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Tryptophan metabolism in animals: important roles in nutrition and health

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1. ABSTRACT

L-Tryptophan is a nutritionally essential amino acid for monogastric animals and preweaning ruminants because it cannot be synthesized in the body. Besides serving as a building block for proteins, tryptophan is a critical nutrient for the functions of nervous and immune systems. Over the past decades, much attention has been directed to study the role of tryptophan as a limiting amino acid in mammalian and avian nutrition. However, emerging evidence from recent studies shows that tryptophan and its metabolites [e.g., serotonin (5-hydroxytryptamine, 5-HT) and melatonin)] can regulate feed intake, reproduction, immunity, neurological function, and anti-stress responses. Additionally, tryptophan may modulate gene expression and nutrient metabolism to impact whole-body homeostasis in organisms. Thus, adequate intake of this amino acid from the diet is crucial for growth, development, and health of animals and humans.

2. INTRODUCTION

L-Tryptophan (TRP; L-α-aminoindole-3-propionic acid) is a nutritionally essential amino acid for monogastric animals (e.g., humans, pigs, dogs, rats, mice, and chickens) and preweaning ruminants (e.g., calves and lambs) due to the lack of endogenous synthesis (1). It is a white powder and a neutral amino acid with the pI value of 5.96 [pKa (α-COOH) = 2.46; pKa (α-NH_3^+ = 9.41). TRP was first isolated from casein in 1902 by F.G. Hopkins using base hydrolysis. Like some amino acids (e.g., homocysteine and cysteine), TRP binds non-covalently with serum albumin. The primary function of TRP is to serve as a building block in protein biosynthesis. However, TRP's metabolites are key neurotransmitters, thereby regulating immune responses and the function of the nervous system (1). Thus, TRP plays an important role in metabolism, physiology, growth and development of organisms (2). The aim of this review is to highlight recent developments in TRP metabolism and

nutrition, with particular reference to the regulation of feed intake, reproduction, immunity, growth, neurological function, and anti-stress response.

3. METABOLISM AND NUTRITION OF TRP IN ANIMALS

3.1. Pathways of TRP metabolism

Two sources contribute to the free TRP pool in plasma: the diet and intracellular protein degradation. They provide approximately 1/3 and 2/3 of the TRP's whole-body flux, respectively. Because TRP is not synthesized by animal cells, the diet is the ultimate source of this amino acid in the body. In monogastric animals, microbes in the lumen of the large intestine can ferment undigested foods and produce TRP. However, this synthetic event provides little TRP to the host because the amount is quantitatively small and the absorption of TRP by colonocytes is limited. Thus, monogastric animals cannot grow or maintain a positive nitrogen balance when fed a TRP-free diet (1). TRP is metabolized via three pathways in mammals: (a) hydroxylation and decarboxylation of TRP to generate serotonin (5-hydroxytryptamine, 5-HT); (b) deamination and decarboxylation of TRP to yield indoleacetic acid; and (3) degradation of TRP to niacin, pyruvate and acetyl-CoA through kunurenine formation (Figure 1). Nicotinamide, serotonin and melatonin (N-acetyl- 5-methoxytryptamine) are important bioactive compounds derived from TRP (2). In healthy adult mammals, over 95% of the ingested TRP is catabolized primarily in the liver via the kynurenine (KYN) pathway. However, only 1–2% and 2-3% of dietary TRP are converted into serotonin (mainly in the small intestine but, to a much lesser extent, other tissues including the lactating mammary gland) and indoleacetic acid (mainly in the gastrointestinal tract and liver), respectively (3-5). The gastrointestinal tract contains 80-90% of serotonin in the body.

The first and rate-controlling step in this pathway (namely the conversion of TRP to KYN) is catalyzed by either the ubiquitous indoleamine 2, 3-dioxygenase (IDO) (4, 5) or TRP 2, 3-dioxygenase (TDO) which is primarily localized to the liver (6). Notably, tetrahydrobiopterin is an essential cofactor for IDO, TDO, and TRP hydroxylase. The expression of IDO is strongly influenced by the state of the immune system in that IDO activity is potently induced by inflammatory cytokines (e.g., interferon-γ) and endotoxin. In contrast, TDO activity is increased by TRP and its analogues via an allosteric binding site, but is competitively inhibited by some common indoleamines, including tryptamine (6).

Metabolism through the KYN pathway primarily results in the formation of quinolinic acid, particularly via the production of 3-hydroxykynurenine and 3-hydroxyanthranilic acid. Quinolinic acid may be metabolized further to nicotinamide or nicotinic acid (7). The kynurenine pathway also produces kynurenic acid, picolinic acid, 5-hydroxyanthranilic acid, and xanthurenic acid, leading to the generation of pyruvate and acetyl-CoA. The KYN- and serotonin-synthetic pathways share TRP as the common nitrogenous substrate. Therefore, competition for TRP exists between nicotinic acid and serotonin synthesis in animals. Proinflammatory cytokines can induce IDO under stressful or disease conditions, activate the KYN pathway, and reduce 5-HT synthesis (8).

3.2. TRP metabolites

Nitrogenous products of TRP catabolism include serotonin, N-acetylserotonin, melatonin, anthranilic acid, and ammonia (1). Serotonin is a biogenic amine which functions as: (a) a neurotransmitter; (b) a regulator of gastrointestinal secretion, motility, and sensation; (c) a modulator of cognition, sleep, mood, and appetite; and (d) a mediator of a number of neurological diseases [e.g., mental disorders (2,9-11)]. At elevated concentrations, serotonin is capable of promoting oxidative stress in cellular systems or tissues (12). There is also evidence that an increase in serotonin synthesis can be a sensitive biomarker of oxidative stress and the generation of reactive oxygen/nitrogen species (11,12). Serotonin can also act through specific membrane receptors involved in numerous physiological functions (1,2). Interestingly, exogenous serotonin can increase fecal pellet output in rats and cause diarrhea in mice (13).

Melatonin is a versatile and ubiquitous hormonal molecule (14). It is widely distributed throughout the body, especially in the gastrointestinal tract (15) where melatonin is produced by mucosal enteroendocrine cells. Melatonin exerts strong anti-inflammatory effects due to an inhibition of NF-kB and TNF-α expression (16). Melatonin and TRP show strong protective efforts on the gastric mucosa and accelerate ulcer healing, while stimulating pancreatic exocrine function via mechanisms involving enteropancreatic reflexes and cholecystokinin (CCK) (17). Additionally, melatonin and TRP may limit or reverse some of the changes that occur in age-related sleep-wake rhythms and body temperatures (18).

Metabolites of the KYN pathway have either neurotoxic or neuroprotective activities depending on products, in that 3-hydroxykynurenine and quinolinic acid are neurotoxic whereas kynurenic acid is neuroprotective (8). For example, quinolinic acid, as one of the metabolites of TRP produced along an alternative branch of the KYN pathway, has excitotoxic properties in the brain and the peripheral nervous system due to: (a) potent action on NR2A and NR2B; (b) activation of N-methyl-D-aspartic acid (NMDA) receptor subtypes; and (c) an ability to generate free radicals independently of receptor-mediated mechanisms (19). Of particular note, physiological concentrations of kynurenic acid acts as an antagonist of ionotropic glutamate receptors (20,21) and an NMDA receptor antagonist through its competitive blockade of the glycine co-agonist site (19). However, pathological levels of kynurenic acid contribute to the pathogenesis of neurological diseases by interfering with membrane receptors and cell signaling (22-25).

Niacin is a component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) (1).Nicotinic acid (nicotinate) is the form

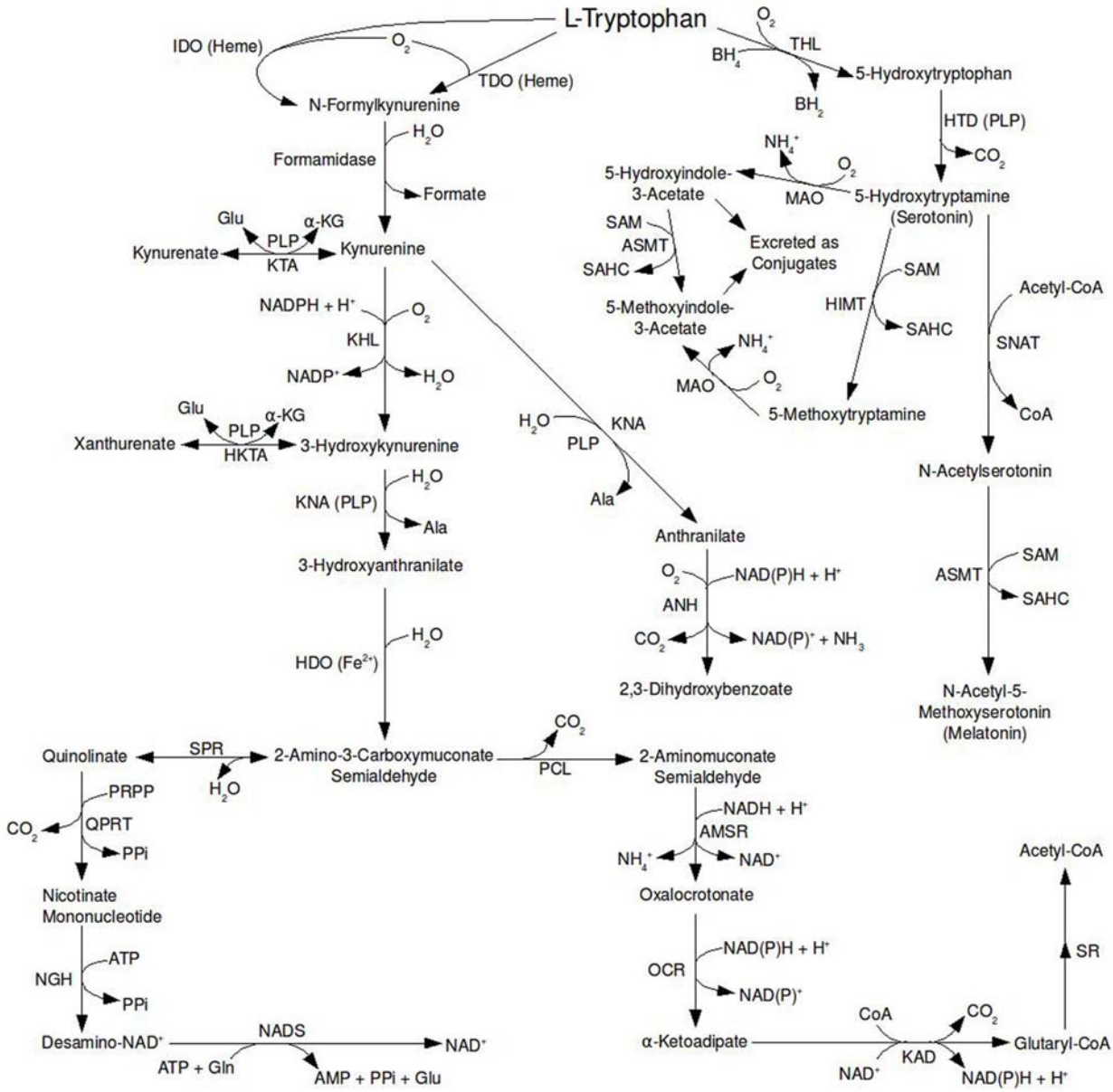

Figure 1. L-Tryptophan catabolism in animals. Degradation of L-tryptophan is initiated by indoleamine 2, 3-dioxygenase, tryptophan 2, 3-dioxygenase, and tryptophan hydroxylase. Important products include NAD, serotonin, melatonin, kynurenine, indoles, and acetyl-CoA. L-tryptophan is both a ketogenic and glucogenic amino acid.

of niacin required for the synthesis of NAD and NADP by enzymes present in the cytosol of most cells. NAD and NADP are coenzymes for many oxidoreductase enzymes involved in the metabolism of nutrients (e.g., carbohydrate, fatty acids, and amino acids) and exogenous substances (e.g., alcohol). In addition, NAD is as a substrate for poly(ADP-ribose) polymerase which catalyzes the attachment of ADP-ribose to various chromosomal proteins, thereby participating in the post-translational modifications of a variety of proteins. Thus, nicotinamide is essential for normal physiological function through the formation of NAD(P) and redox reactions in all cells.

3.3. TRP and immunity

A new, exciting development in TRP research is that TRP metabolism is altered markedly in immune cells and many of other cell types (e.g., neurons) in response to proinflammatory cytokines. This new knowledge may help explain the etiological and pathophysiological mechanisms responsible for impaired immunity and depression in subjects under stressful conditions (8). Most of indolic compounds in living organisms are derived from TRP. These TRP products are not sensitive to nitric oxide, oxygen or superoxide anion, but react directly with other reactive oxygen and reactive nitrogen species, yielding various derivatives (26-28). Additionally, TRP metabolites may

contribute to pathological alterations in diabetes (27) and the KYN pathway has been identified as a potential source of biomarkers for the irritable bowel syndrome (28).

As noted previously, IDO can affect serotonergic and glutamatergic functions through immune activation, including infection and autoimmunity (29). This enzyme also has a complex role in pregnancy, transplantation, and neoplasia (15,30-32). For example, exerting a fine control over inflammatory and adaptive antifungal responses can suppress the growth of intracellular bacteria, viruses, and parasites (5, 33, 34), as well as mediate the inflammatory–anti-inflammatory state of dendritic cells in response to Candida and Aspergillus infection (35,36). The IFN-γ–IDO axis may also accommodate fungal persistence in the host (37). Moreover, the expression of IDO is regulated by factors produced in the immune system, with IFNγ and TNFα being the main inducers. Interestingly, IDO is expressed in nearly all human cells in response to stimulation by these cytokines. Furthermore, IDO expression is regulated by other immunologically active molecules such as prostaglandins (38) and the surface proteins CTLA4 (39), CD40 (40), and toll-like receptors (TLR) (41). Activation of IDO results in a decreased availability of TRP, which can inhibit T-cell proliferation (42). A particularly high IDO activity can lead to a nearly complete depletion of TRP at the site of infection, which arrests the growth of several TRP-dependent microorganisms (43,44). Histochemical studies revealed the presence of IDO in female reproductive organs and alterations of its expression during pregnancy, a physiological event that is associated with immunological activation in the placenta and uterus (45). Interestingly, concentrations of KYN and TRP in plasma reflect poorly IDO expression in the conceptus during early gestation, but a closer relationship was detected during the last month of pregnancy in humans (45-48). This is likely due to multiple factors that regulate TRP absorption and catabolism, intracellular protein turnover, and excretion of KYN from the body.

3-Hydroxy-DL-kynurenine and α-picolinic acid may contribute to the anti-infectious activity of allografts by directly inhibiting the growth of microorganisms (49). The antimicrobial mechanism of 3-hydroxy-DL-kynurenine is unknown but may involve blockage of protein synthesis. In contrast, there is evidence that deprivation of iron by α-picolinic acid is attributable to its direct antimicrobial activity (50). This raises an important question of whether TRP in the lumen of the gastrointestinal tract may be beneficial for controlling microbial population and numbers.

In patients with multiple trauma, TRP deficiency has been found to be associated with the decline of lymphocyte numbers (51) as a result of IDO activation (52). Inflammatory conditions are associated with increased TRP catabolism and decreased TRP availability in cells (53). For example, Increases in IDO activity and TRP incorporation into acute phase proteins could explain TRP deficiency in pigs suffering from chronic lung inflammation (54). A moderate inflammatory response is evident in animals when the sanitary quality of environment is compromised. Additionally, poor sanitary conditions lead to alterations of TRP metabolism, therefore reducing that the amount of TRP available for growth and other metabolic functions in the host (55). Similarly, the induction of TRP degradation by inflammatory agents results in reduced growth of pathogens and cancer cells by depriving them of TRP (4). TRP deficiency also occurs in people with wounds (56) due to elevated catabolism of TRP via the KYN pathway. Thus, while KYN production plays an important role in mediating tolerance to infection (57), TRP supply from the diet may be augmented in response to immunological challenges.

Oral administration of TRP (125 mg/kg body weight) enhanced the phagocytic activity of macrophages and detoxification of superoxide anion radicals derived from immune cells, possibly through the generation of immunoregulatory molecules, serotonin, and melatonin (58). In a porcine model of dextran sodium sulfate (DSS)-induced colitis, oral administration of TRP could reduce inflammation and enhance the rate of recovery from the disease (59). The TRP treatment also decreased the expression of proinflammatory cytokines [including TNF-α, interleukin (IL)-6, interferon (IFN)-γ, IL-12p40, IL-1β, IL-17, and IL-8] and intracellular adhesion molecule-1 (59). These findings indicate that TRP may be an effective immunomodulatory agent for the treatment of the irritable bowel syndrome (59)

3.4. TRP and neurological function

Like other essential amino acids, TRP must be supplied in the diet to support the growth, development, and function of the brain and peripheral nervous organs (1). TRP is transported into neurons by neutral amino acid carriers which are also shared by other large neutral amino acids (phenylalanine, leucine, isoleucine, tyrosine and valine) (61). Through changes in serotonergic activity, TRP has been implicated in the regulation of synthesis of key neurotransmitters (1, 60). Thus, TRP has been used to treat neurological disorders, including depression, schizophrenia, dysregulation of food intake, and other neuropsychiatric diseases (1).

An appropriate balance of dietary amino acids is important for neuronal TRP metabolism and thus the function of the nervous system. For example, serotonin synthesis depends on extracellular concentrations of both TRP and other large neutral amino acids because they compete with TRP for transport across the blood-brain barrier. When serum TRP concentrations are elevated, the availability of TRP in the brain and other organs is increased, resulting in enhanced synthesis of serotonin in serotonergic neurons and pinealocytes of the pineal gland (62). Thus, oral administration of TRP enhances serotonin levels in both plasma and different brain regions (63). Conversely, dietary deficiency of TRP leads to low levels of brain serotonin (64) and altered neurological function (65). Acutely lowering serotonin synthesis by TRP depletion promoted the intake of sweet-tasting foods by overweight individuals due to serotonergic involvement in the control of food consumption (66). Hydrolyzed protein could augment brain TRP and serotonin levels, therefore

improving mood and cognitive reactivity to depression (67). Additionally, oral administration of TRP (150-300 mg/kg) to rats and chicks results in a rapid and dose-dependent elevation of melatonin in plasma (68, 69). Also, TRP supplementation may ameliorate poor appetite in human subjects (70).

3.5. Dietary requirements of TRP

Accurate data on dietary TRP requirements by animals and humans critically depend on accurate analysis of TRP in diets. Unfortunately, many investigators did not determine TRP content in experimental diets for animals or humans due to its complete loss under conditions of acid hydrolysis. Based on nitrogen balance studies, good-quality protein intake and TRP intake of healthy adult subjects (both men and women) could be recommended at 0.8 g and 4 mg/day per kg body weight, respectively (67). There has been much research on TRP requirements by poultry, pigs, cattle and sheep because they are agriculturally important species worldwide (70-79). This work has made important contributions towards enhancing the efficiency of nutrient utilization by animals.

TRP is considered as the third or fourth limiting amino acid in typical corn- and soybean meal-based diets for young pigs after lysine, methionine, and threonine (73). TRP deficiency reduces food intake, protein synthesis rate, RNA activity, and growth in undernourished early-weaned piglets (73,77). Interestingly, piglets are able to detect metabolic changes induced by TRP deficiency and respond with an aversion against the TRP-deficient diet (74). Feeding a TRP-supplemented diet to pigs increased feed intake, the amounts of Cl^- and H^+ secreted from the intestinal mucosa, efficiency of nutrient utilization for protein accretion, and growth performance, when compared with unsupplemented controls (74,77,78). The TRP supplementation may also reduce aggression and alleviate stress in many species, including pigs (78) and chickens (79). Notably, oral ingestion of TRP enhanced plasma concentrations of ghrelin [a gastrointestinal hormone which regulates food intake in both piglets and lactating sows (71,80)] and serotonin (81) in pigs.

The current NRC recommendations for the requirements of dietary TRP (total TRP in diets) by swine were based on a summary of studies published by various scientists (82-88). The values are 0.27, 0.24, 0.21, 0.17, 0.14, and 0.11% of diets for pigs weighing 3-5, 5-10, 10-20, 20-50, 50-80, and 80-120 kg, respectively (82). In the ideal protein, lysine is used as a reference amino acid relative to requirements of other amino acids. A ratio of TRP to lysine between 0.17 and 0.18 appeared to be sufficient to yield high feed intake and high growth rates in young pigs fed a diet containing adequate amounts of lysine and other amino acids (83,84). However, this ratio should be increased to 0.195 to maximize growth performance in young pigs fed wheat- and barley-based diets deficient in TRP (85,86). Dietary TRP requirements (total TRP in diets) for gestating and lactating pigs have been estimated to be 0.11% and 0.15-0.19% of diets, respectively, depending on body weight change (82). The efficiency of crystalline TRP for growth or protein deposition may be lower than that of protein-bound TRP (89,90), but compelling evidence is required to test this hypothesis. Nonetheless, dietary supplementation with TRP is effective in increasing growth performance and feed efficiency in young pigs fed a TRP-deficient diet.

3.6. Safety of oral TRP and its metabolites

TRP is widely available on the market as a supplement for both animals and humans. However, there have been concerns that excess administration of TRP may cause oxidative stress in the cerebral cortex (91), as well as other adverse effects, including ataxia, tremors, diaphoresis, blurred vision, dry mouth, muscle stiffness, palpitations, urticaria, and the "eosinophilia–myalgia syndrome" (EMS) (92-97). However, some of these side effects might have been caused by contaminated substance(s) in the former TRP preparations, but not TRP itself. Two lines of evidence indicate that growing-finishing pigs (79-119 kg body weight) pigs can tolerate considerable excesses of TRP and that oral ingestion of TRP is safe for swine. First, supplementing 0.1 or 1% TRP to a typical com- and soybean meal-based diet did not adversely affect growth performance or blood variables (leukocyte and eosinophil counts, as well as activities of aspartate transferase, creatine phosphokinase, and lactate dehydrogenase). Second, mortality did not occur in pigs receiving acute intragastric administration of TRP at doses of 2 and 5.71 g/kg body weight. TRP excretion and the ratio of anthranilic acid to kynurenic acid in urine could be useful indicators of excessive TRP intake (94).

5-Hydroxy-L-tryptophan (5-HTP), an intermediate in the biochemical synthesis of serotonin from TRP, is a popular dietary supplement for humans. This TRP metabolite may ameliorate depression, improve the debilitating symptoms of fibromyalgia, aid in weight loss, reduce blood pressure, prevent headaches, and treat insomnia (98-100). Dietary supplementation with 5-HTP may be beneficial for subjects who could not tolerate a large dose of TRP. An important difference between TRP and 5-HTP is that 5-HTP can act as an antioxidant whereas excess TRP can cause oxidative damage (98). Oral 5-HTP is well absorbed and can be taken with meals (99). Additionally, 5-HTP easily crosses the blood-brain barrier and is readily transported by neurons (99). There is no evidence to implicate 5-HTP as a cause of the EMS or related disorders (100).

4. SUMMARY AND PERSPECTIVES

Tryptophan plays versatile roles in nutrition and physiology, particularly food intake, neurological function and immunity (1,101,102). Thus, there is growing interest in TRP requirements by mammalian, avian, and aquatic species (103-107). Diets for animals and humans must contain adequate TRP to maintain growth, nitrogen balance, and health, because this amino acid cannot be synthesized in the body (102). Optimal amounts of TRP in diets likely depend on species, developmental stages, environmental factors, and health status. Tryptophan is usually the fourth limiting amino acid in cereal-based diets for weanling and growing pigs under practical conditions (after lysine,

methionine, and threonine). Through reduction in syntheses of proteins and neurotransmitters, deficiency of TRP results in retarded growth and neurological dysfunction. Available evidence shows that dietary supplementation with up to 1% TRP is safe for swine (an excellent animal model for studying human nutrition). Undoubtedly, research on TRP is exciting and fruitful. At present, little is known about effects of TRP on (a) pregnancy or lactation, which are important events in the mammalian life (108-111); (b) cellular signaling, which is a major mechanism for metabolic control (112-119); or (c) gene expression (including epigenetics), a highly specific process in which a gene can be switched on or off in response to regulatory factors (120). With the recent developments of omics techniques (e.g., genomics, proteomics, and metabolomics) (121-128) and bioinformatics (126), researchers now have powerful tools to study regulatory roles for TRP in gene and protein expression. Such a revolutionary approach is expected to rapidly provide new and comprehensive information about TRP metabolism and nutrition in organisms under both physiological and pathophysiological conditions.

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6. REFERENCES

1. Gerald Huether, Walter Kochen, Thomas J Simat and Steinhart Hans: Tryptophan, serotonin, and melatonin: Basic aspects and applications. *Kluwer Academic/Plenum Publ*, NY (1999)

2. Nathalie Le Floc'h and Bernard Seve: Biological roles of tryptophan and its metabolism: Potential implications for pig feeding. *Livest Sci* 112, 23-32 (2007)

3. Robert Schwarcz, Arash Rassoulpour, Hui-Qiu Wu, Deborah Medoff, Carol A. Tamminga and Rosalinda C. Roberts: Increased cortical kynurenate content in schizophrenia. *Biol Psychiatry* 50(7), 521-30 (2001)

4. Milton W. Taylor and Gensheng Feng: Relationship between interferon-gamma, indoleamine-2,3-dioxygenase, and tryptophan catabolism. *FASEB* 5(11), 2516-22 (1991)

5. R. R. Brown, Y. Ozaki, S. P. Datta, E. C. Borden, P. M. Sondel and D. G. Malone: Implications of interferon-induced tryptophan catabolism in cancer, auto-immune diseases and AIDS. *Adv Exp Med Biol* 294, 425-35 (1991)

6. Jon P. Ruddick, Andrew K. Evans, David J. Nutt, Stafford L. Lightman, Graham A.W. Rook and Christopher A. Lowry: Tryptophan metabolism in the central nervous system: medical implications. *Expert Rev Mol Med* 8(20), 1-27 (2006)

7. Trevor W. Stone and L. Gail Darlington: Endogenous kynurenines as targets for drug discovery and development. *Nat Rev Drug Discov* 1(8), 609-20 (2002)

8. Hideki Miura, Norio Ozaki, Makoto Sawada, Kenichi Isobe , Tatsuro Ohta and Toshiharu Nagatsu: A link between stress and depression: Shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. *Stress* 11(3), 198-209 (2008)

9. Peter G. McLeana, Richard A. Bormana and Kevin Lee: 5-HT in the enteric nervous system: gut function and neuropharmacology. *Trends Neurosci* 30(1), 9-13 (2007)

10. Dennis S. Charney: Monoamine dysfunction and the pathophysiology and treatment of depression. *J Clin Psychiatry* 59 Suppl 14, 11-4 (1998)

11. Irwin Lucki: The spectrum of behaviors influenced by serotonin. *Biol Psychiatry* 44(3), 151-62 (1998)

12. Luciane Rosa Feksa, Alexandra Latini, Virgínia Cielo Rech, Moacir Wajner, Carlos Severo Dutra-Filho, Angela Terezinha de Souza Wyse and Clovis Milton Duval Wannmacher: Promotion of oxidative stress by L-tryptophan in cerebral cortex of rats. *Neurochem Int* 49(1), 87-93 (2006)

13. Keiji Miyata, Takeshi Kamato, Akito Nishida, Hiroyukito, Hidenobu Yuki, Mayumi Yamano, Aie Tsutsumi, Yoshinori Katsuyama and Kazuo Honda: Role of the serotonin3 receptor in stress-induced defecation. *J Pharmacol Exp Ther* 261(1), 297-303 (1992)

14. Rüdiger Hardeland, S.R. Pandi-Perumal and Daniel P. Cardinali: Melatonin. *Int J Biochem Cell Biol* 38(3), 313-316 (2006)

15. S. J. Konturek, P. C. Konturek, T. Brzozowski, G. A. Bubenik: Role of melatonin in upper gastrointestinal tract. *J Physiol Pharmacol* 58 Suppl 6, 23-52 (2007)

16. P. C. Konturek, G. Burnat, T. Brzozowski, Y. Zopf, S. J. Konturek: Tryptophan free diet delays healing of chronic gastric ulcers in rat. *J Physiol Pharmacol* 59 Suppl 2, 53-65 (2008)

17. Nawrot-Porabka K, Jaworek J, Leja-Szpak A, Szklarczyk J, Kot M, Mitis-Musioł M, Konturek SJ, Pawlik WW: Involvement of vagal nerves in the pancreatostimulatory effects of luminal melatonin, or its precursor L-tryptophan. Study in the rats. *J Physiol*

Pharmacol 58 Suppl 6, 81-95 (2007)

18. Sergio D. Paredes, Ana M Marchena, Ignacio Bejarano, Javier Espino, Carmen Barriga, Ruben V. Rial, Russel J. Reiter and Ana B. Rodríguez: Melatonin and tryptophan affect the activity-rest rhythm, core and peripheral temperatures, and interleukin levels in the ringdove: changes with age. *J Gerontol A Biol Sci Med Sci* 64(3), 340-50 (2009)

19. Robert Schwarcz and Roberto Pellicciari: Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. *J Pharmacol Exp Ther* 303(1), 1-10 (2002)

20. Kenton J. Swartz, Matthew J. During, Andrew Freese and M. Flint Beal: Cerebral synthesis and release of kynurenic acid: an endogenous antagonist of excitatory amino acid receptors. *J Neurosci* 10(9), 2965-73 (1990)

21. Trevor W Stone: Inhibitors of the kynurenine pathway. *Eur J Med Chem* 35(2), 179-86 (2000)

22. Erhardt S, Engberg G: Increased phasic activity of dopaminergic neurones in the rat ventral tegmental area following pharmacologically elevated levels of endogenous kynurenic acid. *Acta Physiol Scand* 175(1), 45-53 (2002)

23. Sophie Erhardt, Lilly Schwieler, Carolina Emanuelsson, Mark Geyer: Endogenous kynurenic acid disrupts prepulse inhibition. *Biol Psychiatry* 56(4), 255-60 (2004)

24. R. Carpenedo, A. Pittaluga , A. Cozzi , S. Attucci, A Galli, M. Raiteri, F. Moroni: Presynaptic kynurenate-sensitive receptors inhibit glutamate release. *Eur J Neurosci* 13(11), 2141-7 (2001)

25. Hui-Qiu Wu, Kjell Fuxe and Robert Schwarcz: Neuronal A1 receptors mediate increase in extracellular kynurenic acid after local intrastriatal adenosine infusion. *J Neurochem* 90(3), 621-8 (2004)

26. Fabienne Peyrot and Claire Ducrocq: Potential role of tryptophan derivatives in stress responses characterized by the generation of reactive oxygen and nitrogen species. *J Pineal Res* 45(3), 235-46 (2008)

27. Naho Sasaki, Yukari Egashira and Hiroo Sanada: Production of L-tryptophan-derived catabolites in hepatocytes from streptozotocin-induced diabetic rats. *Eur J Nutr* 48(3), 145-53 (2009)

28. Gerard Clarke, Peter Fitzgerald, John J Cryan, Eugene M Cassidy, Eamonn Quigley and Timothy G Dinan: Tryptophan degradation in irritable bowel syndrome: evidence of indoleamine 2,3-dioxygenase activation in a male cohort. BMC Gastroenterol 9:6 (2009)

29. N. Müller and M.J. Schwarz: The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry* 12(11), 988-1000 (2007)

30. Ursula Grohmann, Francesca Fallarino and Paolo Puccetti: Tolerance, DCs and tryptophan: much ado about IDO. *Trends Immunol* 24(5), 242-8 (2003)

31. Peng Li, Yu-Long Yin, Defa Li, Sung Woo Kim and Guoyao Wu: Amino Acids and Immune Function. *Br J Nutr* 98, 237-252 (2007)

32. Sung Woo Kim, Ronald D. Mateo, Yu-long Yin and Guoyao Wu: Functional amino acids and fatty acids for enhancing production performance of sows and piglets. *Asian-Aust. J. Anim. Sci*. 20: 295-306 (2007)

33. E. R. Pfefferkorn: Interferon gamma blocks the growth of Toxoplasma gondii in human fibroblasts by inducing the host cells to degrade tryptophan. *Proc Natl Acad Sci* USA 81(3), 908-12 (1984)

34. J. M. Carlin, Y. Ozaki, G I. Byrne, R. R. Brown and E. C. Borden: Interferons and indoleamine-2,3-dioxygenase: role in antimicrobial and antitumor effects. *Cellular and Molecular Life Sciences* 45(6), 535-41 (1989)

35. Silvia Bozza, Francesca Fallarino, Lucia Pitzurra, Teresa Zelante, Claudia Montagnoli, Silvia Bellocchio, Paolo Mosci, Carmine Vacca, Paolo Puccetti and Luigina Romani: A crucial role for tryptophan catabolism at the host/Candida albicans interface. *J Immunol* 174(5), 2910-8 (2005)

36. Claudia Montagnoli, Francesca Fallarino, Roberta Gaziano, Bozza S, Silvia Bellocchio, Teresa Zelante, Wiswanath P. Kurup, Lucia Pitzurra, Paolo Puccetti and Luigina Romani: Immunity and tolerance to Aspergillus involve functionally distinct regulatory T cells and tryptophan catabolism. *J Immunol* 176(3), 1712-23 (2006)

37. Luigina Romani and Paolo Puccetti: Protective tolerance to fungi: the role of IL-10 and tryptophan catabolism. *Trends Microbiol* 14(4), 183-9 (2006)

38. Deborah Braun, Randy S. Longman and Matthew L. Albert: A two-step induction of indoleamine-2,3-dioxygenase (IDO) activity during dendritic-cell maturation. *Blood* 106(7), 2375-2381 (2005)

39. Francesca Fallarino, Ciriana Orabona, Carmine Vacca, Roberta Bianchi, Stefania Gizzi, Carine AsselinPaturel, Maria Cristina Fioretti, Giorgio Trinchieri, Ursula Grohmann and Paolo Puccetti: Ligand and cytokine dependence of the immunosuppressive pathway of tryptophan catabolism in plasmacytoid dendritic cells. *Int Immunol* 17(11), 1429-1438 (2005)

40. Patrick Hwu, Mark X. Du, Rejean Lapointe, My Do, Milton W. Taylor and Howard A. Young: Indoleamine-2,3-Dioxygenase Production by Human Dendritic Cells Results in the Inhibition of T Cell Proliferation. *J Immunol* 164(7), 3596-3599 (2000)

41. Tomoko Hayashi, Lucinda Beck, Cyprian Rossetto, Xing Gong, Osamu Takikawa, Kenji Takabayashi, David H.

Broide, Dennis A. Carson and Eyal Raz: Inhibition of experimental asthma by indoleamine 2,3-dioxygenase. *J Clin Invest* 114(2), 270-279 (2004)

42. Andrew L. Mellor and David H. Munn: Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol Today* 20(10), 469-73 (1999)

43. Wei Dai, Huiqi Pan, Oliver Kwok, J.P. Dubey: Human indoleamine-2, 3-dioxygenase inhibits Toxoplasma gondii growth in fibroblast cells. *J Interferon Res* 14(6), 313-7 (1994)

44. Christian Hucke, Colin R. MacKenzie, Koku D. Z. Adjogble, Osamu Takikawa and Walter Däubener: Nitric oxide-mediated regulation of gamma interferon-induced bacteriostasis: inhibition and degradation of human indoleamine-2, 3-dioxygenase. *Infect Immun* 72(5), 2723-30 (2004)

45. U. von Rango, C.A. Krusche, H.M. Beier, I. Classen-Linke: Indoleamine-dioxygenase is expressed in human decidua at the time maternal tolerance is established. *J Reprod Immunol* 74(1-2), 34-45 (2007)

46. P. Sedlmayr, A. Blaschitz, R. Wintersteiger, M. Semlitsch, A. Hammer, C.R. MacKenzie, W. Walcher, O. Reich, O. Takikawa and G. Dohr: Localization of indoleamine-2,3-dioxygenase in human female reproductive organs and the placenta. *Mol Hum Reprod* 8(4), 385-91 (2002)

47. Yoshiki Kudo, C.A.R. Boyd, Isabella Spyropoulou, C.W.G. Redman, Osamu Takikawa, Takafumi Katsuki, Tetsuaki Hara, Koso Ohama and I.L. Sargent: Indoleamine-2,3-dioxygenase: distribution and function in the developing human placenta. *J Reprod Immunol* 61(2), 87-98 (2004)

48. P. Ligam, U. Manuelpillai, E. M. Wallace and D. Walker: Localisation of indoleamine-2,3-dioxygenase and kynurenine hydroxylase in the human placenta and decidua: implications for role of the kynurenine pathway in pregnancy. *Placenta* 26(6), 498-504 (2005)

49. Koji Narui, Norihisa Noguchi, Aya Saito, Kazuhiro Kakimi, Noboru Motomura, Kinya Kubo, Shinichi Takamoto and Masanori Sasatsu: Anti-infectious activity of tryptophan metabolites in the L-tryptophan-L-kynurenine pathway. *Biol Pharm Bull* 32(1), 41-4 (2009)

50. Shanshan Cai, Katsumasa Sato, Toshiaki Shimizu, Seiko Yamabe, Miho Hiraki, Chiaki Sano and Haruaki Tomioka: Antimicrobial activity of picolinic acid against extracellular and intracellular Mycobacterium avium complex and its combined activity with clarithromycin, rifampicin and fluoroquinolones. *J Antimicrob Chemother* 57(1), 85-93 (2006)

51. Katharina Pellegrin, Gabriele Neurauter, Barbara Wirleitner, Arthur W Fleming, Verlyn M Peterson, Dietmar Fuchs: Enhanced enzymatic degradation of tryptophan by indoleamine-2, 3-dioxygenase contributes to the tryptophan-deficient state seen after major trauma. *Shock* 23(3), 209-15 (2005)

52. Martin Ploder, Andreas Spittler, Katharina Schroecksnadel, Gabriele Neurauter, Linda E. Pelinka, Erich Roth and Dietmar Fuchs: Tryptophan degradation in multiple trauma patients: survivors compared with non-survivors. *Clin Sci (Lond)* 116(7), 593-8 (2009)

53. N. Le Floc'h, D. Melchior, B. Sève: Dietary tryptophan helps to preserve tryptophan homeostasis in pigs suffering from lung inflammation. *J Anim Sci* 86(12), 3473-9 (2008)

54. D. Melchior, N. Le Floc'h, B. Sève: Effects of chronic lung inflammation on tryptophan metabolism in piglets. *Adv Exp Med Biol* 527, 359-62 (2003)

55. N. Le Floc'h, L. Lebellego, J.J. Matte, D. Melchior, B. Sève: The effect of sanitary status degradation and dietary tryptophan content on growth rate and tryptophan metabolism in weaning pigs. *J Anim Sci* 87(5), 1686-94 (2009)

56. Beryl APD Dawson and Emmanuel J. Favaloro: High rate of deficiency in the amino acids tryptophan and histidine in people with wounds: implication for nutrient targeting in wound management--a pilot study. *Adv Skin Wound Care* 22(2), 79-82 (2009)

57. Maria L. Belladonna, Ciriana Orabona, Ursula Grohmann and Paolo Puccetti: TGF-beta and kynurenines as the key to infectious tolerance. *Trends Mol Med* 15(2), 41-9 (2009)

58. S. Sanchez, S.D. Paredes, C.L. Sanchez, C. Barriga, R.J. Reiter, A.B. Rodriguez: Tryptophan administration in rats enhances phagocytic function and reduces oxidative metabolism. *Neuro Endocrinol Lett* 29(6), 1026-32 (2008)

59. ConnieJ. Kim, Jennifer A. Kovacs-Nolan, Chengbo Yang, Tania Archbold, Ming Z. Fan, Yoshinori Mine: L-Tryptophan exhibits therapeutic function in a porcine model of dextran sodium sulfate (DSS)-induced colitis. *J Nutr Biochem* 21, 468-475 (2010)

60. C Rob Markus, Berend Olivier, Geert EM Panhuysen, Jan Van Der Gugten, Martine S Alles, Adriaan Tuiten, Herman GM Westenberg, Durk Fekkes, Hans F Koppeschaar and Edward EHF de Haan: The bovine protein alpha-lactalbumin increases the plasma ratio of tryptophan to the other large neutral amino acids, and in vulnerable subjects raises brain serotonin activity, reduces cortisol concentration, and improves mood under stress. *Am J Clin Nutr* 71(6), 1536-44 (2000)

61. Susana Esteban, Cristina Nicolaus, Antonio Garmundi, Ruben Victor Rial, Ana Beatriz Rodríguez, Eduardo Ortega and Carmen Barriga Ibars: Effect of orally administered L-tryptophan on serotonin, melatonin, and the innate immune response in the rat. *Mol Cell Biochem* 267(1-2), 39-46 (2004)

62. Patricia Gaspar, Olivier Cases and Luc Maroteaux: The developmental role of serotonin: news from mouse molecular genetics. *Nat Rev Neurosci* 4(12), 1002-12 (2003)

63. Soledad Sánchez Mateos, Cristina L. Sánchez, Sergio D. Paredes, Carmen Barriga and Ana B. Rodríguez: Circadian levels of serotonin in plasma and brain after oral administration of tryptophan in rats. *Basic Clin Pharmacol Toxicol* 104(1), 52-9 (2009)

64. A. Neumeister: Tryptophan depletion, serotonin, and depression: where do we stand? *Psychopharmacol Bull* 37(4), 99-115 (2003)

65. Michael S. McCloskey, Dror Ben-Zeev, Royce Lee, Mitchell E. Berman and Emil F. Coccaro: Acute tryptophan depletion and self-injurious behavior in aggressive patients and healthy volunteers. *Psychopharmacology (Berl)* 203(1), 53-61 (2009)

66. Sherry L. Pagoto, Bonnie Spring, Dennis McChargue, Brian Hitsman, Malaina Smith, Bradley Appelhans and Donald Hedeker: Acute tryptophan depletion and sweet food consumption by overweight adults. *Eat Behav* 10(1), 36-41 (2009)

67. Christine Firk and C. Rob Markus: Mood and cortisol responses following tryptophan-rich hydrolyzed protein and acute stress in healthy subjects with high and low cognitive reactivity to depression. *Clin Nutr* 28(3), 266-271 (2009)

68. Gerald Huether, Burkhard Poeggeler, Andreas Reimer and Annette George: Effect of tryptophan administration on circulating melatonin levels in chicks and rats: evidence for stimulation of melatonin synthesis and release in the gastrointestinal tract. *Life Sci* 51(12), 945-53 (1992)

69. Ken Yaga, Russel J. Reiter and Bruce A. Richardson: Tryptophan loading increases daytime serum melatonin levels in intact and pinealectomized rats. *Life Sci* 52(14), 1231-8 (1993)

70. Maurizio Bossola, Donata Scribano, Luigi Colacicco, Barbara Tavazzi, Stefania Giungi, Cecilia Zuppi, Giovanna Luciani, Luigi Tazza: Anorexia and plasma levels of free tryptophan, branched chain amino acids, and ghrelin in hemodialysis patients. *J Ren Nutr* 19(3), 248-55 (2009)

71. Huawei Zhang, Jingdong Yin, Defa Li, Xuan Zhou and Xilong Li: Tryptophan enhances ghrelin expression and secretion associated with increased food intake and weight gain in weanling pigs. *Domest Anim Endocrinol* 33(1), 47-61 (2007)

72. A. A. Pontera1, N. O. Cortamira, B. Sevea, D. N. Saltera and L. M. Morgana: The effects of energy source and tryptophan on the rate of protein synthesis and on hormones of the entero-insular axis in the piglet. *Br J Nutr* 71(5), 661-74 (1994)

73. A. J. M. Jansman, J. Th. M. van Diepen and D. Melchior: The effect of diet composition on tryptophan requirement of young piglets. *J Anim Sci* 88, 1017-27 (2010)

74. T. Ettle and F. X. Roth: Specific dietary selection for tryptophan by the piglet. *J Anim Sci* 82(4), 1115-21 (2004)

75. A. C. Guzik, J. O. Matthews, B. J. Kerr, T. D. Bidner and L. L. Souther: Dietary tryptophan effects on plasma and salivary cortisol and meat quality in pigs. *J Anim Sci* 84(8):2251-9 (2006)

76. T. K. Chung, H. B. Geiberg, J. L. Domer and D. H. Bake: Safety of L-tryptophan for pigs. *J Anim Sci* 69(7), 2955-60 (1991)

77. K. Edera, Svetlana Peganovab, H. Kluge: Studies on the tryptophan requirement of piglets. *Arch Tierernah* 55(4), 281-97 (2001)

78. P. Trevisi, D. Melchior, M. Mazzoni, L. Casini, S. De Filippi, L. Minieri, G. Lalatta-Costerbosa and P. Bosi: A tryptophan-enriched diet improves feed intake and growth performance of susceptible weanling pigs orally challenged with Escherichia coli K88. *J Anim Sci* 87(1), 148-56 (2009)

79. Yvonne M. van Hierden, Jaap M. Koolhaas, S. Mechiel Korte: Chronic increase of dietary L-tryptophan decreases gentle feather pecking behaviour. *Appl Anim Behav Sci* 89, 71–84 (2004)

80. Nathalie L. Trottier and Robert A. Eastel: Dietary and plasma branched-chain amino acids in relation to tryptophan: effect on voluntary feed intake and lactation metabolism in the primiparous sow. *J Anim Sci* 73(4), 1086-92 (1995)

81. D. W. Pethick, R. D. Warner, D. N. D'Souza, F. D. Dunshea. Nutritional manipulation of meat quality. Pages 100–115 in Manipulating Pig Production VI. P. D. Cranwell, ed. Australasian Pig Sci. Assoc, Roseworthy, SA, Australia (1997)

82. NRC. Nutrient Requirements of Swine. 10th ed. National Academy Press, Washington, DC. 1998.

83. J. Heger, T. Van Phung, L. Krizová: Efficiency of amino acid utilization in the growing pig at suboptimal levels of intake: lysine, threonine, sulphur amino acids and tryptophan. *J Anim Physiol Anim Nutr (Berl)* 86(5-6), 153-65 (2002)

84. A. Susenbeth, U. Lucanus: The effect of tryptophan supplementation of diets of restricted- and unrestricted-fed young pigs. *J Anim Physiol Anim Nutr (Berl)* 89(9-10), 331-6 (2005)

85. A. C. Guzik, M. J. Pettitt, E. Beltranena, L. L. Southern, B. J. Kerr. Threonine and tryptophan ratios fed to nursery pigs. *J Anim Physiol Anim Nutr (Berl)* 89(7-8):297-302 (2005)

86. S. J. Koopmans, A. C. Guzik, J. van der Meulen, R. Dekker, J. Kogut, B. J. Kerr, L. L. Southern: Effects of supplemental L-tryptophan on serotonin, cortisol, intestinal integrity and behavior in weanling piglets. *J Anim Sci* 84(4), 963-71 (2006)

87. A. C. Guzik, L. L. Southern, T. D. Bidner, B. J. Kerr: The tryptophan requirement of nursery pigs. *J Anim Sci* 80(10), 2646-55 (2002)

88. Yanming Han, Thau Kiong Chung and David H. Baker: Tryptophan requirement of pigs in the weight category 10 to 20 kilograms. *J Anim Sci* 71(1), 139-43 (1993)

89. M. L. Sawadogo, A. Piva, A. Panciroli, E. Meola, A. Mordenti , B. Sève: Marginal efficiency of free or protected crystalline L-tryptophan for tryptophan and protein accretion in early-weaned pigs. *J Anim Sci* 75(6), 1561-8 (1997)

90. K. Shibata, M. Swabe, T. Fukuwatari, E. Sugimoto: Efficiency of D-tryptophan as niacin in rats. *Biosci Biotechnol Biochem* 64(1), 206-9 (2000)

91. L. R. Feksa, A. Latini, V. C. Rech, P. B. Feksa, G. D. Koch, M. F. Amaral, G. Leipnitz, C. S. Dutra-Filho, M. Wajner, C. M. Wannmacher: Tryptophan administration induces oxidative stress in brain cortex of rats. *Metab Brain Dis* 23(2, 221-33 (2008)

92. P. A. Hertzman, W. L. Blevins, J. Mayer, B. Greenfield, M. Ting, G. J. Gleich: Association of the eosinophilia-myalgia syndrome with the ingestion of tryptophan. *N Engl J Med* 322(13), 869-73 (1990)

93. E. M. Kilbourne: Eosinophilia-myalgia syndrome: coming to grips with a new illness. *Epidemiol Rev* 14, 16-36 (1992)

94. A. Okuno, T. Fukuwatari, K. Shibata: Urinary excretory ratio of anthranilic acid/kynurenic acid as an index of the tolerable amount of tryptophan. *Biosci Biotechnol Biochem* 72(7), 1667-72 (2008)

95. R. I. Horwitz, S. R. Daniels: Bias or biology: Evaluating the epidemiologic studies of L-tryptophan and the eosinophilia-myalgia syndrome. *J Rheum* 23(Suppl 46), 60–72 (1996)

96. S. R. Daniels, K. I. Hudson, R. I. Horwitz: Epidemiology of potential association between L-tryptophan ingestion and eosinophilia-myalgia syndrome. *J Clin Epidemiol* 48, 1413–1427 (1995)

97. J. B. Houpt, M. A. Ogryzlo, M. Hunt: Tryptophan metabolism in man (with special reference to rheumatoid arthritis and scleroderma). *Semin Arthritis Rheumatism* 2(4), 333–353 (1973)

98. M. Aviram, U. Cogan, S. Mokady: Excessive dietary tryptophan enhances plasma lipid peroxidation in rats. *Atherosclerosis* 88(1), 29-34 (1991)

99. I. Magnussen, F. Nielsen-Kudsk: Bioavailability and related pharmacokinetics in man of orally administered L-5-hydroxytryptophan in steady state. *Acta Pharmacol Toxicol (Copenh)* 46(4), 257-62 (1980)

100. Y. T. Das, M. Bagchi, D. Bagchi, H. G. Preuss: Safety of 5-hydroxy-L-tryptophan. *Toxicol Lett* 150(1), 111-22 (2004)

101. Peng Li, Yu-Long Yin, Defa Li, Sung Woo Kim and Guoyao Wu: Amino acids and immune function. *Br J Nutr* 98, 237-252 (2007)

102. Guoyao Wu: Amino acids: metabolism, functions, and nutrition. *Amino Acids* 37, 1-17 (2009)

103. Rajavel Elango, Ronald O. Ball, Paul B. Pencharz: Amino acid requirements in humans: with a special emphasis on the metabolic availability of amino acids. *Amino Acids* 37, 19-27 (2009)

104. David H. Baker: Advances in protein-amino acid nutrition of poultry. *Amino Acids* 37, 29-41 (2009)

105. Peng Li, Kangsen Mai, Jesse Trushenski and Guoyao Wu: New developments in fish amino acid nutrition: towards functional and environmentally oriented aquafeeds. *Amino Acids* 37, 43-53 (2009)

106. Lixiang Chen, Peng Li, Junjun Wang, Xilong Li, Haijun Gao, Yulong Yin, Yongqing Hou, Guoyao Wu: Catabolism of nutritionally essential amino acids in developing porcine enterocytes. *Amino Acids* 37, 143-152 (2009)

107. W. W. Wang, S. Y. Qiao and D. F. Li: Amino acids and gut function. *Amino Acids* 37, 105-110 (2009)

108. Sung W. Kim and Guoyao Wu: Regulatory role for amino acids in mammary gland growth and milk synthesis. *Amino Acids* 37, 89-95 (2009)

109. Xiangfang Zeng, Fenglai, Xia Fan, Wenjun Yang, Bo Zhou, Pengfei Li, Yulong Yin*, Guoyao Wu and Junjun Wang. Dietary arginine supplementation during early pregnancy enhances embryonic survival in rats.*J Nutr*138:1421-1425 (2008)

110. G. Wu, F. W. Bazer, J. M. Wallace and T. E. Spencer: Intrauterine growth retardation: Implications for the animal sciences. *J Anim Sci* 84, 2316-2337 (2006)

111. G. Wu, F. W. Bazer, R. C. Burghardt, G. A. Johnson, S. W. Kim†, X. L. Li, M. C. Satterfield and T. E. Spencer: Impacts of amino acid nutrition on pregnancy outcome in pigs: mechanisms and implications for swine production. *J Anim Sci* 88, E195-E204 (2010)

112. Xilong Li, Fuller W. Bazer, Haijun Gao, Wenjuan Jobgen, Gregory A. Johnson, Peng Li, Jason R. McKnight, M. Carey Satterfield, Thomas E. Spencer and Guoyao Wu: Amino acids and

gaseous signaling. *Amino Acids* 37, 65-78 (2009)

113. Bie Tan, Yulong Yin, Zhiqiang Liu, Xinguo Li, Haijun Xu, Xiangfeng Kong, Ruilin Huang, Wenjie Tang, Izuru Shinzato, Stephen B. Smith and Guoyao Wu: Dietary L-Arginine supplementation increases muscle gain and reduces body fat mass in growing-finishing pigs. *Amino Acids* 37, 169-175 (2009)

114.Bie Tan, Yulong Yin, Xiangfeng Kong, Peng Li, Xilong Li, Haijun Gao, Xinguo Li, Ruilin Huang and Guoyao Wu. L-Arginine stimulates proliferation and prevents endotoxin-induced death of intestinal cells. *Amino Acids* 38:1227-1235 (2010)

115. A. Suryawan, P. M. J. O'Connor, J. A. Bush, H. V. Nguyen, T. A. Davis. Differential regulation of protein synthesis by amino acids and insulin in peripheral and visceral tissues of neonatal pigs. *Amino Acids* 37, 97-104 (2009)

116. J. Marc Rhoads and Guoyao Wu: Glutamine, arginine, and leucine signaling in the intestine. *Amino Acids* 37, 111-122 (2009)

117. Kang Yao, Yu-Long Yin, Wuyin Chu, Zhiqiang Liu,Dun Deng, Tiejun Li, Ruilin Huang, Jianshe Zhang, Bie Tan,Wence Wang, and Guoyao Wu . Dietary Arginine Supplementation Increases mTOR Signaling Activity in Skeletal Muscle of Neonatal Pigs. *J Nutr* 138, 867–872 (2008)

118. Xin Wu, Zheng Ruan,Yunling Gao, Yulong Yin, Xihong Zhou, Lei Wang, Meimei Geng, Yongqing Hou Guoyao Wu. Dietary supplementation with L-arginine or N-carbamylglutamate enhances intestinal growth and heat shock protein-70 expression in weanling pigs fed a corn- and soybean meal-based diet. *Amino Acids* 39, 831-839

119. Dun Deng, Kang Yao, Wuying Chu, Tiejun Li, Ruiling Huang, Yulong Yin, Zhiqiang Liu, Janshe Zhang and Guoyao Wu. Impaired translation initation activation and reduced protein synthesis in weaned piglets fed a low-protein diet. *J Nutr Biochem* 20, 544-552 (2009)

120.C. Brasse-Lagnel, A. Lavoinne, A. Husson: Control of mammalian gene expression by amino acids, especially glutamine. *FEBS J* 276, 1826-1844 (2009)

121. S. S. Palii, C. E. Kays, C. Deval, A. Bruhat, P. Fafournoux, M. S. Kilberg. Specificity of amino acid regulated gene expression: analysis of gene subjected to either complete or single amino acid deprivation. *Amino Acids* 37, 79-88 (2009)

122. Junjun Wang, Guoyao Wu, Huaijun Zhou and Fenglai Wang: Emerging technologies for amino acid nutrition research in the post-genome era. *Amino Acids* 37, 177-186 (2009)

123. Wenjuan Jobgen, Wenjiang J. Fu, Haijun Gao, Peng Li, Cynthia J. Meininger, Stephen B. Smith, Thomas E. Spencer and Guoyao Wu: High fat feeding and dietary L-arginine supplementation differentially regulate gene expression in rat white adipose tissue. *Amino Acids* 37, 187-198 (2009)

124. Q. H. He, X. F. Kong, G. Wu, P. P. Ren, H. R. Tang, F. H. Hao, R. L. Huang, T. J. Li, B. E. Tan, P. Li, Z. R. Tang, Y. L. Yin, Y. N. Wu: Metabolomic analysis of the response of growing pigs to dietary L-arginine supplementation. *Amino Acids* 37, 199-208 (2009)

125. Xiaogiu Wang, Deyuan Ou, Jingdong Yin, Guoyao Wu, Junjun Wang: Proteomic analysis reveals altered expression of proteins related to glutathione metabolism and apoptosis in the small intestine of zinc oxide-supplemented piglets. *Amino Acids* 37, 209-218 (2009)

126.Yulan Liu, Jingjing Huang, Yongqing Hou, Huiling Zhu, Shengjun Zhao, Binying Ding, Yulong Yin, Ganfeng Yi, Junxia Shi and Wei Fan. Dietary arginine supplementation alleviates intestinal mucosal disruption induced by Escherichia coli lipopolysaccharide in weaned pigs Dietary arginine supplementation alleviates intestinal mucosal disruption induced by Escherichia coli lipopolysaccharide in weaned pigs.*British Journal of Nutrition,* 100:552-5608 (2008)

127. Christopher M Dekaney, Guoyao Wu, Yu Long Yin and Laurie A Jaeger. Regulation of ornithine aminotransferase gene expression and activity by all-transretinoic acid in Caco-2 intestinal epithelial cells.*The Journal of Nutritional Biochemistry*,19 : 674-681(2008)

128. Ping Kang, Yu Long Yin, Zhen Ruan,Jie Pan, Qing Hu, Ze Yuan Deng,Hua Xiong and Ming Yong Xie. Effect of replacement of lactose with partially hydrolysed rice syrup on small intestine development in weaned pigs from 7 to 21days. *Journal of the Science of Food and Agriculture*, 88:1932-1938(2008)

129□Yulong Yin, Kang Yao, Zhaojin Liu, Min Gong, Zheng Ruan, Dun Deng, Bie Tan, Zhiqiang Liu, Guoyao Wu. Supplementing L-leucine to a low-prote -protein diet increases tissue protein synthesis in weanling pigs. Amino Acids.DOI 10.1007/s00726-010-0612-5

130. Wenjiang J. Fu, Arnold J. Stromberg, Kert Viele, Raymond J. Carroll, Guoyao Wu: Statistics and bioinformatics in nutritional sciences: analysis of complex data in the era of systems biology. J Nutr Biochem 21, 561-572 (2010)

Abbreviations: AMSR: 2-aminomuconate semialdehyde reductase; ANH: anthranilate hydroxylase [also known as Anthranilate 3-monooxygenase (deaminating)]; ASMT: N-acetylserotonin *O*-methyltransferase; CCK: cholecystokinin; DSS: dextran sodium sulfate; EMS: Eosinophilia–myalgia syndrome; HDO: 3-hydroxyanthranilate dioxygenase; HIMT: 5-hydroxyindole-*O*-methyltransferase; HKTA: 3-hydroxykynurenine transaminase; 5-HT: 5-hydroxytryptamine; 5-HTP: 5-hydroxy-l-tryptophan; IDO:

indoleamine 2, 3-dioxygenase; IFN: interferon; IL: interleukin; KAD: α-ketoadipate dehydrogenase; KHL: kynurenine hydroxylase; KNA: kynureninase; KTA: kynurenine transaminase; KYN: kynurenine; MAO: monoamine oxidase; NADS: NAD synthase; NF-kB: NF-kappaB; NGH: NAD glycohydrolase; NMDA: N-methyl-D-aspartic acid; OCR: oxalocrotonate reductase; PCL, picolinate carboxylase; PLP: pyridoxal phosphate; PRPP: 5-phosphoribosyl-1-pyrophosphate; QPRT: quinolinate phosphoribosyl transferase; SNAT: serotonin-N-acetyltransferase; SAM: S-adenosylmethionine; SAHC, S-adenosylhomocyteine; SPR: spontaneous reaction; SR: a series of reactions (glutaryl-CoA → glutaconyl-CoA → Crotonyl-CoA → Acetoacetyl-CoA → Acetyl-CoA); TDO: tryptophan 2, 3-dioxygenase; THL: tryptophan hydroxylase; TLR: toll-like receptors; TNF-α: tumor necrosis factor-α; TRP: L-tryptophan

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