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Supplementation of functional amino acids in pig diets and its impact on the intestine

Suplementación de aminoácidos funcionales en dietas de cerdos y su impacto en el intestino

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ABSTRACT
The study aimed to review the importance of the supplementation of functional amino acids (AA) in diets of starting-growing pigs on the intestinal health, development and growth. Functional AAs are those that participate in and regulate key metabolic pathways to improve the health, survival, growth, development, lactation, and reproduction of pigs at some specific physiological stages. During stress periods and critical physiological stages, pigs have a higher dietary requirement for some AAs (1-1.5 % arginine, 1 % glutamate, 0.8-2 % glutamine, 0.5-1 % proline, 0.5-2 % glycine, branched-chain AA, 0.4-0.6 % threonine, 0.12-1 % methionine, and 0.2-0.4 % tryptophan) to achieve the optimum growth performance. The increase of these AA allows maintaining the intestinal health and facilitates the normal functioning of the intestine. The application of the functional AA concept in the diet formulation allows to understand and assess that the extra addition represents a viable option to fortify the immune system and to promote intestinal growth and development. In conclusion, the dietary inclusion of functional AA in young pigs improves intestinal health, development and growth.
Keywords: crystalline amino acids, protein, supplementation.
RESUMEN
Este estudio tuvo como objetivo revisar la importancia de la inclusión de aminoácidos (AA) funcionales en la alimentación de cerdos en iniciación-crecimiento sobre la salud, desarrollo y crecimiento intestinal. Los AA funcionales son aquellos que participan y regulan las vías metabólicas clave para mejorar la salud, la supervivencia, el crecimiento, el desarrollo, la lactancia y la reproducción de los cerdos en alguna etapa fisiológica especifica. Durante los períodos de estrés y etapas fisiológicas críticas, los cerdos tienen un requerimiento nutricional superior de algunos AA [1-1.5% de arginina, 1% de glutamato, 0.8-2% de glutamina, 0.5-1% de prolina, 0.5-2% de glicina, AA de cadena ramificada (0.19-0.55% isoleucina, 0.07-0.82% leucina y 0.27-0.57% valina), 0.4-0.6% de treonina, 0.12% de metionina y 0.2-0.4% de triptófano] para optimizar el comportamiento productivo, ya que, el incremento de estos AA permite mantener la salud intestinal y facilita el funcionamiento normal del intestino. La aplicación del concepto de AA funcionales en la formulación de raciones permite entender y valorar que la inclusión extra representa una opción para fortalecer el sistema inmune y favorecer el desarrollo y crecimiento intestinal. En conclusión, la adición de AA funcionales a la dieta de cerdos jóvenes favorece la salud, desarrollo y crecimiento intestinal.
Palabras clave: aminoácidos sintéticos, proteína, suplementación.

INTRODUCTION

The extra inclusion of unconventional (arginine, glycine, glutamine, leucine and proline) and conventional (methionine, threonine, tryptophan and valine) synthetic amino acids (AA) in the diet, at specific physiological stages, may imply benefits in modulating gene expression, immunity, improvement in intestinal and skeletal muscle growth, as well as modification of body fat content (Wu *et al*., 2014). These findings led to the concept of functional AA, which are defined as those that participate in and regulate key metabolic pathways to improve the health, survival, growth, development, lactation and reproduction of organisms at some specific physiological stage (Wu, 2013). Therefore, under stress conditions, extra supplementation with synthetic essential and non-essential AAs (with respect to recommended levels) can be considered functional AAs, because they can modify immune status and improve resistance to clinical and subclinical diseases (van der Meer *et al*., 2016). In addition, the use of functional AA can improve intestinal health, immune response, alter intestinal growth and development, and modify the composition of the intestinal microbiota (Liu *et al*., 2017; Liao, 2021).

In pig nutrition, there is a need to understand the roles and dietary requirements of AA in young pigs to improve the efficiency of dietary protein utilization and minimize nitrogen excretion to the environment (Rezaei *et al*., 2013a); as dietary requirements of AA depend on developmental stage, physiological state, health, environmental factors and pathological states (Dai *et al*., 2012). Therefore, the objective of the present review was to know the importance of the inclusion of functional amino acids in feed on the health, development and intestinal growth of pigs in initiation-growth.

Arginine (Arg)

Arg is involved in antioxidant response, neurotransmission, immunity, urea synthesis (Wu *et al*., 2014), gut microbiota growth (Dai *et al*., 2012), nitric oxide (NO) production and regulation of gene expression (Zheng *et al*., 2018). The endogenous synthesis of Arg for good productive behavior is sufficient in the adult pig, so it is not considered as an essential AA (Ma *et al*., 2015); however, when the animal is under stress and/or in a period of immunosuppression, Arg requirements increase, becoming a functional AA (Wijnands *et al*., 2015).

A standard sorghum or corn-soybean paste-based diet does not provide sufficient arginine for protein synthesis in weaning pigs. This is because the pig at this stage is under oxidative stress, intestinal maturation and in the establishment of its immune system; therefore, the extra addition of Arg is conditionally essential, because needs are greater than the synthesis rates (Zheng *et al*., 2018). In particular, extra dietary intake (0.5-1.5 %) to the recommended level of L-Arg can function as a nutrient to promote oxidative stress response by enhancing antioxidant capacity and inhibiting the expression of inflammatory cytokines (Zheng *et al*., 2013; Zheng *et al*., 2018).

Arg addition is effective in decreasing intestinal injury, improving intestinal barrier function and vascular development (Chen *et al*., 2012; Zhu *et al*., 2013; *Zheng et al*., 2018).

supplementation (0.5-1 %) protects and improves intestinal mucosal immune barrier function and maintains intestinal integrity in weaned piglets after exposure to *E. coli* (Dai *et al*., 2012; Zhu *et al*., 2013) and attenuates the negative effects caused by inoculation with *Salmonella enterica* (Chen *et al*., 2012). In addition, the extra inclusion of 1 % Arg in the diet of growing pigs decreases stress and improves the immune response, upon consumption of the mycotoxin deoxynivalenol (Wu *et al*., 2013).

In some studies (Yao *et al*., 2011; Wang *et al*., 2012; Yang *et al*., 2016) Arg supplementation (0.2-1.2 %) was observed to improve growth and intestinal development in weaned piglets. Yang *et al*. (2016) observed that the addition of 0.4 or 0.8 % Arg in milk replacer improved growth in piglets (4 to 24 d of age) and intestinal development (height and area of villi and intestinal mucosa) in pigs from 25 to 45 d of age. Arg (1 %) supplementation improved intestinal growth (weight), intestinal villus height, and expression of protein levels for vascular endothelial growth factor in pigs weaned at 21 d (Yao *et al*., 2011). Exposure of pigs to heat stress damages the intestinal epithelium, affecting AA absorption, but adding 0.16 % L-Arg in the diet helps improve small intestinal epithelium function by increasing villus height, abundance of AA transporters, and availability of essential AA (Morales *et al*., 2021).

Glutamate (Glu) and Glutamine (Gln)

Animal studies indicate that Glu and Gln play versatile roles in intestinal metabolism and function (Yi *et al*., 2018). Dietary supplementation of 1 % Glu in diets for weaned piglets is a therapeutic feeding strategy to decrease intestinal disorders during inflammatory process states (Wang *et al*., 2015a). Piglets weaned at 21 d supplemented with monosodium Glu (0.5, 1, 2 and 4 %) for 21 d reduced the incidence of diarrhea, proportional to the dose, in the first week after weaning, and improved antioxidant capacity in the small intestine (Rezaei *et al*., 2013a; Rezaei *et al*., 2013b).

Gln is a non-essential amino acid. However, during periods of stress and at critical stages of development, pigs have a higher dietary requirement for Gln to achieve maximum productive behavior and facilitate normal gut function, particularly in hypercatabolic states (Wu *et al*., 2014). In weaned piglets, extra Gln addition to the diet can improve productive behavior, intestinal morphology, reduce oxidative damage, stimulate enterocyte proliferation, modulate cell survival and death; it also improves intestinal paracellular permeability (Ji *et al*., 2019). Some studies have shown that Gln (0.8-1 %) can improve the structure and function of intestinal epithelium (Rezaei *et al*., 2013b; Wang *et al*., 2014a). While the addition of 0.8-2 % synthetic Gln to the diet shows beneficial effects on intestinal morphology and growth, particularly during the first two weeks after weaning (Molino *et al*., 2012; Teixeira *et al*., 2014).

Proline (Pro)

Pro is an indispensable amino acid in young pigs due to their limited ability to synthesize proline from glutamine, glutamate or arginine in the intestine (Wu, 2013). In pigs, it has been shown that Pro can improve intestinal integrity and function under normal and pathological conditions, which can potentially protect it from different diseases (Wang *et al*., 2015b; Liu *et al*., 2017). Dietary supplementation with Pro plays an important role in the intestine of weaned piglets by regulating cell differentiation and de novo synthesis of arginine and polyamines (involved in early maturation of intestinal mucosal integrity) in enterocytes to promote intestinal cell growth and migration (Wang *et al*., 2016).

The addition of Pro (0.5 or 1 %) to diets for weanling pigs can improve growth rate, increase superoxide dismutase enzyme activities, and improve digestive function of the gastrointestinal tract (Kang *et al*., 2014), as Pro metabolism involves redox balance and ammonia detoxification in intestinal epithelial cells (Phang *et al*., 2015). Furthermore, piglets fed additional Pro (25 mg/kg PV) were observed to increase villus height, improve mucosal proliferation and intestinal morphology, as well as tight protein binding and potassium channel protein expression; with implications for epithelial restitution and intestinal barrier function after stress injury (Wang *et al*., 2015b).

Glycine (Gly)

There is evidence that endogenous Gly synthesis is insufficient to support optimal intestinal health or maximize whole-body growth (including the small intestine) in young pigs (Wang *et al*., 2014b). *In vitro* studies showed that Gly inhibits oxidative stress in porcine intestinal epithelial cells (Wang *et al*., 2014c) and improves the intestinal mucosal barrier (Li *et al*., 2016a).

In seven-day-old piglets, reared with their dams, which were orally supplemented with 0, 50, 100 or 200 % extra Gly intake, relative to the Gly content in the sow's milk, for 14 days and then weaned at 21 days of age. It was observed that the extra intake (100-200 %) of Gly was associated with an improved intestinal mucosal barrier, increased villus height, a better relationship between villus height and crypt depth in the jejunum, and reduced apoptosis of intestinal enterocytes (Fan *et al*., 2019). Similarly, in weaned piglets supplemented with 0 (control), 0.5, 1 or 2 % Gly for seven days, modification in intestinal microbial composition and improvements in intestinal mucosal immunity were observed. The colon contents of piglets fed 2 % Gly reduced the count of pathogenic bacteria (*Escherichia-Shigella*, *Clostridium* and *Burkholderiales*) and increased the count of short-chain fatty acid-producing bacteria (*Blautia*, *Lachnospiraceae*, *Anaerostipes* and *Prevotella*) compared to the control treatment (Ji *et al*., 2021).

Branched-chain AAs

Branched-chain amino acids include leucine, isoleucine and valine, which play a key role in regulating gut health, immunity and disease in animals (Nie *et al*., 2018). Supplementation with isoleucine induces the expression of antimicrobial AA in porcine intestinal epithelial cells, essential for innate immunity (Mao *et al*., 2013). While the addition of leucine (1.4 g/kg BW) to the diet promotes intestinal development in young pigs (Sun *et al*., 2015). Likewise, the additional inclusion of 1 % leucine in the diet of pigs attenuated the negative effect of rotavirus infection on diarrhea; it also improved the production of mucin, immunoglobulins, antibodies and cytokines (Mao *et al*., 2018).

The extra addition of branched-chain AA can enhance the productive behavior of pigs fed low protein diets by improving the metabolic profile in liver and muscle (Wang *et al*., 2015c), oxidative capacity of muscle (Duan *et al*., 2017), intestinal morphology, enterocyte cell proliferation (Duan *et al*., 2018) and by positively altering the intestinal microflora (Spring *et al*., 2020).

By adding synthetic branched-chain AA (0.55 % isoleucine, 0.82 % leucine and 0. 57 % valine) to low protein diets for weanling pigs offered for 4 weeks increased *Paludibacteraceae* and *Synergistaceae* populations and reduced *Streptococcaceae*, *Oxyphotobacteria_unclassified*, *Pseudomonadaceae* and *Shewanellaceae* populations in feces compared to a standard diet and a low protein diet without the addition of branched-chain AA (Spring *et al*., 2020). While the addition of synthetic branched-chain AA (0.19 % isoleucine, 0.1 % leucine, and 0.34 % valine) to the diet, offered to weanling pigs for 14 d, improved their productive behavior, intestinal development, and expression of amino acid transporters (Zhang *et al*., 2013). In weaned pigs, consumption of diets supplemented with extra levels of leucine (0.07 %), valine (0.27 %) and isoleucine (0.19 %) for 14 d improved intestinal immune defense, protecting villus morphology and increasing intestinal immunoglobulin levels (Ren *et al*., 2015).

Threonine

Stimulation of the immune system increases dietary threonine requirements (greater than 0.60%) for protein retention in growing pigs due to increased requirements for maintenance, as a dietary threonine concentration less than 0.40 % suppresses the immune response (McGilvray *et al*., 2019). High threonine intake (0.90 vs. 0.85 %) in starter pigs increases serum IgG concentration and promotes a healthy gut microbiota (Trevisi *et al*., 2015); however, it should be considered that the beneficial effect on immune response requires a higher concentration than the level used to obtain maximum weight gain (Xie *et al*., 2013). In weanling pigs fed a standard diet, with 0.76 % threonine level (NRC, 2012), systemic and intestinal inflammation was observed, while the inclusion of 15 % extra threonine improved intestinal integrity, although the inflammation induced by the diet change was not normalized (Koo *et al*., 2020).

Dietary threonine restriction may decrease digestive enzyme production and increase mucosal paracellular permeability, allowing pathogens and toxins to cross the mucosal epithelial barrier. In addition, threonine requirement has been shown to increase in pathological conditions such as ileitis and sepsis to maintain intestinal morphology and physiology (Mao *et al*., 2011). When formulating diets for weaned piglets, it should be considered that threonine levels depend on the physiological state, as healthy or infected animals; for example, with *E. coli*, require different concentrations (Ren *et al*., 2014). Wang *et al*. (2006) observed, in weaned piglets, that consumption of diets to which the threonine level was increased increased IgG and IgA concentrations in the intestinal mucosa and improved intestinal morphological characteristics in piglets exposed to *E. coli*, concluding that, to optimize pig immunity, pigs should consume 0.66 % of true ileal digestible threonine. Trevisi *et al*. (2015) observed that consumption of a diet supplemented with

0.90 % threonine reduced *E. coli* counts in the feces of weanling pigs compared to the 0.85 % threonine diet.

Feeding starter pigs with lower threonine concentration reduces mucin production (Wang *et al*., 2010) and affects intestinal function (0.65 % threonine; Hamard *et al*., 2010). However, deficiency (0.37 % threonine) or excess (1.11 %) threonine in the diet of weanling pigs affects the intestinal mucosal barrier, whereas a moderate increase of 0.74-0.89 % improved intestinal barrier function, maintenance, and mucosal mucin synthesis (Wang *et al*., 2010).

Methionine (Met)-Cysteine (Cis)

Increasing dietary sulfur AAs could produce additional beneficial effects as functional AAs (Wu, 2013). The recommendation of Met+Cis for starter pigs varies, depending on the expected productive response and the literature source consulted, averaging 0.71 % (NRC, 2012). Extra supplementation (0.25-0.25 %) with Met+Cis) in the diet of pigs is associated with positive effects on the immune system, since the increased intake of sulfur-containing AA increases the synthesis of key proteins in the immune response (Li *et al*., 2014; Pinheiro *et al*., 2015). Increased Met intake above the requirement necessary to achieve optimal productive behavior during weaning or periods of stress is important for maintaining mucosal integrity (Chen *et al*., 2014), development and intestinal antioxidant capacity (Su *et al*., 2018; Zhang *et al*., 2019).

Oxidative stress can cause poor productive performance, health problems and even death (Zheng *et al*., 2018). Theoretically, a deficiency of Met (0.24 %) with respect to the level (0.37 %) set by the NRC (2012) could affect the amounts of Cis and glutathione peroxidase, with a consequent increase in oxidative stress. The addition of extra Met (0.12 %) optimizes protein synthesis, increases cysteine and glutathione disulfide concentrations in plasma and tissues, leading to reductions in redox potential, aiding in the maintenance of small intestinal mucosal integrity of weaned piglets (Chen *et al*., 2014). Met deficiency (less than 0.25 %) suppresses intestinal mucosal growth, reduces intestinal epithelial cell proliferation and increases intestinal oxidative stress in piglets (Bauchart-Thevret *et al*., 2009; Chen *et al*., 2014).

The weaning period in pigs increases oxidative stress. Dietary supplementation with N-acetylcysteine (0.05 %) increases antioxidant capacity and decreases jejunal expression of inflammatory cytokines (Guo *et al*., 2016); in addition, the intestinal bacterial population can be modified, increasing *Lactobacillus* and *Bifidobacterium* counts and reducing *E. coli* (Xu *et al*., 2014). Coupled with the above, a deficiency of Met in pigs increases adhesion and increases both cytotoxicity and apoptotic responses of cells infected with *E. coli* (Tang *et al*., 2015). When pigs exhibit a stress-activated immune system, Met+Cis requirements may be higher (0.90 %), as Cis synthesis from Met tends to increase (Li *et al*., 2014; Pinheiro *et al*., 2015). In contrast, there is evidence that diets with lower methionine concentration could improve adipose tissue lipid metabolism, decrease oxidative damage, alter antioxidant pathways and improve inflammatory response in growing pigs (Ying *et al*., 2015; Zhou *et al*., 2016).

Tryptophan (Trp)

Trp plays an important role in the immune response through the products of its catabolism, such as serotonin, melatonin and N-acetylserotonin that can inhibit the production of superoxide and tumor necrosis factor-alpha, scavenge free radicals and modulate inducible nitric oxide synthesis (Kim *et al*., 2007). Trp is important for regulating physiological function in the intestine, such as intestinal permeability, motility and secretion (Wang *et al*., 2015d; Tossou *et al*., 2016); also, it plays a crucial role in immune balance and maintenance of intestinal microbiota (Gao *et al*., 2018). In addition, Trp supplementation can improve the immune response in viral infectious processes in young pigs (Wang *et al*., 2013).

Trp in feed influences the growth and health of intestinal epithelial cells as well as intestinal epithelial tight junction proteins in weaned piglets (Wang *et al*., 2015d). Addition with 0.2-0.4 % Trp (relative to the recommended level of 0.25 %; NRC, 2012) in diets for weanling pigs improved intestinal mucosal barrier function compared with those fed the basal diet, suggesting that Trp-metabolizing bacteria in the small intestine mainly mediated the beneficial effects of dietary Trp on mucosal integrity, health, and function (Liang *et al*., 2019). Furthermore, this same level of supplementation can alleviate or decrease the altered composition and/or functions of microorganisms in the intestine. In addition, it alters intestinal microbial composition and diversity, activate receptor signaling associated with cell regeneration, immune reaction, intestinal homeostasis and cell proliferation, and reduce inflammatory cytokine expression in the large intestine of weaned piglets (Liang *et al*., 2018; Wang *et al*., 2020). In addition, consumption of a diet with levels of 0.35 % Trp improved productive behavior reduced the presence of diarrhea, improved intestinal mucosal barrier integrity and intestinal microbial ecology (increased *Lactobacillus*) in weaned piglets. In addition to effects associated with Trp metabolites such as activation of energy expenditure-promoting protein complex signaling for macromolecule biosynthesis and probiotic enrichment in the small intestine (Rao *et al*. (2021). Likewise, supplementation with 0.15 % Trp increased the ratio of villus height to crypt depth without affecting intestinal permeability (Tossou *et al*., 2016). In contrast, dietary addition of 0.75 % extra Trp negatively influenced intestinal epithelium morphology (Tossou *et al*., 2016), significantly increasing intestinal permeability (Li *et al*., 2016b; Tossou *et al*., 2016); inclusion levels of 0.1 % extra decreased gene expression of intestinal epithelial tight junction proteins (Li *et al*., 2016b).

Differences in response to Trp supplementation may be because piglets under stress conditions may need more Trp to maintain intestinal integrity and optimal growth, as extra addition with 0.15 % Trp improved intestinal integrity, restored redox status, and improved mitochondrial function of piglets challenged with a chemical agent to induce oxidative stress (Liu *et al*., 2019).

CONCLUSION

In conclusion, the inclusion of functional AA in the diet for starter-grower pigs, at levels higher than those recommended to maximize weight gain, promotes intestinal health, development and growth, especially when subjected to stressful or immunologically challenged conditions.

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Errata Erratum

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