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Review Article

Intestinal tryptophan metabolism in disease prevention and swine production

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ABSTRACT

Tryptophan (Trp) is an essential amino acid that cannot be synthesized by animals. It has been characterized into two different isomers, levorotation-Trp (L-Trp) and dextrorotation-Trp (D-Trp), based on their distinct molecule orientation. Intestinal epithelial cells and gut microbiota are involved in metabolizing L-Trp in the gut via the activation of the kynurenine, serotonin, and indole pathways. However, knowledge regarding D-Trp metabolism in the gut remains unclear. In this review, we briefly update the current understanding of intestinal L/D-Trp metabolism and the function of their metabolites in modulating the gut physiology and diseases. Finally, we summarize the effects of Trp nutrition on swine production at different stages, including growth performance in weaned piglets and growing pigs, as well as the reproduction performance in sows.

1. Introduction

The gastrointestinal (GI) tract is a complex organ which harbors a variety of microorganisms collectively known as the gut microbiota. An increasing number of studies have suggested that the gut microbiota can be considered as a new "organ system", because of its physiological interaction with the host as well as its inheritance capacity (McFarland, 2014; Zhang and Davies, 2016). For instance, the gut–kidney axis has been used to explain how the gut microbiota modulates the functional relationship between the gut and kidney (Lobel et al., 2020). Similarly, the roles of the gut microbiota in the establishment of the gut–brain axis, gut–liver axis, and gut–lung axis have also been reported (Caputi and Giron, 2018; Hamoud et al., 2018). These interorgan interactions require the involvement of a series of metabolites that are produced either by the gut microbes or intestinal epithelial cells. The gut microbiota produces bioactive compounds that trigger various biological reactions both in the proximal and distal connected organs. A disorganized gut microbial diversity and composition causes deleterious effects on the maintenance of the host health (Agus et al., 2018). Three gut microbial metabolites have increasingly been recognized as major bioactive compounds that modulate host–microbe interactions. The first is short-chain fatty acids (SCFAs) that are produced through fiber fermentation; the second is methylamines that are generated from choline; and the third is indoles which are derived from dietary tryptophan (Trp) metabolism (Monnerie et al., 2020).

2. Origin and metabolic outcomes of dietary Trp

Trp consists of a carbon connected to the third position of an indole group and is divided into two distinct isomers, levorotation-Trp (L-Trp) and dextrorotation-Trp (D-Trp) (Zelante et al., 2013).

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Mammals cannot naturally synthesize L-Trp, which is normally obtained through dietary supplementation (Liu et al., 2016b; Yin et al., 2021). Only a small amount of L-Trp is directly utilized as a substrate for protein synthesis, while most L-Trp is degraded to produce various metabolites which modulate host physiology. However, many D-amino acids (D-AA) including D-Trp have been reported to directly originate from the intestinal commensal bacteria (Bastings et al., 2019). Various racemases are involved in the conversion of D-AA in the animal body (Kobayashi, 2019). While the endogenous synthesis of D-Trp in any tissues has not yet been clearly reported, this is probably due to its extremely low expression.

There are three major intestinal L-Trp metabolic pathways as described below: (a) the indole pathway in which L-Trp is directly converted into indoles and derivates and tryptamine by the gut microbes (Sardar and Kempken, 2018); (b) the kynurenine (KYN) pathway in which L-Trp is degraded into KYN by a key rate-limiting enzyme indoleamine-2,3-dioxygenase 1 (IDO-1) in the intestinal epithelial cells (Muneer, 2020); (c) the serotonin or 5-hydroxytryptamine (5-HT) pathway which is mainly activated in the enterochromaffin cells to metabolize L-Trp into serotonin through the enzymatic activation of tryptophan hydroxylase 1 (TpH1) (Thomas et al., 2013). Regarding the metabolism of D-Trp, it appears to be metabolized by the gut commensal bacteria via diamine oxidase (DAO) and its metabolites may act as an immune modulatory substance in the gut (Kobayashi, 2019) (Fig. 1).

2.1. Indole pathway

The indole pathway is the main pathway of Trp metabolism by the gut microbiota, generating numerous indole derivatives including indole-3-aldehyde (IAld), indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), indole-3-acetaldehyde (IAAld), and indoleacetic acid. More than 85 different bacterial species are involved in the indole pathway including *Oribacterium sinus, Symbiobacterium thermophilum*, *Escherichia coli*, *Escherichia albertii,* and *Klebsiella oxytoca* (Carlier et al., 2004; Lee and Lee, 2010). The activation of the indole pathway requires the involvement of a

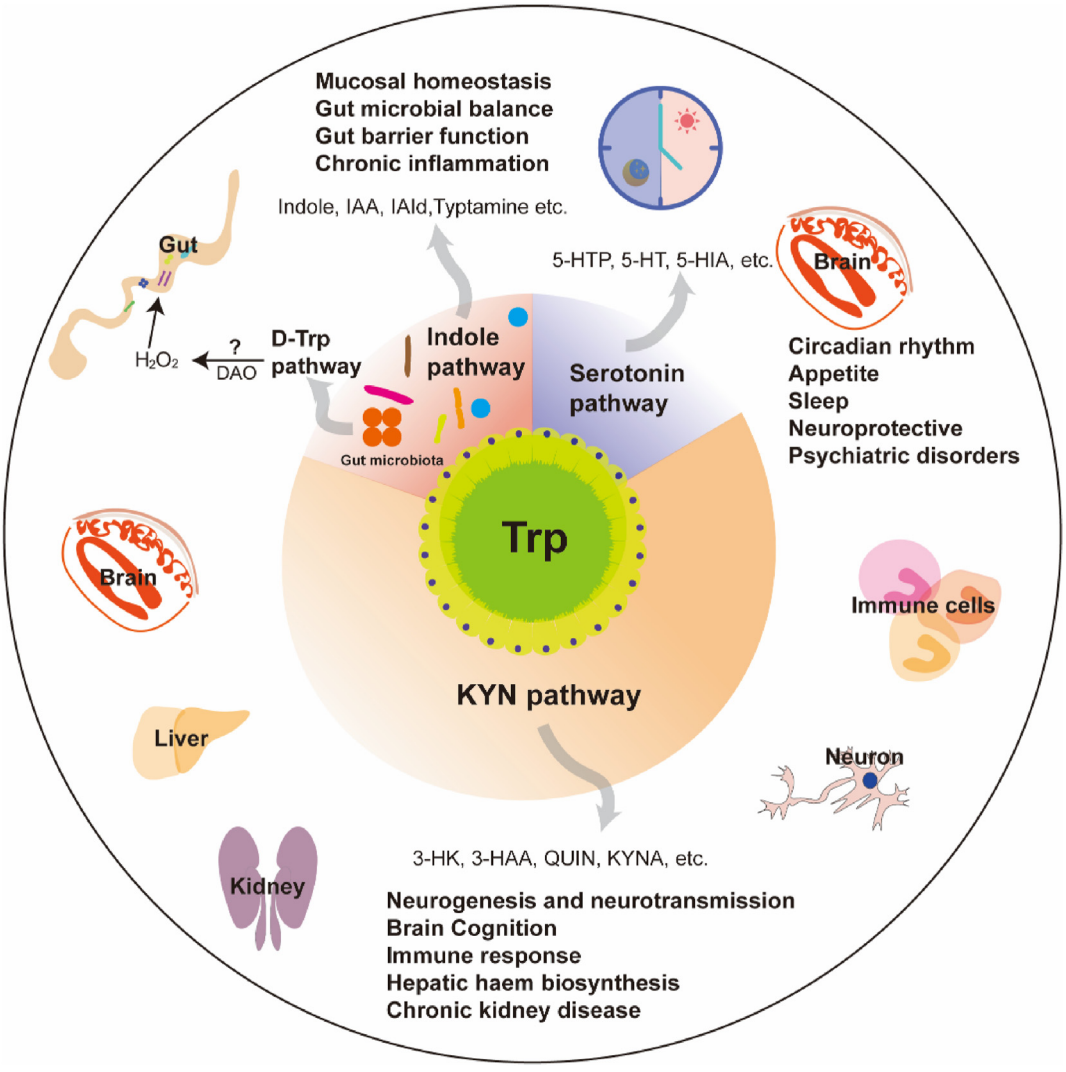

Fig. 1. Model of dietary Trp metabolism. Dietary Trp metabolism consists of three major outcomes. Most Trp is degraded by the KYN pathway in the host cells to convert Trp into KYN and derivates, regulating physiological function in the brain, liver, kidney and gut. Serotonin pathway occurs in the enterochromaffin cells to convert Trp into 5-HT to modulate the gut-brain communication, neuron function and circadian rhythm. While the gut microbiota-derived indole pathway metabolizes Trp into indole and its derivates to regulate gut barrier integrity and immune function. Additionally, gut commensal bacteria-generated D-Trp may also contribute to the maintenance of gut immune homeostasis. KYN = kynurenine; Trp = tryptophan; DAO = diamine oxidase; IAA = indole-3-acid-acetic; IAld = indole-3-aldehyde; 5-HTP = 5-hydroxytryptophan; 5-HT = 5-hydroxytryptamine; 5-HIA = 5-hydroxyindolacetate; 3-HK = 3-hydroxy-kynurenine; 3-HAA = 3-hydroxyanthranilic acid; QUIN = quinolinic acid; KYNA = kynurenic acid.

subset of catalytic enzymes (Fig. 2). For instance, L-tryptophan 2-monooxygenase (TMO) converts L-Trp into indole-3-acetamide (IAM). Aromatic amino acid aminotransferase (ArAT) catalyzes the metabolic process of L-Trp to produce indole-3-pyruvic acid (IPYA). IPYA is then sequentially converted into indole-3-lactic acid (ILA), indole acrylic acid (IA), and indole-3-propionic acid (IPA) under the activation of phenyllactate dehydrogenase (FldH), phenyllactate dehydratase (FldBC), and acyl-CoA dehydrogenase (AcdA), respectively (Covarrubias et al., 2021). Moreover, Trp decarboxylase 1 is involved in metabolizing L-Trp to tryptamine, which is further converted to IAAld via the activation of Trp decarboxylase (TDC) (Shah et al., 2021). Additionally, IAA and IPA can conjugate with glutamine or glycine to further produce indolyl-acetyl-glutamine, which is oxidized to IAld by peroxidase-catalyzed aerobic oxidation, and indolyl-acryloyl-glycine (IAcrGly) in the liver or kidney (Mello et al., 1980). The excessive excretion of these two urinary indoles causes coeliac disease and Hartnup disorder (Keszthelyi et al., 2009).

The aryl hydrocarbon receptor (AhR) is a ligand-activated sensor that interacts with microbial stimuli to regulate the intestinal epithelium renewal, barrier integrity, and immune homeostasis (Lamas et al., 2018). Many metabolites from the indole pathway act as AhR ligands (Hubbard et al., 2015; Lamas et al., 2020; Szelest et al., 2021). For instance, IAA binds AhR to regulate the expression of interleukin 22 (IL-22) in the gut. Restored intestinal IAA levels protected mice from ethanol-induced steatohepatitis by inducing the expression of intestinal IL-22 and regenerating family member 3 gamma (Hendrikx et al., 2019). Additionally, the increased expression levels of IAA and IPA can enhance the AhR activity and modulate the $CD4^+$ T cell differentiation (Ferrario et al., 2017). Importantly, AhR activity needs to be appropriately controlled, as excessive activation of the AhR pathway by the overexpression of IAA promoted the growth of pancreatic tumors in mice (Hezaveh et al., 2022). Moreover, the excessive production of indole inhibits the intracellular growth of *Chlamydia trachomatis* under hypoxic conditions by affecting the scavenging activity of AhR (Zhang et al., 2023).

2.2. Kynurenine pathway (KP)

Two key rate-limiting enzymes, IDO and tryptophan-2,3-dioxygenase (TDO), are involved in metabolizing L-Trp into KYN (Savitz, 2020). KYN is then sequentially converted into 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), quinolinic acid (QUIN), and nicotinamide adenine dinucleotide (NAD) through the activation of kynurenine 3-monooxygenase (KMO), kynureninase (KYNU), and quinolinate phosphoribosyltransferase (QPRT), respectively. In addition, KYN can be converted into kynurenic acid (KYNA) and anthranilic acid (AA) by kynurenine aminotransferase and KYNU (Fig. 2). Despite that the KP is mainly activated in the host cells, recent studies found that a few bacterial species like *Burkholderia cepacia J2315* and *Pseudomonas fluorescens strain KU-7* also activate the KP (Hasegawa et al., 2000; Sun et al., 2022). *B. cepacia J2315* metabolizes L-Trp into 2-amino-3-

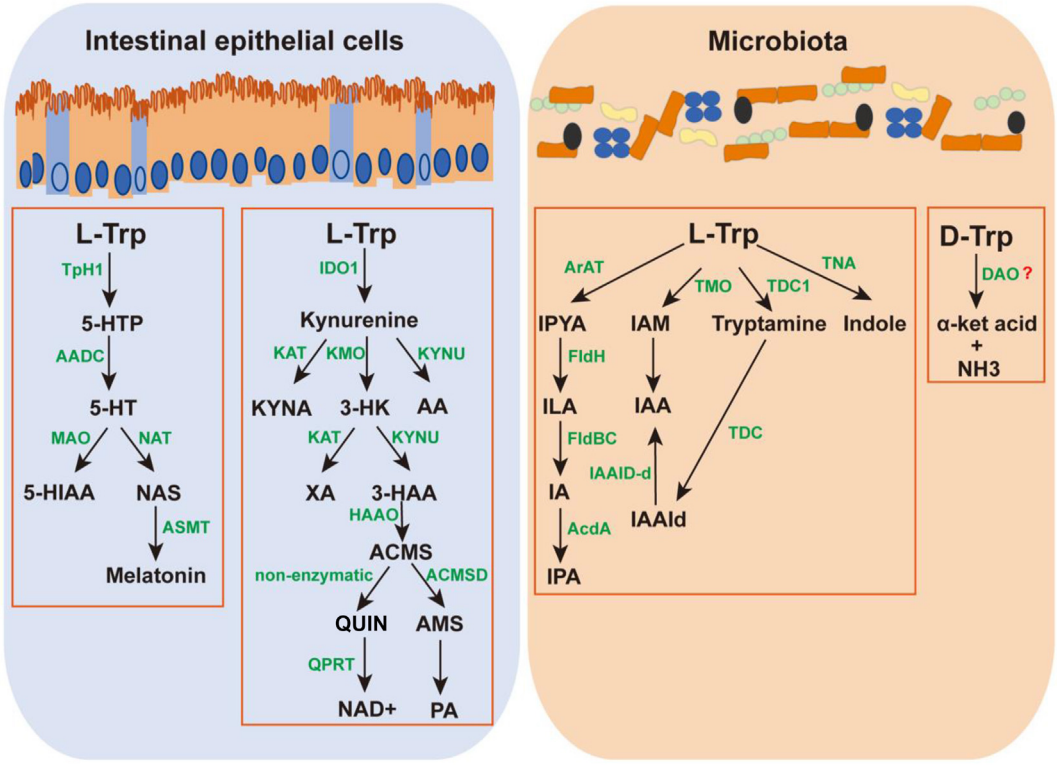

Fig. 2. Intestinal Trp metabolic pathways and their intermediates. Green colors denote key enzymes involved in Trp metabolism in the gut epithelial cells and microbes. Trp = tryptophan; TpH1 = tryptophan hydroxylase 1; AADC = aromatic l-amino acid decarboxylase; MAO = monoamine oxidase; NAT = N-acetyltransferase; ASMT = N-acetylserotonin O-methyltransferase; IDO1 = indoleamine-2,3-dioxygenase 1; KAT = kynurenine aminotransferase; KMO = kynurenine 3-monooxygenase; KYNU = kynureninase; HAAO = 3-hydroxyanthranilicacid 3,4-dioxygenase; ACMS = 2-amino-3-carboxymuconate-6-semialdehyde; ACMSD = α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase; QPRT = quinolinate phosphoribosyltransferase; ArAT = aromatic amino acid aminotransferase; FldH = phenyllactate dehydrogenase; FldBC = phenyllactate dehydratae; AcdA = acyl-coA dehydrogenase; TMO = tryptophan 2-monooxygenase; IAAID-d = indole-3-acetaldehyde dehydrogenase; TDC1 = tryptophan decarboxylase 1; TNA = tryptophanase; DAO = diamine oxidase; 5-HTP = 5-hydroxytryptophan; 5-HT = 5-hydroxytryptamine; 5-HIAA = 5-hydroxyindoleacetate; NAS = normelatonin; KYNA = kynurenic acid; 3-HK = 3-hydroxy-kynurenine; AA = anthranilic acid; XA = xanthurenic acid; 3-HAA = 3-hydroxyanthranilic acid; ACMS = α-amino-β-carboxymuconate-ε-semialdehyde; QUIN = quinolinic acid; AMS = α-amino-β-muconate-ε-semialdehyde; NAD^+ = nicotinamide adenine dinucleotide; PA = picolinic acid; IPYA = indole-3-pyruvic acid; ILA = indole-3-lactic acid; IA = indole acrylic acid; IPA = indole-3-propionic acid; IAM = indole-3-acetamide; IAA = indole-3-acid-acetic; IAAld = indole-3-acetaldehyde.

carboxymuconate semialdehyde, which is further degraded to pyruvate and acetate (Colabroy and Begley, 2005).

The KP is largely activated in the peripheral tissues, such as the liver, kidney, and central nervous system (Kennedy et al., 2017). Metabolites of the KP are capable of affecting the activity of neurocytes in the brain to modulate the host physiology. Approximately 60% of KYN was transferred by the peripheral circulation system and then entered the brain via the large amino acid transporter 1 (LAT1) (Proietti et al., 2020). KYN can be directly converted into KYNA, a broad-spectrum lipotropic glutamate receptor antagonist, through the KP in nerve cells to reduce glutamine and dopamine levels (Rossi et al., 2019). Many downstream metabolites of KYN are neuroactive and capable of modulating neuroplasticity and/or exerting neurotoxic activities, partially through N-methyl-D-aspartate (NMDA) receptor signaling and glutamatergic neurotransmission (Erhardt et al., 2017). Similar to the indole derivates, KYN has been also identified as an endogenous AhR ligand in the immune and tumor cells, acting in both autocrine and paracrine manners to extend the survival of tumor cells (Opitz et al., 2011). Tumor-repopulating cells promote the expression of programmed cell death protein 1 in the $CD8^+$ T cells through the activation of the KYN-AhR pathway (Liu et al., 2018). Moreover, KYN has been shown to activate AhR signals to promote western diet induced-obesity by enhancing the IDO activity stimulated by the transforming growth factor β1 (TGFβ1) signaling pathway via PI3K and nuclear factor kappa B (NF-κB) in a mouse model (Moyer et al., 2016; Xu et al., 2015).

2.3. Serotonin pathway

The intestinal serotonin pathway is mainly activated in the enterochromaffin (EC) cells to produce hydroxytryptophan (5-HTP) through the activation of tryptophan hydroxylase 1 (TpH1) (Walther and Bader, 2003). The 5-HTP is sequentially converted into 5-HT, N-acetylserotonin (NAS) and melatonin via aromatic amino acid decarboxylase (AADC), aralkylamine N-acetyltransferase (NAT), and N-acetylserotonin O-methyltransferase (ASMT). Moreover, serotonin can also be converted to 5-hydroxyindoleacetate (5-HIAA) through the activation of monoamine oxidase (MAO) (Das et al., 2004) (Fig. 2). Apart from EC cells, some bacterial species like *Bacillus cereus, Clostridium tetani*, and *Neisseria meningitidis* are also capable of activating the serotonin pathway to produce 5-HT in the gut (Taj and Jamil, 2018).

Most 5-HT is produced in the gut and trigger intestinal peristalsis, secretion, vasodilatation, and absorption by activating the specific 5-HT receptors (Lund et al., 2018). Additionally, 5-HT serves as an endogenous activator of AhR in the intestinal epithelial cells to regulate the downstream target gene cytochrome P450 1A1 (*CYP1A1*) expression, thus modulating the immune response in the gut (Manzella et al., 2018). The expression level of serotonin transporter (SERT) in the gut determined the progression of inflammatory bowel diseases, with decreased SERT levels inducing more severe colitis (Sharma et al., 2021). The 5-HT is also produced in the brain via the activation of TpH2, which acts as an important neuromodulator. The 5-HT itself cannot cross the blood–brain barrier (BBB) and its synthesis is mediated by the transportation of L-Trp to the brain. The majority of 5-HT is found in the hypothalamus and epiphysis and acts as a neurotransmitter to regulate sleep, pain, and heat (De Deurwaerdere and Di Giovanni, 2021; Hardeland, 2010).

Melatonin, a downstream product of the serotonin pathway, is produced by the pineal gland and approximately 80% of pineal secretory products in the brain regulate sleep. In mammals, melatonin can be metabolized to 6-hydroxymelatonin (6-OHM) through the catalyzation of the CYP1A2 enzyme which produces 6-sulfatoxymelatonin in conjunction with sulfate (Hardeland, 2017). Melatonin is also converted to N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) through the activation of IDO and cytochrome P450 (Semak et al., 2005). Both 6-OHM and AFMK have been reported to be produced non-enzymatically by interacting with various oxidants, including reactive oxygen species and reactive nitrogen species (Tesoriere et al., 2001).

2.4. D-Trp metabolism

Almost all amino acids are naturally found in two forms, either as levorotation (L) or dextrorotation (D) enantiomers (Sasabe and Suzuki, 2018). Previously, researchers have mostly focused on the dominant L-amino acids and revealed their important functions in regulating host physiology. Recently, the emerging roles of D-AA have been recognized in bacteria and the intestinal bacterial-generated free D-AA have an indispensable function in modulating the gut microbial homeostasis and mucosal immunity (Cava et al., 2011; Sasabe et al., 2016). L-Trp is converted into D-Trp via racemase which is normally produced by the gut commensal bacteria (Kato and Oikawa, 2018; Kobayashi, 2019). The addition of D-Trp increased the D-KYN metabolism in the mice/rat liver and plasma, which is dependent on D-amino acid oxidase activity (Ishii et al., 2010; Notarangelo et al., 2016). Feed supplemented with D-Trp also elevated the production of the gut regulatory T cells to ameliorate allergic airway inflammation and increased the diversity of gut microbes in mice (Kepert et al., 2017). D-Trp can be absorbed by the intestinal epithelial cells or secreted into gut lumen, which may be converted to hydrogen peroxide (H_2O_2), a broad-spectrum antibacterial agent, by DAO in the gut to eliminate pathogenic bacterial infection (Molla et al., 2006). D-AA can affect the gut commensal bacterial growth, biofilm formation, and peptidoglycan metabolism as well as pathogenic bacterial colonization in the gut (Hochbaum et al., 2011; Lam et al., 2009). Hence, D-Trp metabolism may have the ability to determine the composition and diversity of gut commensal microbiota. In a recent study, it was reported that D-Trp inhibited the growth of *Citrobacter rodentium* in the mice gut by reducing the IA level to shape the structure of intestinal microbial community (Seki et al., 2022).

3. Trp nutrition in diseases prevention

3.1. Effect on irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder that causes chronic diarrhea or constipation, stomach bloating, and abdominal cramping by affecting the gastrointestinal motility and immunity (Ford et al., 2018; Lee et al., 2022; Raskov et al., 2016). However, the mechanism of IBS-related pathophysiology remains poorly understood. It is suggested that gut microbiota-derived metabolites may contribute to the development of IBS symptoms. L-Trp and its metabolites improved IBS by positively regulating the gut microbial composition, intestinal barrier integrity, and immunity (Gershon, 2013; Stakenborg et al., 2019; Wouters et al., 2007). For example, indole metabolites activate AhR activity in a *Citrobacter reddentium*-infection-induced IBS model in mice. The expression of TpH1, a key enzyme involved in the biosynthesis of the neurotransmitter serotonin, is regulated by the gut bacteria *Corynebacterium* spp., *Streptococcus* spp., and *Enterococcus* spp. (Jun et al., 2011; Kerckhoffs et al., 2012; Spacova et al., 2020). Two probiotics *Lactobacillus* spp. and *Enterococcus* spp. improved the gut barrier and immune function through the generation of indoles and its derivates (Schepper et al., 2020). It is suggested that changing the composition of the gut bacteria related to L-Trp metabolism affects the gut immune function, which in turn may be linked to IBS-related symptoms in livestock and poultry.

Clostridium butyricum and *Enterococcus faecalis* enhanced the intestinal barrier integrity and improved the intestinal immune function in lipopolysaccharide-challenged piglets (Wang et al., 2019). *C. butyricum, Bacillus subtilis,* and *B. licheniformis* also improved the growth performance and intestinal morphology in chickens, ducks, and cows (Sun et al., 2022; Wang et al., 2017, 2023; Xing et al., 2015). Moreover, dietary L-Trp supplementation significantly increased the levels of total antioxidant capacity (T-AOC), glutathione peroxidase (GSH-Px), and catalase (CAT) in the serum and stocking density in white pekin ducks (Liu et al., 2015). Administration of D-Trp increased the number of gut regulatory T cells and altered the diversity of the gut microbiota, which further affected IBS progression (Kepert et al., 2017). IBS is often associated with an increase in intestinal epithelium permeability and lipopolysaccharide levels. Indoles and its derivates have been reported to act as AhR ligands to regulate the intestinal epithelium permeability and immunity. Therefore, L/D-Trp metabolites may contribute to IBS pathology by regulating the gut epithelial integrity and immunity.

3.2. Effect on metabolic syndrome and lipid metabolism

Metabolic syndrome (MS) is intricately linked with the dysregulation of the gut microbiota and host metabolism, causing fatty liver disease and obesity. Several studies have found that various gut metabolites like bile acids, indole derivates, and other bioactive molecules are involved in the modulation of metabolic diseases. Individuals with obesity or multiple sclerosis have active type 1 T helper cell (Th1) immune responses, with increased interferon-gamma (IFN-γ) and interleukin-1beta (IL-1β) expression (Gostner et al., 2015). IFN-γ activates the rate-limiting enzyme IDO in the monocyte-derived macrophages and dendritic cells. IDO1-deficient mouse reduced development of atherosclerosis lesions through the activation of interleukin-10 (IL-10) (Kim et al., 2019). Besides, D-Trp may be transferred to liver, kidney and lung where it can be further metabolized into H_2O_2 to induce low-grade chronic inflammation, causing metabolic imbalance. Even though 5-HT cannot cross the BBB, it is still capable of inducing satiety to prevent excessive food intake, and thereby avoiding obesity progression (Garfield et al., 2014; Hansson et al., 2016). Melatonin acts as a metabolic regulator to improve sleep efficiency and exhibits antioxidant and anti-inflammatory properties. Melatonin treatment improved insulin sensitivity and lipid metabolism in type 2 diabetic rats and increased the hepatic glycogen content in the mouse liver (Ayyash and Holloway, 2021, 2022). Abolished synthesis of melatonin resulted in hyperinsulinemia and fatty liver disease in mice (Stacchiotti et al., 2019).

Trp metabolites play an important role in lipid metabolism. 5-HT has been shown to stimulate lipolysis in adipose tissue and promote gluconeogenesis in hepatocytes. 5-HT increased the lipid accumulation through activation of prostaglandin endoperoxide synthase 1 in the mouse liver (Garfield et al., 2014; Hansson et al., 2016). Supplementation with L-Trp increased the amount of triglycerides and non-esterified fatty acids in chickens and ducks (Rogers and Pesti, 1992). Supplementation with AhR agonists or *Lactobacillus reuteri* improved the glucose dysmetabolism and liver steatosis by compensating the gut microbiota-mediated AhR signaling (Hwang et al., 2016). In addition, lipid metabolism also affected the reproduction performance and shaped the quality of gametes and embryos in livestock. Upregulation of genes related to lipid metabolism such as perilipin 2, apolipoprotein A-1, and sterol O-acyltransferase-1 promoted lipid accumulation and enhanced blastocyst formation and cell differentiation in pigs and cows (Kajdasz et al., 2020; Kelly et al., 2016).

SCFAs consist of acetate, propionate, and butyrate which are generally produced by the gut bacteria-mediated fiber fermentation to modulate lipolysis and adipogenesis. Acetate and propionate inhibit endogenous lipolysis and acetate promotes adipocyte differentiation (Al-Lahham et al., 2012; Li et al., 2014). Diet modulates the SCFA production via regulating the gut microbial composition. Dietary Trp supplementation changed the abundance of SCFA-producing bacteria *E. faecalis, E. coli, Lactobacillus* spp., *Bifidobacterium* spp., and *Clostridium sporogene* in the gut (Belzer et al., 2017; Louis et al., 2010; Reichardt et al., 2014; Scott et al., 2006). Supplementation with *Lactobacillus plantarum JL01* improved the L-Trp metabolism and fat digestion and absorption in the cecum of weaned piglets (Geng et al., 2021). Both L-Trp metabolites and fatty acids relieved the necrotizing enterocolitis induced by fish oil treatment in piglets (Yakah et al., 2021). The n-6:n-3 polyunsaturated fatty acid (PUFA) (1:1–5:1) facilitated the absorption and utilization of fatty acids and improved the adipose composition in the longissimus dorsi of pigs (Li et al., 2015). Feeding sows with a high–low Trp diet (0.39% Trp in the morning and 0.13% Trp in the afternoon) significantly increased the n-6:n-3 PUFA ratio in the livers of their newborn piglets (Xu et al., 2019). L-Trp improved the lipid metabolism to overcome oxidative stress and metabolic challenges in piglets fed with oxidized corn oil (Gao et al., 2022). Dietary supplementation with 0.8% L-Trp increased the expression level of peripheral serotonin, which in turn affected the hepatic lipogenesis and gluconeogenesis, and increased glycolysis in low body weight piglets (Goodarzi et al., 2021). The TpH1 inhibitor oxyphenylalanine and heterocyclic phenylalanine interacts with the peripheral system to decrease the fat accumulation in the liver (Pagire et al., 2022).

3.3. Effect on bacterial infection and growth

The combination of *E. coli Nissle* (EcN) and L-Trp, but not EcN or L-Trp alone, improved the rotavirus infection-induced diarrhea in malnourished piglets by reducing the expression levels of proinflammatory genes (Michael et al., 2022). Dietary supplementation with L-Trp compensated the body weight loss and growth performance in weaned piglets infected with enterotoxigenic *E. coli K88* (Capozzalo et al., 2015; Trevisi et al., 2009). The indole pathway-derived AhR agonists have been reported to protect against a variety of microorganism infections. For example, IAld induced the production of IL-22 to defend against mucosal candidiasis infection (D'Onofrio et al., 2021). Lack or degradation of AhR led to an increased susceptibility to *C. rodentium* infection in mice (Meynier et al., 2022). In contrast, the restoration of AhR levels decreased the host susceptibility to the same bacterial infection (Meynier et al., 2022). Moreover, $CD4^+$ T cells limited *Chlamydia* and *Leishmania* parasite infection through the over-activation of IDO1 expression (Dey et al., 2020). Recent study has shown that D-Trp, similar to other D-AA, plays an important role in inhibiting bacterial growth (Chen et al., 2018). Supplementation with D-Trp, but not L-Trp alone, in peptone yeast glucose broth significantly inhibited the growth of *Listeria monocytogenes*, *Salmonella enterica,* and *E. coli* 0157:H7 (Elafify et al., 2020; Koseki et al., 2015). Moreover, dietary addition of D-Trp significantly decreased the biofilm formation of *Pseudomonas mendocina* and *Staphylococcus aureus* (Ghosh et al., 2019). These findings suggested a potential strategy to protect against bacterial growth and infection through dietary supplementation with D-Trp.

3.4. Effect on neuronal activity

Increasing evidence suggests that gut-derived metabolites can regulate the neuronal activity in the brain to control host behavior

via the gut-brain axis (Chu et al., 2019; Gracie et al., 2019; O'Donnell et al., 2020; Sharon et al., 2019). Intestinal L-Trp metabolism catalyzed by *Bacteroides* regulated numerous behaviors in weaned piglets such as feeding, attacking, and sleeping. Serotonin levels affected the secretion of anorexigenic hormones in the brain to regulate feeding in piglets (Cui et al., 2012; Lam et al., 2010). The serotonin pathway metabolized L-Trp to 5-HT whose low expression in the brain is a key symptom of depression (Saitow et al., 2020). Augmentation of 5-HT levels by supplementing with a high Trp diet increased positive emotions and alleviated depression (Firk and Markus, 2009). The non-competitive NMDA receptor antagonist acts as an inhibitor of serotonin reuptake to improve obsessive-compulsive disorder (Guo et al., 2020). Melatonin, the key Trp metabolite from the serotonin pathway, regulates the circadian rhythm and periodical hormone secretion and is often utilized to treat chronic insomnia (Bhattacharya et al., 2019; Ferracioli-Oda et al., 2013). Depletion of TpH2, a core enzyme that catalyzes the conversion of Trp to serotonin, impaired the normal growth of Bama miniature pigs before the weaning stage (Ze et al., 2017). KYNA is a KP metabolite that negatively regulates NMDA activity and positively modulates the immune responses by activating AhR (Blanco-Ayala et al., 2020; Martos et al., 2022; Walczak et al., 2021). A positive correlation between KYNA levels and dopaminergic activity has been found in the brain (Muller et al., 2013). Additionally, KYNA could relieve the stress responses and positively affect the retina development in cows (Gurdita et al., 2023; Rejdak et al., 2003; Yoshida et al., 2013; Zarnowski et al., 2004). QUIN, another neuroactive metabolite derived from the KP, acts as an NMDA receptor agonist to inhibit the reuptake of glutamate in astrocytes and disrupts the energy homeostasis in the brain (Notarangelo et al., 2016). The role of QUIN in eliciting cognitive deficits has recently been reported in mice and piglets (Huang et al., 2021; Lee et al., 2020, 2021; Millischer et al., 2021). The increased QUIN levels are associated with several neurodegenerative disorders, such as Alzheimer's and Huntington's disease (Campesan et al., 2011).

4. Trp nutrition in swine production

4.1. Effect on gut microbial homeostasis and growth performance in weaned piglets

Post weaning diarrhea causes great economic loss in the swine industry worldwide. Undernutrition and dysbacteriosis are two major etiological factors causing diarrhea in weaned piglets (Li et al., 2021). Recently, nutritional intervention has been utilized as an effective strategy to improve or prevent malnutrition caused-diarrhea in weaned piglets by optimizing the dietary nutrition levels, such as amino acids (He et al., 2022), proteins (Hamoud et al., 2018; Kennedy et al., 2017), bioactive compounds from medicinal plants (Liu et al., 2016a), yeast-derived nucleotides, and gut microbiota-generated metabolites (Erhardt et al., 2017).

The effect of L-Trp supplementation in a corn and soybean meal-based diet on regulating the diversity and composition of gut microbes became evident in weaned piglets. Dietary supplementation with 0.35% L-Trp increased the abundance of *Ruminococcaceae*, *Lactobacillus*, and *Muribaculaceae* and decreased the abundance of *Turicibacter, Prevotella,* and *Methanobrevibacter* in the colon of weaned piglets (Rao et al., 2021). Similarly, feeding weaned piglets with 0.2% and 0.4% L-Trp also changed the microbial composition and diversity, with an increased population of *Prevotella*, *Roseburia,* and *Succinivibrio genera* and decreased the population of *Clostridium sensu stricto*, *Clostridium XI*, and opportunistic pathogens in the cecum (Liang et al., 2018a). In contrast, dietary addition of 0.2% to 0.4% L-Trp increased the abundance of *Lactobacillus* and *Clostridium XI* and reduced the abundance of *C. sensu stricto* and *Streptococcus* in the jejunum of weaned piglets. Moreover, L-Trp supplementation activated AhR and the expression of immune responsive genes CYP1 A1/B1, tight junction protein zonula occludens-1 (ZO-1) and occludin, antimicrobial peptide porcine β-defensin-2 (pBD-2) (Chen et al., 2019; Liang et al., 2018a). However, dietary supplementation with 0.75% L-Trp negatively affected the gut barrier function in the jejunum of weaned piglets, with decreased levels of tight junction protein ZO-1 and occludin (Tossou et al., 2016). Additionally, dietary supplementation with L-Trp alleviated dysbacteriosis and may improve lipopolysaccharide infection-induced diarrhea in weaned piglets (Liu et al., 2022; Xia et al., 2022). *Folium sennae* extracts in an infection-caused diarrhea model has been found to shape the mouse gut microbial structures by reducing the abundance of *Adlercreutzia*, *Lactobacillus*, *Dehalobacterium*, *Dorea,* and *Oscillospira,* all of which are involved in Trp metabolism (Zhang et al., 2020). It is possible that the modulation of the gut microbial composition and gut immune function may contribute to the prevention of diarrhea in weaned piglets.

Notably, the effect of dietary L-Trp supplementation on the improvement of growth performance in weaned piglets remains controversial. Feeding with 0.21%, 0.28%, and 0.35% of L-Trp significantly improved the average daily feed intake (ADFI) average daily gain (ADG) weight, feed conversion ratio (FCR), visceral organ index, and decreased the diarrhea rate in weaned piglets (Rao et al., 2021). However, other studies found that dietary addition of 0.15% and 0.75% L-Trp did not affect the growth performance but increased the crypt depth and ratio of villus height to crypt depth in the jejunum of weaned piglets. It seems that the effect of dietary Trp on the growth performance of piglets is dose-dependent, low or excessive addition of L-Trp does not significantly improve the growth performance but may improve feed utilization in weaned piglets (Liu et al., 2017; Sterndale et al., 2020).

4.2. Effect on growth performance in growing pigs

L-Trp is often formulated with other indispensable amino acids to regulate the growth performance of growing pigs (Table 1). Increasing the standardized ileal digestible (SID) leucine (Leu) to Trp or valine (Val) to Trp ratios partially alleviated the negative effects caused by excessive Leu on the ADG, ADFI, and hypothalamic serotonin level in growing pigs (Kerkaert et al., 2021; Kwon et al., 2021a, 2021b). Additionally, elevating the SID Trp to lysine (Lys) ratio from 0.150 to 0.225 increased the ADG, ADFI, and gain-to-feed (G:F) ratio in grower–finisher pigs (Liu et al., 2019b). Maintaining the levels of Lys, methionine (Met), threonine (Thr), and L-Trp in early protein-restricted diets during the grower phase improved the growth performance, with an increased growth rate and FCR, and decreased diarrhea rate (Sun et al., 2020). Additionally, the addition of different L-Trp concentrations to the diet with low crude protein levels enhanced the ADG and G:F ratio in growing barrows (Sato et al., 2021). Intensified housing conditions and poor sanitation are often associated with decreased growth performance and the abnormal activation of the immune system during pig farming. Increased dietary levels of Trp, Thr, and Met + cysteine (Cys) have been shown to improve the growth performance and protein deposition in growing pigs with *Salmonella typhimurium* infection and under poor sanitation conditions (Valini et al., 2023). The dietary Trp requirements of growing female pigs at different body weights have been analyzed by Eder et al., they found that Trp-deficient diets at the body weights of 25 to 50 kg and 50 to 80 kg reduced the feed consumption through the reduced production of serotonin, but insufficient Trp supplementation in the later age had

Table 1
Effect of Trp nutrition in swine production.

Stage	Experimental duration, days	Trp level	Effects	Reference
Piglets				
Duroc × (Landrace × Yorkshire)	21	0.15%	Improved growth performance	Liu et al. (2019a)
Landrace × Yorkshire	28	0.2% or 0.4%	Improved intestinal mucosal barrier function	Liang et al. (2018b)
PIC	14	0.30% or 0.45%	Enhanced the antioxidant capacity	Mao et al. (2021)
Great Yorkshire × (Pietrain × Dalland)	28	0.5 g/kg	Increased feed intake and decrease FCR	Jansman et al. (2019)
Duroc sire line and Large White × Landrace dam	21	0.80%	Improved lipid and glucose metabolism	Goodarzi et al. (2021)
Pietrain × dbNaima/Porcus	34	Trp:Lys ratio (16.8%)	Improved feed to gain ratio	Naatjes et al. (2014)
Duroc × Landrace	21	0.16% Trp + 0.41% Phe + 0.22% Tyr	Promoted the amino acid absorption	Duanmu et al. (2021)
Large White × Landrace	21	0.34% SID Trp:4.6% SID LNAA	Improved aspects of post-weaning performance	Sterndale et al. (2020)
Landrace	14	15 μM ICA	Enhanced intestinal epithelial proliferation	Zhang et al. (2022)
Growing pigs				
Duroc × Yorkshire × Landrace	28	SID Trp:Lys ratio (22.5%)	Increased ADG, ADFI, gain to feed ratio	Liu et al. (2019b)
PIC		SID Trp:Lys (23%)	Prevented negative effects of excessive Leu in diets	Kwon et al. (2021b)
PIC TR4 × (Large White × PIC L02)	103	Moderate L-Lys HCl + high Ile, Val, and Trp + Val	Increased ADFI	Kerkaert et al. (2021)
Landrace	42	0.06% Trp in low CP diet	Increased ADG, ADFI	Sato et al. (2021)
	28	Trp + Thr + Met	Improved growth performance and protein deposition	Valini et al. (2023)
[Deutsches Edelschwein or Landrace × Deutsches Edelschwein (dam)] × [Pietrain (sire)]	14	Trp-deficient diet	Reduced the feed consumption	Eder et al. (2003)
	50	0.16%	Improved the growth performance and meat quality	Jiao et al. (2016); Ma et al. (2020)
Sows				
Landrace × Yorkshire	Began on day 103 of gestation and ended on day 28 of lactating	0.12%	Improved reproduction performance	Miao et al. (2019)
French Landrace × Large White	28	0.3%	Tendency of increased litter weaning weight	Mosnier et al. (2010)
Large White × Landrace	28	0.37%	Reduced aggressive behavior	Poletto et al. (2014)
Large White × Landrace	28	Trp-enriched diet	Increased exploratory activities	Lay et al. (2021)
Landrace × Yorkshire		0.35% in gestation and 0.48% in lactation	Decreased head-to-head knocking behaviors	Li et al. (2011)
Large White	Lasted approximately 30 days until delivery	0.39%	Decreased piglet birth weight	Xu et al. (2019)
Landrace × Large White	Late pregnancy until 7 days of lactation	0.42% or 0.56%	Increased piglet survival	Munn et al. (2021)

PIC = pig improvement company; Trp = tryptophan; Lys = lysine; Thr = threonine; Met = methionine; Phe = phenylalanine; Tyr = tyrosine; Ile = isoleucine; Val = valine; LNAA = large neutral amino acid; ICA = indole-3-carboxaldehyde; FCR = feed conversion ratio; ADG = average daily gain; ADFI = average daily feed intake; SID = standard ileal digestibility; CP = crude protein; SID = standardized ileal digestibility.

no effect on feed consumption (Eder et al., 2003). Additionally, supplementation with 0.16% L-Trp improved the growth performance and meat quality of finishing pigs through the secretion of serotonin in the brain to alleviate stress responses (Jiao et al., 2016; Ma et al., 2020).

4.3. Effect on reproduction performance in sows

The effect of Trp supplementation on the reproduction performance of gestating/lactating sows has been studied (Table 1). Feeding lactating sows with 0.12% L-Trp increased the milk yield by activating the 5-HT levels in the porcine mammary epithelial cells, induced milk calcium concentration via the activation of CaM, increased the ADFI in lactating sows, and the ADG weight of their piglets (Miao et al., 2019). In addition, 0.3% Trp supplementation in lactating sows did not significantly affect the sow or litter performance, and only multiparous sows showed a tendency of increased litter weaning weight (Varvel, 2019). The dynamic dietary L-Trp requirements have been reported in gestating sows, with an increased Trp intake in late pregnancy compared to early pregnancy (Franco et al., 2014). Feeding sows with 0.42% or 0.56% L-Trp during the late pregnancy stage increased the piglet survival rate but had no significant effect on the serum melatonin and calcium levels (Munn et al., 2021). Sows fed with 0.37% L-Trp for a short duration during early gestation did not affect the birth weight and mortality, but the reduced aggression behavior was displayed in both sows and their piglets (Poletto et al., 2014). Supplementation with 0.35% L-Trp in the gestation diet and 0.48% L-Trp in the lactation diet decreased the total duration of head-to-head knocking behaviors in sows (Li et al., 2011). Additionally, L-Trp-enriched diet also increased the exploratory activities like nosing, rooting, and standing in gestating multiparous sows (Poletto et al., 2014). Notably, excessive L-Trp feeding to sows caused negative effects on their newborn piglets. Dietary supplementation of 0.39% L-Trp in sows at the late pregnancy stage decreased the average piglet birth weight, live farrowing rate, and hepatic fatty acid composition in the newborn piglets (Xu et al., 2019).

5. Conclusions and perspectives

Intestinal Trp metabolism and its metabolites play pivotal roles in regulating the host physiology and pathology. Strikingly, both L-Trp and D-Trp metabolites can determine the composition and diversity of the gut microbes and subsequently modulate the host–microbe interactions. It is important to further delineate the detailed mechanisms of L/D-Trp metabolism in the gut at different levels, from the gene regulation within a single cell to its functional interaction between the inter-connected organs, by combining metagenomics, transcriptomics, proteomics, and metabolomics. Additionally, the molecular mechanisms underlying how Trp metabolites modulate the swine production at various feeding stages also await further investigation.

Author contributions

Zhenguo Hu, Xiongzhuo Tang, Yulong Yin: Conceptualization, Revision. **Zhenguo Hu, Xiongzhuo Tang**: Writing-Original draft. **Zhenguo Hu, Luya Feng, Qian Jiang, Wenliang Wang, Bi'e Tan, Xiongzhuo Tang, Yulong Yin**: Writing-Review & Editing.

Declaration of competing interest

We confirm that the manuscript has not been published elsewhere and is not under consideration by other journals. All authors have approved the manuscript and agree with submission to Animal Nutrition. The authors have no conflicts of interest to declare.

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