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-NH3⁺) = 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
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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 TRP is not digested 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 kynurenine 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.

Metabolism through the KYN pathway primarily results in the formation of quinolinic acid, particularly via the production of 3-hydroxykynurenine and 3-hydroxynanthranilic acid. Quinolinic acid may be metabolized further to nicotinamide or nicotinic acid (7). The kynurenine pathway also produces kynurenic acid, picolinic acid, 5-hydroxynanthranilic 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-acetylsertotonin, melatonin, antranilic 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 kynurenine 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
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 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...
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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 the 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).

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). A moderate lower 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 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).
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 (76) 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 transference, creatine phosphokinate, 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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Abbreviations: AMSR: 2-amonomuconate semialdehyde reductase; ANH: anthranilate hydroxylase [also known as Anthramilate 3-monoxygenase (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:
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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: quinolinolate 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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