Gut health : Amino acids for intestinal barrier

Ji Eun Kim CJ Bio, Headquarters

Introduction

'Gut Health' is a key factor for the health and wellbeing. In this aspect, the primary organ is the gastrointestinal (GI) tract which has an important role to absorb nutrients and shuttle waste back out of the body. Besides the role, it is a well-known defensive barrier that will protect from invasive pathogens and regulate mucosal immune system. Various infections, imbalanced nutrients and stressful environments may weaken the integrity of gut barrier and results in lower performance and productivity of livestock animals. In this article, the functions of intestinal epithelium barrier are explained and dietary Amino Acids (AA) will be discussed as a way to maintain a healthy gut status.

What is the intestinal epithelium barrier?

The intestinal epithelium is a monolayer of cells lining the gut lumen and has two important functions. It allows the absorption of nutrients while also functioning as a barrier, which prevents pathogens entering the mucosal tissues (Blikslager, 2007). The intestinal epithelial cells (IEC) are composed of absorptive enterocytes (over 80%), enteroendocrine, goblet and Paneth cells (van der Flier, 2009). These epithelial cells are tightly bound together by intracellular junctional complexes that regulate the paracellular permeability and are crucial for the integrity of the epithelial barrier (Figure. 1). The crucial fuction of epithelial cell is transportation of ingested sources between intestinal lumen and lamina propria. Transcellular permeability means transportation through epithelial cells (Dulantha, 2011) and paracellular permeability is associated with transport through the gap between each epithelial cell on the barrier. In the paracellular transportation, tight juctions are crucial. Under normal or pathological conditions, the structure of tight juction is modulated by cell signals for the paracellular transportation (Ahmad, 2016). Herein, the stucture and function of tight juction (TJ) in IEC is discussed.



Figure 1. Intestinal epithelial cells (IEC)

Structure and function of tight junction

Tight junctions (TJ) have the major role of the intestinal physical barrier. TJ are formed by the assembly of a multiple proteins located close at the apical portion of the lateral membrane of epithelial cells (Zihni, 2016).

It is composed of juctional complexes: Demosomes, Adhernes Junctions (AJ) and Tight Junctions (TJ). Tight junctions (TJ) is crucial for the barrier function that inhibits the passage of soluble molecules via the gaps between cells and It is thought to be included in the fence function that keeps the cell surface lipids at the basolateral region seperated form at the apical region. Adhernes Junctions (AJ) and Demosomes have a role in mechanically connecting adjacent cell to resist strong contractile forces and to maintain tissue structure particularly in epithelial cells and regulates the formation and matainance of TJ and demosome (Osler,2005., Kamada, 2013., Suzuki,2009) (Figure 2).

Owing to the physical location and complex mechanism of tight junctions (TJ), there are direct and indirect evidences between impairments of tight junction and intesinal inflammation.



Figure 2. Molecualar structure of the intercellar junction of intestinal epithelial cells. (Suzuki, 2013)

Negative effects from "leaky gut"

When the gut becomes unhealty, intestinal barrier is going to be collapsed and in turn, pathogens leak into the blood stream predisposes animals to disease challenge. It is called the "leaky gut" (Figure 3). In vitro and in vivo studies have demonstrated that "leaky gut" is caused by multiple factors including pathogen invasion, nutritional deficiency, and environmental stresses (Howe, 2004., Muza-Moons, 2006). It leads to dysbiosis, pro-inflammatory response, oxidative stress and nutrient loss (Bruewer, 2003). Subsquently, these events result in decrease growth performance and productivity.



Inflammation Weakened immune system Mal absorption & Nutrient deficiency

Figure 3. Intestinal permeability defects

Amino acids, a helper to avoid "leaky gut"

Amino acids (AA) play a primary role in maintaining the structure and function of the intestinal barrier. For example, Threonine (Thr) is an essential components of mucus in the gut. Threonine participates in mucin synthesis and maintain gut barrier integrity. It is reported that supplementation with Thr in feed improved the intestinal mucin synthesis and immun function in piglet (Zhang, 2019, Chen, 2017). Another example is glutamine. Glutamine is related to metabolic processes like protein bio-synthesis, nitrogen transfer, gluconeogenesis, oxidative fuel the intestine (Wang, 2009). According to a study from Oxford, glutamine improves tight juction protein, pro-inflammatoy cytokines in a chicken challenged with an coccidiosis infection (Oxford, 2019). Arginine is also involved in cell proliferation and works as a precusor for the synthesis of nitric oxide. The addition of arginine in a diet helps to maintain integrity after *E.coli* challenge in swine (Yang, 2016). Another study has shown that Arginine increases mucosal protein contents and suppresses the inflammatory cytokine expression (Zheng, 2017). Therefore, addition of some amino acids could help to avoid "leaky gut".

Amino acids	Functions	Reference
Arginine	Protecting intestinal barrier function Decreased the crypt depth and suppressed the inflammatory Cytokine expression in the jejunum	Yang et al.,(2016) Zheng et al., (2017)
Glutamine	Reducing the mucosal Cytokine response Improving the intestinal barrier function	Ewaschunk et al., (2011) Wang et al., (2009) Oxford, 2019
Threonine	Reducing the mucosal Cytokine response Improving the intestinal barrier function	Ren et al., (2014) Zhang et al., (2019) Chen et al., (2017)
Methionine	Protecting intestinal barrier function and mucosa	Chen et al., (2014)

Table 1. Effects of supplementing amino acids on gut health in poultry and swine

Conclusion

Maintaining a healthy intestinal barrier is essential for the absorption of dietary nutrients and physiological defense. Not only feed additives such as probiotics and essential oils, but also amino acids such as arginine, threonine, glutamine, methionine, tryptophan help to make solid intestinal barriers and in turn, improve the growth performance and health status of livestock animals.

REFERENCES

- 1. Blikslager AT, Moeser AJ, Gookin JL, Jones SL, POdle J. Restoration of barrier function in injured intestinal mucosa. Physiol Rev. 2007, 87.
- 2. Van der Flier LG, Clevers H. Stem cells, self-renewal, and differentiation in the intestinal epithelium. Annu Rev Physiol. 2009, 71:241–60.
- 3. Dulantha .U., Rachel C. A., Warren C. M, Paul J. M., Jerry M. W., Nicole C. R., Regulation of Tight Junction Permeability by Intestinal Bacteria and Dietary Components. The Journal of Nutrition Critical Review, 2011, 769–776.
- 4. Ceniz Z., Karl M., & Maria S. B. Tight junctions: from simple barriers to multifunctional molecular gates. Nature Reviews Molecular Cell Biology, 2016, 17, 564–580.
- 5. Osler, M. E., Chang, M. S. & Bader, D. M. Bves modulates epithelial integrity through an interaction at the tight junction. The Journal of Cell Science. 2005, 118, 4667–4678
- 6. N. Kamada, G.Y. Chen, N. Inohara, G. Nunez. Mechanistic links between gut microbial community dynamics, microbial functions and metabolic health. Nat Immunol. 2014, 14, 685-690
- 7. Groschwitz, K. R., Hogan, S. P. Intestinal Barrier Function: Molecular Regulation and Disease Pathogenesis. The Journal of Allergy and Clinical Immunnology. 2009, 124 (1): 3–22.
- 8. Berkes, J., Viswanathan, V. K., Savkovic, S. D., Hecht, G. Intestinal epithelial responses to enteric pathogens: effects on the tight junction barrier, ion transport, and inflammation, Gut, 2003, 52, 439-451.
- 9. Suzuki T, Elias BC, Seth A, Shen L, Turner JR, Giorgianni F, Desiderio D, Guntaka R, Rao R. PKC eta regulates occludin phosphorylation and epithelial tight junction integrity. Proc Natl Acad Sci USA, 2009, 106:61–66.
- 10. Ahmad R, Sorrell M F, Bartra S K, Dhawan P, Sigh AB. Gut permeability and mucosal inflammation: bad, good or context dependent. Mucosa-IImmunology, 2017, 10,307-317.
- 11. Bruewer M, Luegering A, Kucharzik T, Parkos CA, Madara JL, Hopkins AM, Nusrat A Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. J Immunol, 2003, 171:6164–6172.
- 12. Suzuki T. Regulation of Intestinal Barrier Function by Dietary Polyphenols. Cell. Mol. Life Sci., 2013, 70:631–659.
- 13. Howe KL, Reardon C, Wang A, Nazli A, McKay DM. Transforming growth factor-beta regulation of epithelial tight junction proteins enhances barrier function and blocks enterohemorrhagic Escherichia coli O157:H7-induced increased permeability. Am J Pathol 2005, 167:1587–1597
- 14. Muza-Moons MM, Schneeberger EE, Hecht GA. Enteropathogenic Escherichia coli infection leads to appearance of aberrant tight junctions strands in the lateral membrane of intestinal epithelial cells. Cell Microbiol. 2004; 6:783–93.
- 15. Wu Guoyao, Kim S.W., Li D., Yin Y.L., Li. Amino acids and immune function. Brithsh Journal of nutrition. 2007, 98,237-252.
- 16. Blikslager AT, Moeser AJ, Gookin JL, Jones SL, POdle J. Restoration of barrier function in injured intestinal mucosa. Physiol Rev. 2007, 87.
- 17. Van der Flier LG, Clevers H. Stem cells, self-renewal, and differentiation in the intestinal epithelium. Annu Rev Physiol. 2009, 71:241–60.
- 18. Zhang, H.; Chen, Y.; Li, Y.; Zhang, T.; Ying, Z.; Su, W.; Zhang, L.; Wang, T. L. Threonine improves intestinal mucin synthesis and immune function of intrauterine growth-retarded weanling piglets. Nutrition, 2019, 59, 182–187.
- 19. Chen, Y.P.; Cheng, Y.F.; Li, X.H.; Yang, W.L.; Wen, C.; Zhuang, S.; Zhou, Y.M. Effects of threonine supplementation on the growth performance, immunity, oxidative status integrity, and barrier function of broilers at the early age. Poult. Sci. 2017, 96, 405–413.
- 20. Wang,W.W.; Qiao, S.Y.; Li, D.F. Amino acids and gut function. Amino Acids, 2009, 37, 105–110.
- 21. Yang, X.F.; Jiang, Z.Y.; Gong, Y.L.; Zheng, C.T.; Hu, Y.J.; Wang, L.; Huang, L.; Ma, X.Y. Supplementation of pre-weaning diet with L-arginine has carry-over effect to improve intestinal development in young piglets. Can. J. Anim. Sci. 2016, 96, 52–59.
- 22. Zheng, P.; Yu, B.; He, J.; Yu, J.; Mao, X.; Luo, Y.; Luo, J.; Huang, Z.; Tian, G.; Zeng, Q.; et al. Arginine metabolism and its protective effects on intestinal health and functions in weaned piglets under oxidative stress induced by diquat. Br. J. Nutr. 2017, 117, 1495–1502.
- Zhu, H.L.; Liu, Y.L.; Xie, X.L.; Huang, J.J.; Hou, Y.Q. Effect of L-arginine on intestinal mucosal immune barrier function in weaned pigs after Escherichia coli LPS challenge. Innate Immun. 2012, 19, 242–252.
- 24. Ren, M.; Liu, X.T.; Wang, X.; Zhang, G.J.; Qiao, S.Y.; Zeng, X.F. Increased levels of standardized ileal digestible threonine attenuate intestinal damage and immune responses in Escherichia coli K88+ challenged weaned piglets. Anim. Feed Sci. Technol. 2014, 195, 67–75.
- Ewaschuk, J.B.; Murdoch, G.K.; Johnson, I.R.; Madsen, K.L.; Field, C.J. Glutamine supplementation improves intestinal barrier function in a weaned piglet model of Escherichia coli infection. Br. J. Nutr. 2011, 106, 870–877.
- 26. Chen, Y.; Li, D.; Dai, Z.; Piao, X.; Wu, Z.; Wang, B.; Zhu, Y.; Zeng, Z. L-methionine supplementation maintains the integrity and barrier function of the small-intestinal mucosa in post-weaning piglets. Amino Acids 2014, 46, 1131–1142.