MEETING OPTIMUM ARGININE REQUIREMENTS IMPROVES INTESTINAL HEALTH AND PRODUCTION PERFORMANCE IN WEANED PIGLETS

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ABSTRACT

The gastrointestinal tract is a critical site for the digestion and absorption of nutrients and the largest immune organ in animals. Its functionality is closely linked to the availability of various amino acids, as several functional amino acids are known to play pivotal roles in regulating epithelial integrity. Arginine, in particular is a multi-functional amino acid involved in the provision of absorptive function and scaling down the permeability of epithelial layers. Research has demonstrated that arginine promotes the development of intestinal villi, enhances the expression of intestinal tight-junction proteins, stimulates immune function and enhances the antioxidant capacity within the enterocytes. In this article, supporting evidence demonstrated through collaborative research works with CJ Bio will be presented.

Keyword Arginine, Digestion and absorption, Intestinal health

PROVISIONING INTESTINAL HEALTH IS CRITICAL FOR WEANED PIGLETS

The gastrointestinal tract (GIT) is a multifunctional organ in animals, responsible for nutrient digestion and absorption, and limiting the entrance of unwanted molecules such as antigens and pathogens (Cor et al., 2010). In swine production, the immediate postweaning period is commonly accompanied by intestinal disturbances resulting in increased diarrhea incidence, greater susceptibility to disease, poor growth performance, and increased mortality, which in turn causes economic losses for swine producers (Shen., 2009). Therefore, the health status of the intestinal epithelium has a significant impact on the digestive and absorptive functions, animal health, and subsequent growth during this challenging period (Krajmalnik-Brown et al., 2012).

ARGININE: A MULTIFUNCTIONAL AMINO ACID

Amino acids (AAs) are essential for intestinal development and regulation of nutritional and immunological functions, especially those directly related to gut physiology (Woo et al., 2017). Among functional AAs, arginine participates in important regulatory functions associated with nutrient metabolism, intestinal repair, cell proliferation, and immune response that contribute to the maintenance of intestinal function (Clissold et al., 2012). (Wu et al., 2004).

The synthesis of arginine primarily relies on two precursor substances, glutamine/glutamate and proline, and is predominantly accomplished through the intestinal-renal metabolic axis (Li et al., 2020). In intestinal epithelial cells, glutamine/glutamate and proline are converted into citrulline through a series of enzymatic reactions, a process involving key enzymes such as pyrroline-5-carboxylate synthase and ornithine aminotransferase (Li et al., 2020). Once synthesized in intestinal epithelial cells, citrulline is released into the portal venous blood and subsequently transported to the kidneys via the bloodstream. In the kidneys, citrulline is ultimately converted into arginine through the action of enzymes such as argininosuccinate synthase and argininosuccinate lyase, making it available for utilization by systemic tissues (Wu et al., 2004) (Figure 1). During periods of rapid growth, disease, or stress, the demand for arginine increases, and endogenous synthesis may be insufficient to meet these requirements. However, arginine provision from sow's milk might be insufficient for piglets' protein deposition. Kim et al. (2004) revealed that sow's milk provides less than 40% of the daily requirement in 7-days-old suckling pigs.

Arginine is a crucial amino acid whose metabolites play pivotal roles in various physiological processes. Under the action of nitric oxide synthase (NOS), arginine is converted into nitric oxide (NO), a vital signaling molecule in the body that participates in vasodilation, immune system regulation, and neurotransmission (Luiking et al., 2012). Additionally, arginine is catabolized by arginase to produce ornithine, which serves as a precursor for polyamines (such as putrescine, spermidine, and spermine) and proline (Li et al., 2020). These metabolites are involved in critical biological functions, including cell proliferation, tissue repair, and collagen synthesis (Luiking et al., 2012) Figure 1. Therefore, increasing arginine intake in piglets could be an effective strategy to promote their growth and intestinal health.

A piglet study collaborated with South Dakota University demonstrated that the optimum standardized ileal digestible (SID) arginine level in the diet for weaned piglets should be in the range of 1.5% to 1.9% (100-127% SID Arg:Lys ratios; Perez-Palencia et al., 2024), which is 2.5 to 3.1 times higher than the recommendation by the National Research Council (NRC, 2012). A subsequent nursery pig study collaborated with Iowa State University supports the finding by Perez-Palencia and his colleagues. In this study weaned piglets fed experimental diets containing from 45% to 145% SID Arg:Lys. After 27 days of feeding trial, the optimum SID Arg:Lys ratios for maximum feed intake and maximum daily gain were 97% and 96%, respectively, with the lower bounds of the 95% confidence interval being at least 81% (Humphrey et al., 2024). The results as evident in the above mentioned studies, a large number of studies have shown that arginine improved the average daily weigh gain and body weight gain of piglets Table 1, however, swine industry still significantly underfeed arginine than the requirement for optimum growth of piglets (Hagen et al., 2024; Humphrey et al., 2024; Dong et al., 2022).

Figure 1 **Pathways of arginine metabolism** *(Re-drawn from Wu et al., 2007 and Morris et al., 2002)*

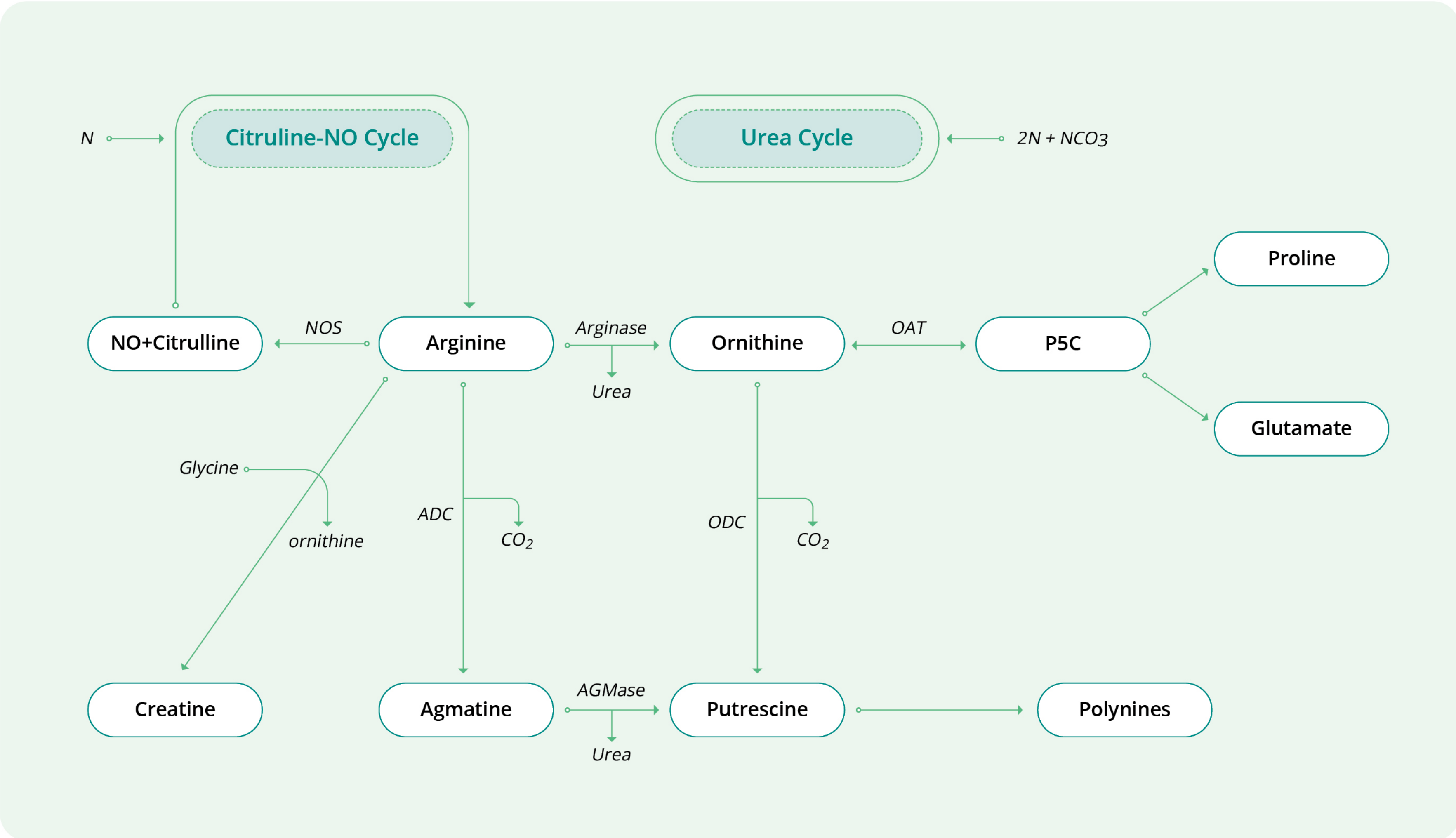


Table 1 Summary of the research on the relationship between arginine and piglet growth and intestinal health

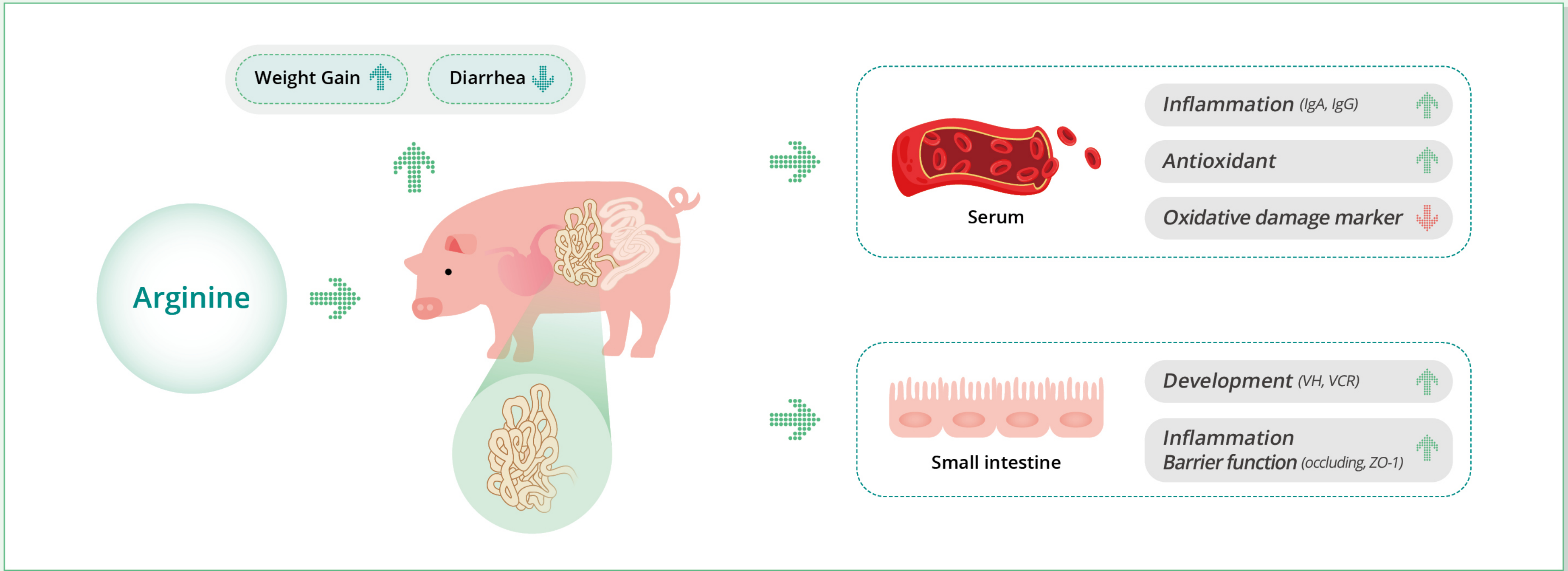
Experimental Animals	Stages	Design	Main Results	Summary	References
40 7-day-old breastfed piglets	7-21 days	Arg (250mg per kg per body weight)	ADG V/C ↑ Immunoglobulins ↑	Arg improved the growth performance and reduced the weaning stress of piglets by affecting intestinal morphology, cytokine secretion and dendritic cell function.	Dong et al. 2022
64 28-day-old weaned piglets	28-35 days 28-42 days 28-49 days	0.5% L Ara 1% L Arg	ADG ↑ FCR ↓	Arg improve the productive performance and enhance the integrity of the intestinal mucosa of weaned piglets.	Silva et al. 2022
35 artificially fed crossbred piglets	3 days post-inoculation porcine rotavirus	Fed a milk diet with or without arginine (0.4 g/kg/d, twice daily by gavage)	Protein synthesis ↑ Mucosal resistance ↓	Arginine enhanced intestinal protein synthesis via a p70S6k-dependent mechanism and reduced transepithelial permeability by a p70S6k-independent mechanism.	Corl et al. 2007
240 pigs (5.06kg)	10-7 days 7-21 days 21-42 days	(0.85, 0.95, 1.05. and 1.15) standardized ileal digestible (SID) Arg to lysine (Lys) ratios	ADG ↑	Increasing dietary SID Arg:Lys increased final weight	Hagen et al. 2024
15 growing pigs (Landrace x Large White)	60 days	1% Arg	SLC7A7 expression ↑ antioxidant system ↑	Arginine exerted a protective role against mycotoxicosis in pigs by enhancing the expression of intestinal amino acid transporters and improving antioxidant capacity.	Yin et al. 2014
480 newly weaned pigs (6.20 ± 0.61 kg)	0-41 days	increasing standardized ileal digestible (SID) Ara:Lys, achieved by substituting corn starch. glycine. and I-alanine withl-arginine	ADG ↑ ADFI ↑	The SID Ara:Lys requirement of 6 - to 13-kg nursery pigs is at least 81%, and excessive arginine supplementation may negatively affect growth performance.	Humphrey et al.2024
240 mixed-sex pigs (24 ± 2 d old: 7.3 ± 0.1 kg BW)	42 days	0.5 % Ara	IgA ↑	Supplementing arginine improved the acute phase response and immune response status.	Wellington et al. 2023
36 weaned piglets	11days	0.8% Arg 1.6% Ara	Crypt depth ↓	Arginine relive intestinal dysfunction of low-birth-weight piglets	Zhang et al. 2021
20 low-birth-weight piglets 20 normal-birth-weight piglets	21days	1.0% Arg	ADG ↑ Intestinal morphologyADG ↑	Arginine improve intestinal morphology and mitochondrial of low-birth-weight piglets	Zheng et al. 2017

ADG: average daily weight gain; V/C: villus length versus crypt depth; FCR: feed conversion

ARGININE AND INTESTINAL MORPHOLOGY

A higher mucosal villus height generally indicates more mature villus epithelial cells and stronger absorptive capacity. Weaning deprives passive immune protection from sows' milk, making them highly susceptible to bacterial toxins in the intestine (Yang et al., 2019). Zhu et al. (2013) found that endotoxin-induced jejunal damage was mitigated by dietary arginine supplementation, with 0.5% and 1% arginine increasing villus height (VH) by 11% and 30%, respectively, and improving the villus height-to-crypt depth ratio (VCR), therefore promoting growth of the animal Figure 2. A collaborative study between CJ Bio and Iowa State University demonstrated that supplementation of arginine in water (0.03-0.06%) for the first week after weaning significantly decreased intestinal permeability when measured by lactulose:mannitol ratio on day 6 post-weaning, and the reduced permeability was maintained when the researchers measured lactulose:mannitol ratio again at day 20 post-weaning, even the water-based arginine supplementation was discontinued on day 7 post-weaning (Hagan et al., 2024). This finding suggests that a short-term provision of arginine in water during the first 7 days after weaning can influence epithelial barrier function for the entire immediate post-weaning period.

Figure 2 Pathways of arginine that modulate intestinal health



ARGININE AND INTESTINAL BARRIER FUNCTION

The intestinal mucosal barrier, comprising the mechanical barrier and the immune barrier, is vital for maintaining intestinal function and growth of animals (Sánchez et al., 2014). The mechanical barrier relies on tight junctions between epithelial cells, regulating permeability between intestinal epithelial cells (Ma., 2006). Studies showed that arginine supplementation decreased LDH (L-lactate:NDA+ oxidoreductase) leakage in the small intestine after weaning, which is a marker of a compromised mechanical barrier, indicating arginine protected cell membrane integrity (Dong et al., 2022). Arginine can increase the expression of the intestinal tight - junction protein occludin and β - defensin 2 (pBD2), alleviating the damage to the intestinal barrier function of fattening pigs caused by heat stress (Yi et al., 2020). Corl et al. (2008) showed a beneficial effect of arginine on the intestinal barrier function by reducing the trans-epithelial permeability via a mammalian target of rapamycin/p70S6k-independent mechanism of suckling piglets. Supplementation with arginine significantly increases the transepithelial electrical resistance (TEER) ratio, reduces the inulin flux, and qualitatively preserves the tight junction proteins through a mechanism dependent on nitric oxide (NO) donors. (Chapman et al., 2012).

The immune barrier includes immune cells and immune molecules that are diffusely distributed among the intestinal epithelial cells and gut-associated lymphoid tissues (Salvo Romero et al., 2015). Compared with piglets induced by endotoxin, adding 1% arginine can reduce the number of intra-epithelial lymphocytes in piglets by 22% (Yang et al., 2019). The concentrations of cytokines and antibodies in the serum are key indicators of the immune function. IgG concentration in the serum was increased in the piglets supplemented with arginine from the 7th to 21st day after weaning (Tan et al., 2009). It was suggested that arginine modulation of the intestinal immune response may be related to the NO pathway in pig (Kvidera et al.,2024;). Notably, many reports have shown that arginine-induced modulation of the intestinal barrier function is related to activation of antioxidant ability (Zheng et al., 2017; Zhang et al. 2021), although the exact mechanism requires further research.

CONCLUSION

Although pigs can synthresize arginine through the urea cycle, the endogenous synthesis of arginine under a specific physiological phase is insufficient to meet the demand for arginine in pigs. For example, piglets can produce arginine only in the epithelium, which is not enough to meet the arginine requirement of fast-growing piglets. Moreover, arginine produced through the urea cycle is not enough to meet the arginine requirement of sows for proper reproduction performance. Arginine plays a key role in maintaining intestinal health by regulating the development of intestinal villi, enhancing barrier function, and modulating immune responses, thereby promoting intestinal health, which eventually translated to the improved production performance in swine. Based on recent collaborative research, SID arginine requirements for optimum feed intake and growth of weaned pigs are 97% and 96%, respectively.