Postprint: The Immunomodulatory Effect of Dietary Tryptophan on Livestock and Poultry

Authors: Xi Qianyun, Liu Hongnan, Wu Xin, Liu Gang, Xu Kang, TOSSOU Myrlene Carine, Bai Miaomiao, Yin Yulong

Date: 2017-10-10T00:00:00+00:00

Abstract

Tryptophan is an essential amino acid that modulates immune function. Its metabolites, including indoleamine 2,3-dioxygenase (IDO), kynurenine, quinolinic acid, and melatonin, can enhance immunity, exert anti-inflammatory effects, and influence tumor cell immune evasion by inhibiting T lymphocyte proliferation, increasing blood immunoglobulin content, and promoting tissue antigen presentation. This article provides a brief review of the regulatory effects and mechanisms of tryptophan and its metabolites on immune function in livestock and poultry.

Full Text

Dietary Tryptophan and Its Immunomodulatory Effects in Livestock and Poultry

Bai Miaomiao[1],[2], Liu Hongnan[2], *Wu Xin[2], Liu Gang[2], Tossou Myrlene Carine[2], Xu Kang[2], Xi Qianyun[1]*, Yin Yulong[1],[2]

[1]College of Animal Science, South China Agricultural University, Guangzhou 510642, China
[2]Key Laboratory of Agro-Ecological Processes in Subtropical Region, Hunan Provincial Engineering Research Center of Healthy Livestock, Institute of Subtropical Agriculture, Chinese Academy of Sciences, Changsha 410125, China

Abstract: Tryptophan is an essential amino acid that regulates immune function in animals. Its metabolites—including indoleamine 2,3-dioxygenase (IDO), kynurenine, quinolinic acid, and melatonin—enhance immunity, induce anti-inflammatory responses, and influence tumor immune escape by inhibiting T lymphocyte proliferation, increasing blood immunoglobulin levels, and promoting antigen presentation in tissues. This review summarizes the regulatory ef-

fects and mechanisms of tryptophan and its metabolites on immune function in livestock and poultry.

Keywords: tryptophan; livestock and poultry; immune function; metabolites

1. Tryptophan Metabolic Pathways

Dietary tryptophan in animals is utilized for protein synthesis and primarily catabolized in the liver. Tryptophan catabolism occurs through two main pathways: the 5-hydroxytryptamine (5-HT) pathway and the kynurenine pathway. Only about 5% of tryptophan is converted to 5-hydroxytryptophan by tryptophan hydroxylase, then decarboxylated to 5-HT, and finally converted to melatonin by N-acetyltransferase. The remaining 95% is metabolized along the kynurenine pathway under the action of two rate-limiting enzymes: tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO). Kynurenine is largely broken down by kynurenine hydroxylase into 3-hydroxykynurenine, which is then hydrolyzed by kynureninase to 3-hydroxyanthranilic acid. Through multiple enzymatic reactions, this yields bioactive molecules including quinolinic acid (QA), picolinic acids, and nicotinamide adenine dinucleotide (niacin). A small fraction is converted to kynurenic acid via kynurenine aminotransferase. Various bioactive substances produced during tryptophan metabolism—such as kynurenine, quinolinic acid, 5-HT, and melatonin—exhibit immunomodulatory effects. The metabolic pathways are illustrated in Figure 1 [Figure 1: see original paper].

2.1 IDO

IDO is the rate-limiting enzyme of the tryptophan/kynurenine pathway, widely expressed in mammalian tissues outside the liver, and plays a crucial role in tryptophan-mediated immune function. IDO can be induced by pro-inflammatory cytokines and other immunomodulatory factors, with interferon-γ being the most potent inducer that provides positive feedback regulation of tryptophan' s immune function during inflammation. Studies show that IDO gene expression increases in wild-type mice following inflammatory infection, while interferon-knockout mice show no change in IDO expression when challenged with the same bacterial infection. Tryptophan inhibits T cell proliferation and promotes apoptosis through IDO. On one hand, IDO depletes local tryptophan, arresting T cells in the G1 phase and inhibiting their proliferation. On the other hand, through the body' s self-regulating immune mechanisms, IDO catalyzes the production of kynurenine, altering intracellular oxidant-antioxidant balance to induce T cell apoptosis. IDO-expressing cells may inhibit T cell proliferation and activity by activating protein kinases on the T cell surface. As an intracellular enzyme, IDO creates a "tryptophan-depleted" microenvironment while activating general control non-derepressible 2 (GCN2) kinase to inhibit lymphocyte proliferation and differentiation, thereby exerting

anti-inflammatory effects. Additionally, tryptophan metabolites from the kynurenine pathway can serve as ligands for the aryl hydrocarbon receptor (AHR), binding to it and exerting immunosuppressive functions.

Recent findings also indicate that IDO can induce mitochondrial production of reactive oxygen species (ROS), which inhibit lymphocyte function and promote apoptosis. Natural killer (NK) cells exhibit higher sensitivity to ROS than other lymphocytes. As IDO metabolite levels increase, the activity or content of intracellular antioxidants such as catalase and glutathione decreases, leading to a relative increase in ROS and more pronounced inhibition of NK cell function. In summary, IDO influences lymphocyte function by degrading tryptophan in local tissues, playing important roles in metabolic immunoregulation during autoimmune diseases, chronic infections, maternal-fetal tolerance, and tumor escape.

2.2 Kynurenine

Kynurenine negatively regulates immune responses and inhibits the proliferative functions of both T cells and NK cells. It also promotes the differentiation of naïve T cells into regulatory T cells while preventing their differentiation into T helper 17 (Th17) cells by negatively regulating the immunogenicity of dendritic cells. Under the action of kynureninase, 3-hydroxykynurenine generates immunologically active substances including hydroxyanthranilic acid and quinolinic acid. Research demonstrates that appropriate levels of kynurenine and its products can suppress production of the pro-inflammatory cytokine interleukin-17 (IL-17), thereby inhibiting Th17 cell maturation and differentiation while promoting the conversion of CD4+ T cells into CD4+CD25+Foxp3+ regulatory T cells to alleviate inflammatory responses. Bauer et al. showed that kynurenine inhibits allogeneic T cell proliferation and induces T cell apoptosis in murine xenograft models. Further studies indicate that low-dose kynurenine can induce T cell apoptosis.

2.3 Quinolinic Acid

Quinolinic acid is an endogenous neurotoxin found at high concentrations in dendritic cells and macrophages rich in T cells, while being virtually absent in non-lymphoid cells. During inflammation, accelerated tryptophan degradation produces large amounts of quinolinic acid until the inflammation resolves. Research shows that quinolinic acid is primarily synthesized in immune cells and cannot be stored in the liver; its levels increase when immune cells are induced by interferon and other immune stimuli. 3-Hydroxykynurenine and quinolinic acid can induce apoptosis in T helper 1 (Th1) cells without affecting T helper 2 (Th2) cells. When administered simultaneously, some thymocytes exhibit atrophy similar to that seen with cyclophosphamide treatment.

2.4 5-HT and Melatonin

5-HT is a neurotransmitter that serves as an important immunomodulatory factor in neuroimmune regulation. It exerts immunological functions by binding different receptors and exhibits chemotactic effects on eosinophils, mast cells, and dendritic cells. 5-HT also increases production of IL-6 and IL-10—cytokines that promote humoral immune responses—in mature dendritic cells, thereby regulating adaptive immune responses. Additionally, 5-HT can enhance NK cell cytotoxicity, though the specific mechanism remains unclear.

Melatonin is a pineal hormone that promotes enlargement of immune organs such as the thymus and spleen, leading to hyperplasia of splenocytes and lymphocytes. It regulates immune balance by inducing macrophage production of interleukins and interferons, promoting immune factor release from immune cells. Administration of melatonin to mammals increases NK cell production and enhances monocyte activity in bone marrow. Esteban et al. demonstrated that melatonin promotes tumor cell apoptosis and may inhibit various cancers including breast, colon, and prostate cancer.

3. Antagonistic Effects of Tryptophan in Immune Function

Tryptophan and its major metabolites—including 5-HT and melatonin—exert immunomodulatory effects in livestock and poultry. However, interactions exist among certain amino acids in the body, particularly antagonistic effects when sharing the same absorption pathways. Tryptophan transport across the blood-brain barrier occurs via the same route as large neutral amino acids (leucine, isoleucine, valine, phenylalanine, and tyrosine). Research shows that tryptophan and branched-chain amino acids require common amino acid transporters (L-type amino acid transporter-1, LAT1) and albumin binding sites to cross the blood-brain barrier. The ratio of serum tryptophan to branched-chain amino acids directly affects brain tryptophan content. When dietary branched-chain amino acids increase, fewer tryptophan molecules cross the blood-brain barrier, reducing brain 5-HT levels. Since 5-HT acts on feeding centers in the hypothalamus to regulate feed intake, an imbalance in the tryptophan to branched-chain amino acid ratio decreases animal feed intake and compromises immune function. Therefore, dietary branched-chain amino acid levels must be adjusted when using tryptophan to modulate immune function.

4. Effects of Tryptophan on Immune Function in Livestock and Poultry

As a functional amino acid, tryptophan exerts varying degrees of immunomodulatory effects in different species and physiological stages. During inflammation or stress, tryptophan catabolism accelerates, promoting lymphocyte and immunoglobulin production to enhance humoral immunity. Tryptophan primarily exerts its immunomodulatory effects through its metabolites in various organs and tissues.

4.1 Pregnant Sows

Gestation is a critical developmental stage in pigs, where fetal growth, nutritional programming, and postnatal piglet health depend on maternal placental nutrient supply. The placenta serves as the site of maternal-fetal exchange, and its nutrient conversion capacity directly determines fetal nutrient acquisition. Research shows that placental trophoblasts, decidual cells, and decidual stromal cells express IDO, which regulates immune tolerance during pregnancy and embryonic development, protecting fetuses from maternal T cell attack and preventing miscarriage. Mosnier et al. found that when equal amounts of tryptophan were added to pregnant sow diets, less sensitive pigs had lower plasma tryptophan levels than sensitive responders, with low reactivity during gestation being more favorable for piglet birth. Kudo et al. observed that when tryptophan was added to physiological concentrations in vitro in human early pregnancy villous and term placental tissues without interferon-γ, only tryptophan and threonine were metabolized, with tryptophan levels decreasing significantly. While tryptophan influences immune tolerance during pregnancy, its mechanisms of action in placental nutrition and metabolism require further investigation.

4.2 Piglets

Piglets acquire immune protection through two main routes: immunoglobulins from colostrum and the development of their own immune system. Weaning imposes significant stress on piglets, and their immature immune systems make them susceptible to *Escherichia coli* infection. Tryptophan promotes differentiation of bone marrow T lymphocytes into mature T cells and increases blood immunoglobulin levels. Trevisi et al. orally challenged 21-day-old weaned piglets with *E. coli* and fed them tryptophan-adequate diets, finding that tryptophan-supplemented piglets showed significantly higher daily weight gain and blood IgA levels. Le Floc' h et al. found that IDO activity and associated lymph node numbers increased in pig lungs after pneumonia infection. When piglets were fed tryptophan-deficient diets, plasma levels of acute-phase protein binding protein (an inflammatory marker) were higher than in piglets receiving adequate tryptophan. These results indicate that the kynurenine pathway accelerates during immune responses, and dietary tryptophan can alleviate the negative effects of inflammation on piglets. Tryptophan requirements may increase when piglets experience inflammatory states or immune stress, which commonly occurs during weaning or lactation. Willemen et al. found that the tryptophan metabolite 5-HT could improve intestinal immunity in low-birth-weight and normal piglets, thereby reducing perinatal mortality.

4.4 Growing Pigs

Tryptophan is the only amino acid that binds to serum albumin and plays a vital role in immune processes. Melchior et al. found that plasma tryptophan levels were lower in pigs with induced pneumonia compared to healthy pigs, with tryp-

tophan being the only amino acid showing this effect, indicating increased tryptophan utilization during inflammation or disease. Tryptophan catabolism is essential for immune cells (macrophages and lymphocytes) to maintain immune function. Platten et al. showed that the tryptophan-IDO metabolic pathway is key to its immune function, with the metabolite anthranilic acid inhibiting pro-inflammatory cytokine production to prevent autoimmune neuroinflammation. Tryptophan metabolites affect T cell differentiation and B cell maturation, thereby influencing B cell capacity to secrete immunoglobulin G (IgG). Wang et al. added different levels of tryptophan and threonine to diets of growing pigs vaccinated with porcine reproductive and respiratory syndrome (PRRS) vaccine, finding increased serum immunoglobulin levels, suggesting tryptophan may enhance immune function by promoting inflammatory cytokine production. These findings align with Xu et al., who reported that diets with varying tryptophan and threonine content increased serum immune antibodies, interferon, IL-10, and interleukin-1β (IL-1β) levels in PRRS-challenged growing pigs, demonstrating tryptophan' s role in inflammatory response regulation.

4.5 Poultry

Tryptophan plays an important role in humoral immune regulation. Immune organs are structural tissues that execute immune functions and serve as critical sites for lymphocyte proliferation, differentiation, and immune responses. Research shows that tryptophan promotes spleen development, thereby enhancing immunity. Wei et al. fed Yangzhou geese diets with different tryptophan levels and found that appropriate dietary tryptophan increased spleen index and blood levels of IgG and IgM, indicating beneficial effects on spleen growth and immune function. Liu et al. also found that different tryptophan levels significantly improved immune organ development (spleen, thymus, bursa of Fabricius) in ducklings, enhancing immune function. Tryptophan stabilizes nucleopolysaccharides to facilitate globulin synthesis; deficiency leads to decreased IgM and IgG levels. Emadi et al. found that feeding tryptophan to broiler chickens challenged with infectious bursal disease virus (IBDV) significantly increased serum interferon-α, interferon-β, and IgG levels after approximately 30 days, indicating protective effects against bursal disease. Another study by Emadi et al. showed that appropriate tryptophan supplementation in IBDV-infected broilers at different ages significantly elevated serum interferon-α, interferon-γ, and IgG levels, demonstrating tryptophan' s importance in protective immune responses against IBDV.

4.6 Ruminants

In both monogastric and ruminant animals, amino acid metabolism is activated during inflammatory responses or immune system activation. As the third limiting amino acid in young lambs, tryptophan deficiency causes growth retardation, reduced feed intake, and poor disease resistance. High doses of tryptophan cause abnormal leukocyte aggregation, indicating active tryptophan metabolism in the

immune system. Preventing mastitis is a major challenge in dairy production; tryptophan acts on the thymic lymphatic system to promote T cell proliferation and differentiation, inducing production of numerous lymphokines that help reduce subclinical mastitis. As a rumen-protected additive, tryptophan can regulate rumen pH to prevent acidosis and subsequent laminitis. Additionally, the terminal metabolite niacin can alleviate energy stress in early lactation, regulate fat metabolism, and prevent ketosis.

In summary, tryptophan and its metabolites play crucial roles in regulating immune mechanisms in livestock and poultry, particularly in humoral immunity. The primary mechanisms involve regulating immunoglobulin and lymphocyte production to enhance immunity. However, current research on tryptophan' s immune-enhancing mechanisms has limitations, with limited understanding of the localization of tryptophan metabolites (such as kynurenine) and IDO in tissues, as well as their effects on immune cell proliferation and chemotaxis. Further research is needed.

References

[1] DOURMAD J Y, NOBLET J, ETIENNE M. Effect of protein and lysine supply on performance, nitrogen balance, and body composition changes of sows during lactation[J]. Journal of Animal Science, 1998, 76(2): 542-550.

[2] ZHOU B, LI H, ZOU X T, et al. Effects of tryptophan on lipid metabolism in laying hens[J]. Chinese Journal of Animal Science, 2011, 47(7): 50-53.

[3] WU G Y. Amino acids: metabolism, functions, and nutrition[J]. Amino Acids, 2009, 37(1): 1-17.

[4] WEINLICH G, MURR C, RICHARDSEN L, et al. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients[J]. Dermatology, 2007, 214(1): 8-14.

[5] WINDER B, LEBLHUBER F, WALLI J, et al. Tryptophan degradation and immune activation in Alzheimer' s disease[J]. Journal of Neural Transmission, 2000, 107(3): 343-353.

[6] ZHU B T. Development of selective immune tolerance towards the allogeneic fetus during pregnancy: role of tryptophan catabolites (Review)[J]. International Journal of Molecular Medicine, 2010, 25(6): 831-835.

[7] YAO K, FANG J, YIN Y L, et al. Tryptophan metabolism in animals: important roles in nutrition and health[J]. Front Biosci, 2011, 3: 286-297.

[8] MOFFETT J R, NAMBOODIRI M A. Tryptophan and the immune response[J]. Immunology and Cell Biology, 2003, 81(4): 247-265.

[9] SIKALIDIS A K. Amino acids immune response: a cysteine, glutamine, phenylalanine, tryptophan and arginine in t-cell function and cancer?[J]. Pathology & Oncology Research, 2015, 21(1): 9-17.

[10] BHUTIA Y D, BABU E, GANAPATHY V. Interferon-γ induces a tryptophan-selective amino acid transporter in human colonic epithelial cells and mouse dendritic cells[J]. Biochimica et Biophysica Acta: Biomembranes, 1848, 1848(2): 453–462.

[11] XU J, YAO N, LI Y D. T-cell proliferation is inhibited by the induction of indoleamine 2,3-dioxygenase spleen-derived dendritic cells rat[J]. Chinese Medical Journal, 2011, 124(19): 3154–3158.

[12] LE FLOC' H N, SEVE B. Biological roles of tryptophan and its metabolism: potential implications for pig feeding[J]. Livestock Science, 2007, 112(1/2): 23–32.

[13] ESTEBAN S, NICOLAUS C, GARMUND A, et al. Effect of orally administered L-tryptophan on serotonin, melatonin, and the innate immune response in the rat[J]. Molecular and Cellular Biochemistry, 2004, 267(1/2): 39–46.

[14] POORMASJEDI-MEIBOD M S, JALILI R B, HOSSEINI-TABATABAEI A, et al. Immuno-regulatory function of indoleamine 2,3 dioxygenase through modulation of innate immune responses[J]. PLoS One, 2013, 8(8): e71044.

[15] JALILI R B, FOROUZANDEH F, MOEENREZAKHANLOU A, et al. Mouse pancreatic islets are resistant to indoleamine 2,3 dioxygenase-induced general control nonderepressible-2 kinase stress pathway and maintain normal viability and function[J]. The American Journal of Pathology, 2009, 174(1): 196–205.

[16] MEZRICH J D, FECHNER J H, ZHANG X J, et al. An interaction between kynurenine and the hydrocarbon receptor generate regulatory T cells[J]. The Journal Immunology, 2010, 185(6): 3190–3198.

[17] KUDO Y, BOYD C A, SARGENT I L, et al. Tryptophan degradation by human placental indoleamine 2,3-dioxygenase regulates lymphocyte proliferation[J]. The Journal Physiology, 2001, 535(Pt 1): 207–215.

[18] PRENDERGAST G C, SMIITH C, THOMAS S, et al. Indoleamine 2,3-dioxygenase pathways pathogenic inflammation immune escape cancer[J]. Cancer Immunology, Immunotherapy, 2014, 63(7): 721–735.

[19] KOLODZIEJ L. Systemic metabolism of tryptophan and its catabolites, kynurenine and 3-HAA, in mice with inflammatory arthritis[J]. Gene, 2013, 512(1): 23–27.

[20] BAUER T M, JIGA L P, CHUANG J J, et al. Studying the immunosuppressive role of indoleamine 2,3-dioxygenase: tryptophan metabolites suppress rat allogeneic T-cell responses in vitro and in vivo[J]. Transplant International, 2005, 18(1): 95–100.

[21] FALLARINO F, GROHMANN U, VACCA C, et al. T cell apoptosis by tryptophan catabolism[J]. Cell Death & Differentiation, 2002, 9(10): 1069–1077.

[22] CHIARUGI A, CALVANI M, MELI E, et al. Synthesis and release of neurotoxic kynurenine metabolites human monocyte-derived macrophages[J]. Journal Neuroimmunology, 2001, 120(1/2): 190–198.

[23] AHERN G P. 5-HT immune system[J]. Current Opinion Pharmacology, 2011, 11(1): 29–33.

[24] LI N, GHIA J E, WANG H, et al. Serotonin activates dendritic cell function in the context of gut inflammation[J]. The American Journal of Pathology, 2011, 178(2): 662-671.

[25] MACGILLIVRAY L, REYNOLDS K B, SICKAND M, et al. Inhibition of the serotonin transporter induces microglial activation and downregulation of dopaminergic neurons in the substantia nigra[J]. Synapse, 2011, 65(11): 1166-1172.

[26] MAESTRONI G J M. The immunoneuroendocrine role of melatonin[J]. Journal of Pineal Research, 1993, 14(1): 1-10.

[27] REITER R J. Oxidative damage the central nervous system: protection by melatonin[J]. Progress in Neurobiology, 1998, 56(3): 359–384.

[28] LECHNER O, DIETRICH H, DOS SANTOS A O, et al. Altered circadian rhythms of the stress hormone and melatonin response in lupus-prone MRL/MP-fasIpr mice[J]. Journal of Autoimmunity, 2000, 14(4): 325-333.

[29] HAWKINS R A, O' KANE R L, SIMPSON I A, et al. Structure of the blood–brain barrier and its role in the transport of amino acids[J]. The Journal of Nutrition, 2006, 136(1): 218S–226S.

[30] YAMAMOTO T, NEWSHOLME E A. Diminished central fatigue by inhibition of the L-system transporter for the uptake of tryptophan[J]. Brain Research Bulletin, 2000, 52(1): 35–38.

[31] ASOR E, STEMPER S, AVITAL A, et al. The role of branched chain amino acid and tryptophan metabolism rat' s behavioral diversity: intertwined peripheral and brain effects[J]. European Neuropsychopharmacology, 2015, 25(10): 1695–1705.

[32] HENRY Y, SÈVE B, COLLÉAUX Y, et al. Interactive effects of dietary levels of tryptophan and protein on voluntary feed intake and growth performance in pigs, in relation to plasma free amino acids and hypothalamic serotonin[J]. Journal of Animal Science, 1992, 70(6): 1873–1887.

[33] BADAWY A A B. The tryptophan utilization concept in pregnancy[J]. Obstetrics & Gynecology Science, 2014, 57(4): 249–259.

[34] MOSNIER E, DOURMAD J Y, ETIENNE M, et al. Feed intake in the multiparous lactating sow: its relationship with reactivity during gestation and tryptophan status[J]. Journal of Animal Science, 2009, 87(4): 1282–1291.

[35] TREVISI P, MELCHIOR D, MAZZONI M, et al. A tryptophan-enriched diet improves feed intake and growth performance of susceptible weanling pigs orally challenged with *Escherichia coli* K88[J]. Journal of Animal Science, 2009, 87(1): 148–156.

[36] LE FLOC'H N, MELCHIOR D, SÈVE B. Chronic lung inflammation affects plasma amino acid concentrations in pigs[J]. Journal of Animal Science, 2004, 82(4): 1091–1099.

[37] WILLEMEN S A, CHE L, DEWILDE S, et al. Enteric and serological distribution of serotonin precursor tryptophan perinatal normal weight piglets[J]. Animal, 2014, 8(5): 792–799.

[38] ROBERTSON S A, CARE A S, SKINNER R J. Interleukin 10 regulates inflammatory cytokine synthesis to protect against lipopolysaccharide-induced abortion and fetal growth restriction in mice[J]. Biology of Reproduction, 2007, 76(5): 738–748.

[39] KUDO Y. The role of placental indoleamine 2,3-dioxygenase in human pregnancy[J]. Obstetrics & Gynecology Science, 2013, 56(4): 209–216.

[40] QIU S X. Effects of dietary tryptophan levels on reproductive performance and immune function in pregnant mice infected with pseudorabies virus[D]. Master' s thesis. Ya' an: Sichuan Agricultural University, 2009.

[41] POLETTO R, KRETZER F C, HÖTZEL M J. Minimizing aggression during mixing of gestating sows with supplementation of a tryptophan-enriched diet[J]. Physiology & Behavior, 2014, 132: 36–43.

[42] MELCHIOR D, LE MELCHIOR N, SÈVE B. Effects of chronic lung inflammation on tryptophan metabolism in piglets[M]//ALLEGRI G, COSTA C V L, RAGAZZI E, et al. Developments in tryptophan and serotonin metabolism. New York: Springer-Verlag, 2003, 527: 359–362.

[43] PLATTEN M, HO P P, YOUSSEF S, et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite[J]. Science, 2005, 310(5749): 850–855.

[44] FALLARINO F, GROHMANN U, YOU S, et al. The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor -chain and induce a regulatory phenotype in naive T cells[J]. The Journal of Immunology, 2006, 176(11): 6752–6761.

[45] WANG J, ZHAO Y F, FANG Z F, et al. Effects of dietary threonine and tryptophan supplementation on immune response in growing pigs vaccinated with porcine reproductive and respiratory syndrome attenuated vaccine[J]. Chinese Journal of Animal Nutrition, 2013, 25(6): 1189–1198.

[46] XU S Y, SHEN J, FANG Z F, et al. Effects of dietary threonine and tryptophan supplementation on growing pigs induced by porcine respiratory and reproductive syndrome vaccination[J]. Archives of Animal Nutrition, 2014, 68(5):

385-397.

[47] WEI Z Y, WANG H R, PAN X H, et al. Effects of feeding methods and dietary tryptophan levels on immune function and antioxidant indices in Yangzhou geese[J]. Chinese Journal of Animal Nutrition, 2012, 24(12): 2356-2365.

[48] LIU X T, WANG A, YANG X R, et al. Effects of tryptophan on growth performance, antioxidant function, and immune organ development in ducklings[J]. Feed Industry, 2012, 33(10): 5-8.

[49] EMADI M, JAHANSHIRI F, Kaveh K, et al. Nutrition and immunity: the effects of the combination of arginine and tryptophan on growth performance, serum parameters and immune response in broiler chickens challenged with infectious bursal disease vaccine[J]. Avian Pathology, 2011, 40(1): 63-72.

[50] EMADI M, JAHANSHIRI F, KAVEH K, et al. Tryptophan stimulates immune response in broiler chickens challenged with infectious bursal disease vaccine[J]. Journal of Animal and Veterinary Advances, 2010, 9(3): 610-616.

[51] VAN E NOLTE J, LÖEST C A, FERREIRA A V, et al. Limiting amino acids for growing lambs ruminally undegradable protein[J]. Journal of Animal Science, 2008, 86(10): 2627-2641.

[52] MELZER N, WITTENBURG D, HARTWIG S, et al. Investigating associations between milk metabolite profiles and milk traits of Holstein cows[J]. Journal of Dairy Science, 2013, 96(3): 1521-1534.

[53] HERNÁNDEZ J, BENEDITO J L, ABUELO A, et al. Ruminal acidosis in feedlot: from aetiology to prevention[J]. The Scientific World Journal, 2014, 2014: 1-8.

[54] RUNGRUANG S, COLLIER J L, RHOADS R P, et al. A dose-response evaluation of rumen-protected niacin in thermoneutral or heat-stressed lactating Holstein cows[J]. Journal of Dairy Science, 2014, 97(8): 5023-5034.

Note: Figure translations are in progress. See original paper for figures.