalerate and can be used in the tricarboxylic acid cycle. During transamination, glutamate is also formed, which can be converted into glutamine or alanine and used in protein synthesis. Leucine and its keto acid are the most powerful stimulators of BCAA catabolic enzymes. Studies have shown that high concentrations of BCAAs, especially leucine, can reduce the absorption of neutral amino acids, such as tryptophan, which is a precursor of serotonin and can significantly impact feed intake regulation, overly stimulating the mTOR signaling pathway and leading to a decrease in appetite (Cemin et al., 2019).

The first two stages of the BCAA catabolic pathway are interconnected among the three amino acids, so excessive intake of one BCAA may enhance the catabolism of the other two, hindering body growth (Humphrey et al., 2023).

Most studies conducted to assess the impact of BCAAs on growth performance in pigs agree that high levels of leucine reduce the daily weight gain, primarily due to reduced feed intake. However, in some studies, mainly with growing pigs, no effects on growth intensity were found even with extremely high levels of leucine. It can be assumed that these discrepancies are due to an imbalanced amino acid profile, rather than just the level of leucine. Diets for the final phase of fattening usually contain high levels of leucine, while other BCAAs also significantly exceed the norms, potentially mitigating the negative impact of leucine on BCAA metabolism (Cemin et al., 2019). For instance, studies have demonstrated that increasing the valine level positively impacts average daily gain and feed efficiency, regardless of the leucine and isoleucine levels in the diet. However, high levels of both leucine and isoleucine negatively impact these parameters. Moreover, an increase in leucine content in the diet reduced feed intake, which was accompanied by a low level of valine. This issue was resolved by increasing the valine content in the diet (Humphrey et al., 2023). Although leucine is abundantly found in sow milk, this amino acid plays a regulatory role in stimulating muscle protein synthesis and the synthesis of glutamate and glutamine in piglets (Hou et al., 2016). Oral administration of leucine to piglets aged 7 to 21 days at 0.7 and 1.4 g per kg body weight increased their daily body weight gain by 10.6% and 11.9%, respectively, and enhanced the expression of leucine transporters in the young piglets' small intestine (Sun et al., 2015).

Inclusion of 1% leucine in the diet improves growth performance and alleviates symptoms of rotavirus-induced diarrhea in weaned piglets, which may reflect an improvement in the digestive and absorption functions of the small intestine and non-specific mucosal barrier mechanisms by activating mTOR signaling in cells (Mao et al., 2015).

It is known that leucine is an important nutrient that stimulates protein synthesis in skeletal muscles in pigs (Columbus et al., 2015). For instance, Hu et al. (2019) reported that adding 1% leucine to the diet of fattening pigs increased the mass of their biceps femoris muscles, while a decrease in muscle mass was associated with reduced intramuscular concentrations of leucine, tryptophan, and valine (Sales et al., 2013). These results further emphasize the key role of leucine in regulating muscle protein anabolism.

Recently, to reduce nitrogen emissions, low-protein diets (LPD) have been applied in pig farming. The crude protein content is reduced by >25%, which results in favorable outcomes in terms of nitrogen excretion, but this impairs pig growth despite the addition and balancing of critical amino acids (lysine, methionine, threonine, and tryptophan) in the diets (Li et al., 2017; Yu et al., 2019; Spring et al., 2020). This indicates that low protein levels create a deficiency of other amino acids that may become limiting in such diets, requiring further research on the use of VLP diets. It has been proven that adding only valine, valine and isoleucine, or all BCAAs improves growth and feed efficiency in pigs fed LPD. This was observed through enhanced muscle protein synthesis, a better blood amino acid profile, changes in gut microbiota composition, and increased feed intake (Zhang et al., 2016; Yin et al., 2020; Habibi et al., 2021).

In a recent study on weaned piglets fed a diet containing 3.5 times higher levels of leucine, an increase in leukocyte levels was observed, along with a decrease in isoleucine and valine levels in plasma and other tissues, and an increase in BCKD activity in most tissues. Taken together, the results indicate that high leucine levels increase the catabolism not only of the BCAA itself but also of other amino acids (Wessels et al., 2016).

Adding 0.4% to 0.8% leucine to the diet of pregnant sows, based on corn and soybean meal, from the 70th day of gestation until farrowing, increases the birth weight of piglets (Wang et al., 2018).

In the mammary gland tissues of lactating sows, leucine is actively broken down, producing glutamate, glutamine, alanine, and aspartate, which support milk production (Li et al., 2009).

Since all BCAAs share the same transporters for entering cells, maintaining the proper balance of these amino acids in the diet and blood is particularly important to avoid antagonism.

Tryptophan

Tryptophan is an essential amino acid for monogastric animals, as its carbon skeleton cannot be synthesized in the body. Adequate amounts of tryptophan are found in animal-based feeds, but it is deficient in most plant-based feeds, which are insufficient for the growth of pigs and the health of their intestines. Tryptophan is a precursor of serotonin, N-acetylserotonin, melatonin, anthranilic acid, niacin, and indoles, all of which have significant physiological importance (Wu, 2017). Therefore, pigs must break down a significant amount of tryptophan for the normal functioning of the nervous and endocrine systems, as well as the intestines, while also using tryptophan for tissue protein synthesis (Hou et al., 2019; Li & Wu, 2020).

In mammals, about 95% of tryptophan undergoes a multi-step enzymatic breakdown through the kynurenine pathway to kynurenine, quinolinic acid, nicotinic acid, and kynurenic acid (Badawy, 2015). Additionally, 1–2% of tryptophan is metabolized to serotonin and melatonin (Bai et al., 2017). Serotonin is predominantly formed in the gastrointestinal tract, while melatonin is mainly produced by the pineal gland, as well as partially in the retina, gastrointestinal tract, skin, and leukocytes (Bai et al., 2017). The remaining tryptophan is primarily metabolized to indole-3-acetic acid in the gastrointestinal tract and liver. Many of the metabolites of tryptophan participate in regulating immune responses (Bai et al., 2017).

When pigs are infected with endotoxins or pathogens, the concentrations of tryptophan in plasma significantly decrease due to high utilization by immune cells (Le Floc'h et al., 2012). It has also been determined that during the inflammatory process, tryptophan catabolism is intensified in the affected tissues, making it unavailable for the growth and development of other healthy tissues, which is why it is added to the diet in amounts greater than necessary for the pigs' physiological needs. Additionally, tryptophan metabolites support intestinal barrier function and modify the gut microbiota (Munn et al., 2021). Adding 0.2% to 0.4% tryptophan to a corn and soybean meal-based diet, which already contained 0.2% tryptophan, reduced the population of *Clostridium* species, which are potentially pathogenic bacteria, and increased the number of *Prevotella* and *Roseburia* species, which can regulate homeostasis in the large intestine of weaned piglets (Liang et al., 2018a). Research findings also suggest that tryptophan-metabolizing bacteria in the gut can positively affect the integrity of the intestinal mucosa and immune cell responses in the intestines (Liang et al., 2018b). For example, Wang et al. (2020) reported that tryptophan supplementation in the diet (0.1 mg/g body weight per day with drinking water) of mice with colitis modulated the intestinal immune response and reduced mucosal damage, partially by attenuating the activation of the TLR4-STAT3 signaling pathway. Tryptophan intake in sows also resulted in a positive effect on the immune system and antioxidant status. Supplementing 0.56% tryptophan during late gestation and up to day 7 of lactation improved piglet survival (Munn et al., 2021). Furthermore, adding 0.4% tryptophan to a typical corn and soybean meal-based diet did not negatively affect pigs in the finishing stage (Liang et al., 2018a, 2018b).

Glycine

Glycine is the most abundant amino acid in animal body proteins, including pigs (Li & Wu, 2018), and is considered a conditionally essential amino acid because it is synthesized in insufficient amounts by the animal's body (Wu, 2021). In pig feeding, plant-based feeds dominate with low glycine content (Hou et al., 2019; Li & Wu, 2020), but to meet the pig's needs, glycine is formed in the body through several pathways (Wu et al., 2019):

1. From serine via serine hydroxymethyltransferase (SHMT).
2. From choline via the formation of sarcosine.
3. From threonine via the threonine dehydrogenase pathway.
4. From glyoxylate via alanine-glyoxylate aminotransferase.
5. From 4-hydroxyproline via mitochondrial hydroxyproline oxidase (OH-POX).

The synthesis of glycine from serine, choline, and threonine provides up to 12% of the glycine requirements for piglets. 4-Hydroxyproline, which is abundant in sows' milk, contributes to the synthesis of most of the glycine up to the piglet's seventh day of life (Wu et al., 2019). In adult pigs, 4-hydroxyproline is formed as a result of collagen hydrolysis, and the catabolism of 4-hydroxyproline to glycine occurs in many tissues, including the small intestine, kidneys, liver, and skeletal muscles (Hu et al., 2023).

About 30% of dietary glycine is metabolized in the small intestine of pigs during its first pass through the portal vein (Wu, 2021). Since enterocytes in the pig intestine have limited ability to break down glycine, the microbiota in the lumen of the small intestine plays an important role in the utilization of glycine by metabolizing it into acetate (Neis et al., 2015). The rate of glycine catabolism to CO_2 and ammonia in the body of pigs is relatively low compared to its synthesis rate (Hou et al., 2016; Wu, 2021). In pigs, the conversion of glycine to serine is limited due to a deficiency of methyl group donors and folic acid; however, serine deficiency may impair glycine synthesis, leading to nutritional imbalances in other amino acids (Blavi et al., 2021). Glycine from maternal milk satisfies only up to 20% of the glycine requirements for suckling piglets. Since piglets' bodies are not sufficiently developed to synthesize glycine, they experience a deficiency of this functional amino acid (Hu et al., 2023). Adding 0.5%, 1.0%, and 2.0% glycine to the diet increases daily weight gain and improves intestinal health, indicating that glycine is an essential amino acid for suckling piglets (Wang et al., 2014b).

Pigs experience the greatest loss of embryos (up to 50%) and the most severe naturally occurring intrauterine growth retardation (IUGR) due to limited uterine capacity and insufficient amino acid nutrition for the mother and fetus (Wu, 2021). As a result, 15–20% of piglets are born with low birth weight (<1.1 kg) and are often culled after birth because they have lower growth performance and feed efficiency during the growing period compared to piglets born with normal weight. Adding 1% glycine to a corn and soybean meal-based diet for piglets with IUGR for 127 days post-weaning did not affect their feed intake but improved their growth rate (He et al., 2019a). Interestingly, by the 120th day of life, the body weight of piglets with IUGR that received the glycine supplement was not different from that of pigs with normal birth weight (He et al., 2023). It has been proven that adding glycine to the diet of pigs with intrauterine growth restriction enhances the synthesis and concentration of glutathione, the main antioxidant, in tissues. Glutathione is a tripeptide synthesized from glutamate, glycine, and cysteine (He et al., 2024).

Stress after weaning leads to disruption of gut health, which negatively impacts animal health, metabolism, immune system development, and overall bodily function. Glycine, along with other amino acids such as glutamine, glutamate, aspartate, arginine, proline, and tryptophan, increases the amount of tight junction proteins in the small intestine, thus improving the barrier function of the intestinal mucosa (Zheng et al., 2018). For instance, piglets fed a diet containing 2% glycine, instead of 0.5% or 1%, showed increased average daily gain and feed conversion ratio compared to the control group. Supplementation with 2% glycine enhances the number of mucins in the jejunum and ileum, as well as the level of secretory immunoglobulin A (sIgA) in the jejunum (Ji et al., 2022).

Additionally, glycine stimulates protein synthesis in skeletal muscle cells through activation of the mammalian target of rapamycin (mTOR) signaling pathway (Caldow et al., 2019), while simultaneously reducing body fat content (He et al., 2023).

Conclusions

The use of functional amino acids in the feeding of modern pig breeds helps address many challenges in modern pig farming and contributes to increased productivity and improved product quality. In particular, arginine, glutamate, and glutamine are essential for the nutrition of newborn piglets, as their deficiency in milk is a major limiting factor for optimal growth in this age group. There are many studies on the effects of different doses of functional amino acids on the body, but most agree that they improve growth and development, promote better health, increase average daily gain, and stimulate protein synthesis. Supplementing with functional amino acids also affects the quality of the final product, improving the chemical composition and quality parameters of pork, such as enhancing the water-holding capacity of muscle tissue, increasing the lean meat content in carcasses, and reducing fat content. By balancing diets, including functional amino acids, it is possible to reduce nitrogen emissions into the environment and achieve significant feed savings by lowering the feed conversion ratio. The use of synthetic functional amino acids in animal nutrition during critical life stages improves overall health and has a positive impact on animal well-being, primarily through improved gut health.

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