

Microorganisms, Tryptophan Metabolism, and Kynurenine Pathway: A Complex Interconnected Loop Influencing Human Health Status

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ABSTRACT: The kynurenine pathway is important in cellular energy generation and limiting cellular ageing as it degrades about 90% of dietary tryptophan into the essential co-factor NAD⁺ (nicotinamide adenine dinucleotide). Prior to the production of NAD⁺, various intermediate compounds with neuroactivity (kynurenic acid, quinolinic acid) or antioxidant activity (3-hydroxykynurenine, picolinic acid) are synthesized. The kynurenine metabolites can participate in numerous neurodegenerative disorders (Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, and Parkinson disease) or other diseases such as AIDS, cancer, cardiovascular diseases, inflammation, and irritable bowel syndrome. Recently, the role of gut in affecting the emotional and cognitive centres of the brain has attracted a great deal of attention. In this review, we focus on the bidirectional communication between the gut and the brain, known as the gut-brain axis. The interaction of components of this axis, namely, the gut, its microbiota, and gut pathogens; tryptophan; the kynurenine pathway on tryptophan availability; the regulation of kynurenine metabolite concentration; and diversity and population of gut microbiota, has been considered.

KEYWORDS: gut microbiota, gut-brain axis, indoleamine 2,3-dioxygenase, kynurenine pathway, neurodegenerative disorder, tryptophan

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Background

Microorganisms are capable of producing a wide range of metabolites from antibiotics,^{1–3} pigments,⁴ and vitamins, to antioxidants,^{5,6} enzymes,⁷ and toxins.⁸ They can exert positive or negative effects through the production of some of these metabolites when they live in the human body as microbiota.⁹ For instance, the human microbiota, particularly gastrointestinal (GI) tract microbiota and their metabolites, influence both the physiology and immunity states of the body. In recent decades, many efforts have been devoted to understand the complex roles of GI microorganisms in several health complications in respect of diversity and population. For example, the microbiota-brain communication and its mechanism of action on the various organs are under investigation.^{10–12} The kynurenine pathway (KP) is a major pathway of L-tryptophan catabolism, contributing to the production of various neuroactive compounds.¹³ It is well documented that the KP metabolites are associated with inflammatory responses, neurological disorders, and immunity regulation.¹⁴ Similarly, the metabolism of L-tryptophan in the GI tract by the host cells and microbiota may be involved in intestinal homeostasis and various health complications through influencing the biosynthesis of some compounds such as neurotransmitters, neurotoxicity, and antimicrobial metabolites. This review discusses the role of GI bacteria in tryptophan metabolism and explains how

tryptophan metabolism, particularly through the KP, can affect the diversity and population of microbiota in the GI. We begin by describing tryptophan catabolism by the KP and its impact on health status. This is followed by discussion on the interactions between GI bacteria and tryptophan metabolism and their effects on various immunity responses and disorders. Understanding the complex communication between GI microbes and tryptophan metabolism can be helpful in exploring new treatment targets in various human diseases.

Tryptophan and Its Importance in Human Body

Tryptophan is an essential amino acid, which cannot be synthesized by the human body. Therefore, it must be provided through nutritional sources. Tryptophan is found in 2 forms in the body: either bound to albumin or in free form. Both are in equilibrium. The transportation of tryptophan across the blood-brain barrier occurs only in the free form through non-specific transporters of L-type amino acids. The amount of L-tryptophan in the tissue of the human body is lower than other amino acids,¹⁵ and minute concentrations of tryptophan are essential for maintaining health.^{16,17} The recommended amount of tryptophan is approximately 250 to 425 mg/d/adult, but usually a higher dose of 900 to 1000 mg/d for each individual is received from the diet.¹⁶ The most common sources of tryptophan in the human diet are fish, bananas, milk, oats, chicken, chocolate, and peanuts.¹⁵



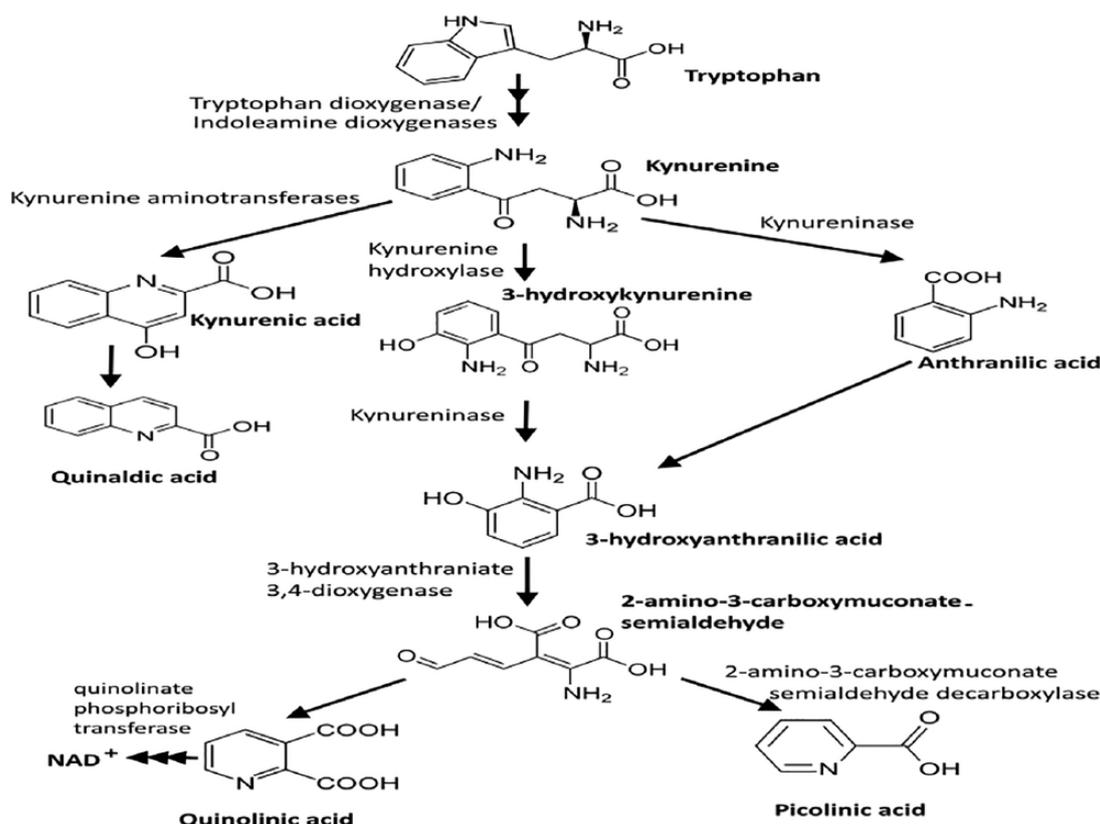


Figure 1. Kynurenine pathway, the main route of tryptophan metabolism. NAD indicates nicotinamide adenine dinucleotide.

In the human body, tryptophan is mainly consumed for proteins synthesis and is produced in smaller amounts than other amino acids. It, therefore, may play a rate-limiting role in the synthesis of proteins.^{16,18} In addition, tryptophan is a precursor of 2 metabolic pathways, including KP and serotonin pathway.^{19,20} Approximately 90% of tryptophan catabolism occurs through KP,²¹ which produces various metabolites with kynurenic acid and quinolinic acid as the most important intermediates. The former is recognized as glutamate receptor antagonist, whereas the latter is a glutamate receptor agonist.²² In mammals, approximately 95% of the serotonin is found in the GI tract, and only 3% of dietary tryptophan is used for serotonin synthesis.¹⁵ The amount of 1% of dietary tryptophan is involved in serotonin synthesis in the brain,²³ which functions as a neurotransmitter and neuromodulator. In addition to protein, kynurenine, and serotonin synthesis, tryptophan is used for the synthesis of tryptamine, which is a neuromodulator of serotonin. In vivo studies have indicated that tryptamine can control the balance between the excitatory and inhibitory activity of serotonin.²⁴ Moreover, tryptamine is recognized as an independent neurotransmitter with a specific receptor.²⁴ Melatonin is another metabolite produced in the serotonin pathway and influences the digestive, immune, and reproductive systems and diurnal rhythms.^{25,26} Tryptophan can also act as a substrate for the synthesis of coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Nicotinamide adenine dinucleotide participates in cellular energy (oxidation-reduction reactions) and aging.

KP: The Major Route of Tryptophan Catabolism

Nicotinamide adenine dinucleotide and several neuroactive intermediates are produced during the KP, that is, the main route of L-tryptophan catabolism (Figure 1).¹³ The intermediates include kynurenine, kynurenic acid, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, picolinic acid, and quinolinic acid.²⁷ In the first step, tryptophan is cleaved by tryptophan 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase (IDO) 1, or IDO2. TDO is mainly present in liver cells, whereas IDO1 is found in other type of cells, including microglia, macrophages, and neurons.²⁸ IDO1 can be upregulated by cytokines and inflammatory molecules such as interferon γ (IFN- γ) (the most potent inducer), amyloid peptides, and lipopolysaccharides. Kynurenine is produced from tryptophan by the catalytic activity of IDO or TDO and is converted into kynurenic acid, 3-hydroxy kynurenine, and anthranilic acid, respectively. 3-hydroxy kynurenine and anthranilic acid are converted into 3-hydroxyanthranilic acid and finally can form either picolinic acid or quinolinic acid in enzymatic (2-amino-3-carboxymuconate-semialdehyde decarboxylase) or nonenzymatic reactions, respectively (Figure 1).

KP and Its Role in Human Health Status

The KP has been tracked in various diseases of the central nervous system (CNS) such as Alzheimer disease, amyotrophic lateral sclerosis, AIDS dementia complex, and Huntington disease.^{14,29-31} Under various CNS disorders, the metabolism of tryptophan increases and the concentration of KP metabolites

arises in the serum and cerebrospinal fluid (CSF) (Table 1). Here, we describe the impact of various intermediates of the KP on human health status.

Kynurenic acid

Kynurenic acid is a neuroprotective molecule which can act as an antagonist of quinolinic acid on both glycine and glutamate modulatory sites of N-methyl-D-aspartate (NMDA) receptor at low and high concentrations, respectively. This molecule also is an antagonist for α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate and α 7 (α 7) nicotinic acetylcholine receptors.⁴⁵ High levels of kynurenic acid in the brain have anticonvulsant, sedative, and protective effects against brain ischaemia.⁴⁶ On the contrary, increases in kynurenic acid in CSF of patients with schizophrenia have been reported, suggesting the effect of this molecule on the glutamatergic and dopaminergic systems as well as its possible activity in the development of schizophrenia.⁴² In vivo studies have shown that in a septic shock mouse model, a significant decrease in the release of tumour necrosis factor α , nitric oxide, and high-mobility group box 1 protein occurred in the presence of kynurenic acid.⁴⁷ Unexpectedly, kynurenic acid can suppress the release of fibroblastic growth factor 1. This compound mainly facilitates the recovery of damaged cells and promotes glial cell proliferation.⁴⁷

3-hydroxyanthranilic acid

This neurotoxin compound is produced through 3-hydroxykynurenine hydrolysis or anthranilic acid oxidation. The presence of copper and 3-hydroxyanthranilic acid causes free radical generation. However, it has been found that this compound can also act as an antioxidant and radical scavenger.⁴⁸ Inhibition of nuclear factor κ B and inducible nitric oxide synthase has been observed in murine macrophages after treatment with 3-hydroxyanthranilic acid at sub-millimolar concentrations.⁴⁹ Studies of the lines of tumorigenesis have indicated that 3-hydroxyanthranilic acid is non-toxic at low concentrations and could not affect the T-cell receptor-induced CD8⁺ T-lymphocyte proliferation. However, it can significantly inhibit the cell proliferation triggered by antigen-independent cytokine.⁵⁰ Moreover, 3-hydroxyanthranilic acid has a selective apoptotic activity on murine thymocytes and T_H1 cells. This selective apoptosis is triggered through the activation of caspase 8 and release of cytochrome c from mitochondria. Notably, this activity is observed at lower concentrations in those cells that are needed for the apoptosis of macrophages, representing a significant role of this compound in peripheral immunoregulation.⁵¹

Picolinic acid

This endogenous neuroprotectant compound is recognized as an iron and zinc chelator. Various activities such as antifungal,

antiviral, antitumoural, and cell growth regulatory activities have been reported for picolinic acid. In vitro studies have exhibited that picolinic acid can potentially arrest the cells in the G1 phase through interaction with NAD⁺.⁵² It has been found that the SK-N-SH neuroblastoma cell line is not capable of synthesizing picolinic acid.⁵³ Therefore, the absence of this antitumour activity may lead to tumour persistence.

Picolinic acid exerts its antifungal activity through a synergistic effect with IFN- γ to boost the inhibitory activity of neutrophils against *Candida albicans*.^{54,55} At concentrations of 1.5 to 3 mM, picolinic acid showed antiviral and cytotoxic activity against HIV-1 and human herpes simplex virus 2, which could be due to the upregulation of the inflammatory protein (MIP-1 α) in macrophages and expression of MIP-1 β messenger RNA (mRNA).^{56,57} It is important to note that this effect of picolinic acid on MIP-1 α and MIP-1 β is counteracted by IFN- γ , showing the significant role of picolinic acid-IFN- γ complex in the regulation of inflammatory responses.⁵⁸

Similar to kynurenic acid, but to a lesser extent, picolinic acid can also inhibit the neurotoxic effect of quinolinic acid through a different mechanism, that is, possibly through chelating zinc and/or decreasing the calcium-dependent glutamate release.^{59,60}

Quinolinic acid

Quinolinic acid can exert neurotoxic activity by activating NMDA receptors in neurons. In the brain, most tryptophan molecules are metabolized into 5-hydroxytryptamine rather than to formylkynurenine, leading to lower concentrations of quinolinic acid than in blood and systemic tissues.⁶¹ Interestingly, during a systemic or central immune response, the IDO1 activity and quinolinic acid concentration increase. The reason for this is unclear.⁶² Infiltrating macrophages, dendritic cells, and microglia provide the main sources of quinolinic acid in the brain during inflammation.⁶³ Astrocytes are unable to synthesize the quinolinic acid due to the fact that these cells do not have the essential enzyme, kynurenine hydroxylase. Quinolinic acid can play a neuroprotective role in low concentration, which could be catabolized to NAD⁺. However, quinolinic acid levels beyond this point cause saturation of the catabolic system, resulting in neurotoxic effects.⁶⁴ In vitro, quinolinic acid can induce the T_H1 target cells' apoptosis and can selectively suppress the proliferation of killer cells, and CD4⁺ and CD8⁺ T lymphocytes that are overstated under the absence of tryptophan.^{65,66} These studies have revealed that the sub-millimolar concentration of quinolinic acid has a toxic effect on neuronal culture and causes cell death.^{67,68} Moreover, in vivo investigations have shown that injection of quinolinic acid to the brain of rats generates axon-sparing lesions.⁶⁹ According to the several studies, quinolinic acid contributes to various neurodegenerative diseases such as Alzheimer disease, AIDS dementia complex, Huntington disease, and multiple sclerosis.^{27,70}

Table 1. Measurement of kynurenine pathway metabolites in plasma/serum and CSF of CNS patients.

DISEASE	ORIGIN OF SAMPLE	COMPOUND	PATIENT	CONTROL	REFERENCES
Anxiety	Plasma/serum	KYN (μM)	9.32 ± 0.2	4.32 ± 0.3	Orlikov et al ³²
Alzheimer disease	Plasma/serum	KYN (μM) KYNA (nM)	2.5 ± 0.1 $15.82.31 \pm 1.1$	2.01 ± 0.2 23.13 ± 2.2	Hartai et al ³³
ALS	Plasma/serum	KYNA (nM)	57.8 ± 35.0 81.6 ± 41.2^a (m.c.s.) 39.9 ± 14.7 (s.c.s.)	59.6 ± 20.5	Ilzecka et al ³⁴
ALS	Plasma/serum	TRP (μM) KYN (μM) QUIN (mM) PIC (mM) K/T ($\times 10^3$)	143.28 ± 5.64 4.02 ± 0.2 0.37 ± 0.018 1.42 ± 0.087 37 ± 2.5	75.0 ± 10.5 2.52 ± 0.19 0.30 ± 0.026 2.38 ± 0.37 39 ± 4	Chen et al ³⁵
Chronic brain injury	Plasma/serum	TRP (μM) KYN (μM) KYNA (μM) 3-HK (μM) 3-HAA (μM) QUIN (μM) K/T ($\times 10^3$)	Data obtained from graph: No difference Higher Lower Lower Lower No difference Higher		Mackay et al ³⁶
CNS pathology	CSF	QUIN (nM) KYN (nM)	31 ± 5 (Hy) 200 ± 113 (H) 282 ± 82 (T) 1084 ± 549 (C) 185 ± 40 (Hy) 254 ± 128 (H) 1698 ± 589 (T) 2610 ± 1067 (C)	20 ± 2 54 ± 7	Heyes et al ³⁷
HD	Plasma/serum	TRP (μM) KYN (μM) KYNA (μM) 3-HK (μM) 3-HAA (μM) QUIN (μM) K/T ($\times 10^3$)	Data obtained from graph: No difference Higher No difference Lower Lower No difference Higher		Stoy et al ³⁸
Major depression	Plasma/serum	TRP (μM) KYN (μM) KYNA (nM) 3-HAA (nM) K/T ($\times 10^3$)	65.8 ± 15.57 1.81 ± 0.56 24.29 ± 8.09 24.53 ± 11.91 25 ± 12	69.71 ± 13.65 1.87 ± 0.43 35.95 ± 13.4 24.12 ± 7.3 17 ± 14	Myint et al ³⁹
MS	CSF	KYNA (nM)	0.41 (MS) 0.67 (OND) 1.7 (ID)		Rejdak et al ⁴⁰
MS and cerebrovascular disease (CVD)	CSF	TRP (nM) 5-HT (pM) 5-HIAA (pM)	1.25 ± 0.14 (MS) 3.34 ± 0.54 (CVD) 5 ± 1 (MS) 7 ± 2 (CVD) 116 ± 15 (MS) 299 ± 50 (CVD)	2.02 ± 0.34 7 ± 2 173 ± 20	Baig et al ⁴¹
Schizophrenia	CSF	KYN (nM)	1.67 ± 0.027	0.97 ± 0.07	Erhardt et al ⁴²
Schizophrenia	CSF	KYNA (nM)	1.45 ± 0.10 (grp) 1.53 ± 0.19 (1st) 1.53 ± 0.17 (T) 1.16 ± 0.06 (noD)	1.06 ± 0.06	Nilsson et al ⁴³
Attention deficit hyperactivity disorder	Serum	KYNA (ng/mL) TRP (ng/mL) KYN (ng/mL)	3.2 ± 0.9 8914.9 ± 1776.3 440.3 ± 158.6	3.6 ± 1.4 8038.6 ± 2219.6 296.0 ± 148.7	Evangelisti et al ⁴⁴

Abbreviations: 1st, drug-naïve first-episode patients; ALS, amyotrophic lateral sclerosis; C, CSF infection; CNC, central nervous system; CSF, cerebrospinal fluid; grp, all patients; H, haemorrhage; Hy, hydrocephalus; ID, infectious inflammatory disease; m.c.s/s.c.s., mild clinical status/severe clinical status; MS, patients with relapsing multiple sclerosis (MS) during remission or not progressing for at least 2 months; noD, patients who had been treated but are now drug-free; OND, non-inflammatory neurological disorders; T, patients undergoing treatment with anti-psychotic drugs; T, tumour.

^aSignificantly lower KYNA in s.c.s. compared with m.c.s.

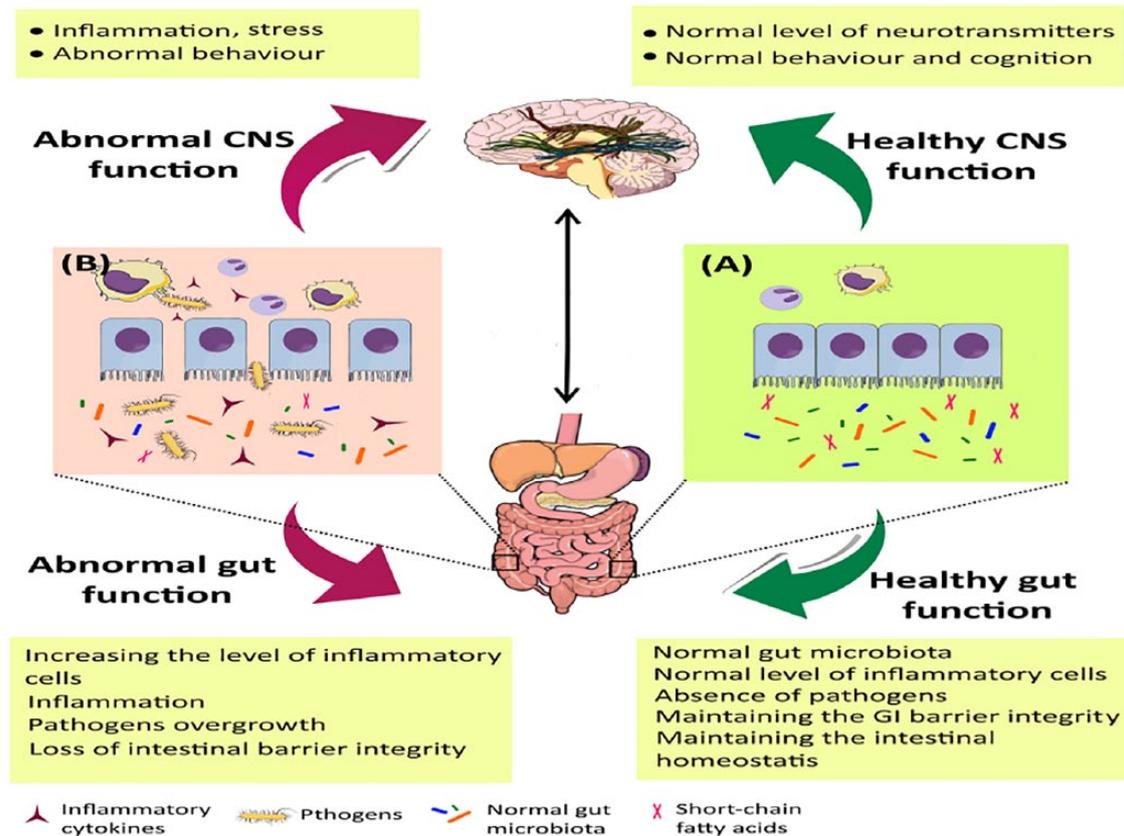


Figure 2. Communication between the gut microbiota and the CNS. (A) Normal microbial community in the GI controls the intestinal homeostasis and contributes to better immunity responses in the intestine and the brain. In contrast, (B) intestinal dysbiosis alters the normal microbial community in the GI and adversely affects immunity regulation in both organs as well as the CNS function. CNS indicates central nervous system; GI, gastrointestinal.

The Gut Microbiota-Brain Communication

The microbiota, a complex dynamic community of microorganisms with a rich pool of genetic materials, has significant roles in the physiological and developmental processes of humans.^{71,72} Microbiota is present in various organs of body such as the skin, oral cavity, respiratory and GI tracts, and vagina. Composition of microbiota is an important factor in determining their positive or negative roles in the human host's health.⁹ The microbiota is a dynamic community evolving during the lifespan of the host, particularly in the first 3 years of life, to form a relatively stable population of microbiota.⁷³ The GI tract harbours the largest community of microbes with a total population of about 10^{14} from 1000 microbial species containing 4×10^6 genes.^{74,75} The gut microbiota of a typical healthy adult consists of 4 main phyla, including *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Verrucomicrobia*. A number of factors such as age, antibiotic intake, diet, genes, infection, and stress affect the community of microbiota in the GI tract.⁷⁶ For example, the population of a microbial community shifts in favour of *Bacteroidetes* species in the gut of old people, compared with young individuals.⁷⁷

The significant regulatory and modulating roles of microbiota in the gut-brain axis and the brain function, as well as developing a bidirectional communication between the brain and gut, have been extensively studied.^{11,72,78} The communication between GI tract and CNS involves the CNS, enteric

nervous system, neuroendocrine and neuroimmune pathways, sympathetic and parasympathetic nerve systems, and the gut microbial community.⁷⁹ The homeostasis preservation which results from the normal gut-brain communication may be disrupted in various diseases. Moreover, any disturbance in the brain-GI bidirectional communication reduces the functions of digestive system, that is, digestion and absorption of food (Figure 2).^{79,80}

The GI microbiota can adjust neurotransmitter levels through either production of the neurotransmitter or regulation of the production of its precursors. For example, it has been reported that the neurotransmitter γ -aminobutyric acid is produced by *Bifidobacterium* and *Lactobacillus* species.⁷⁸ In addition, *Bacillus*, *Escherichia*, and *Saccharomyces* species have the ability to produce the neurotransmitter norepinephrine.⁷⁸ The effects of GI microbiota on neurogenesis have been investigated using in vivo studies in mice.⁸¹ Accordingly, germ-free (GF) mice showed higher hippocampal neurogenesis in the dorsal hippocampus. Post-weaning of microbiota in GF mice could not reverse the changes, emphasizing the significance of the pre-weaning microbial colonization in GI.⁸¹

A number of investigations have concluded that the GI microbiota can influence behaviour, mood, and anxiety.⁸²⁻⁸⁴ These findings have been reported through using various approaches such as GF animal models, antibiotic treatment, probiotic treatment, and GI microbiota transplantation.⁷⁹ A

more recent study has reported that individuals with depressive-like behaviour have a different GI microbiota composition compared with healthy controls.⁸⁵ It is worth mentioning that gut microbiota may also contribute to social behaviour. It has been reported that the faecal microbiota transplantation from depressive-like patients to GF models could induce the depressive-like phenotype and behaviour in the latter group.⁸³ In addition, *in vivo* studies have indicated that GF mice exhibited different social behaviours, compared with normal mice.⁸⁴ This altered behaviour can be normalized through post-weaning the gut microbiota.

Effect of Microbiota on Tryptophan Metabolism and KP

Serotonin is one of the important compounds produced during tryptophan metabolism. The enterochromaffin cells of the mucosa and the nerve terminals of the enteric nervous system neurons are the major serotonin sources in the gut.⁸² Serotonin is mainly responsible for controlling GI motility and secretion in the gut and plays an important role in mood and cognition in the brain.^{86,87} Any changes to the production or amount of this neurotransmitter may cause GI and brain disorders. The availability of tryptophan strongly determines the ability of the brain in serotonin synthesis. The necessary amount of tryptophan in the brain is solely supplied through the diet. Therefore, the peripheral level of tryptophan in GI is essential for serotonin synthesis in the CNS. Interestingly, in the brains of GF animals, alteration in the level of serotonin synthesis was correlated with the availability of tryptophan.⁸⁸ In another study, it has been reported that tryptophan depletion due to a low-tryptophan diet causes low concentration of serotonin in the CNS of human and animal models.⁸⁹ The inhibition of IDO1 that is responsible for the conversion of tryptophan to kynurenine decreases serotonin concentration in the brains of rats and the subsequent alteration in behaviour.⁹⁰

About 90% of tryptophan is metabolized by the KP,⁹¹ and its conversion rate is determined by the expression of IDO1 (in all tissues) and TDO (in liver only). Inflammatory molecules and corticosteroids can affect the activity of these 2 enzymes, respectively. *In vitro* and *in vivo* studies have shown that when INF- γ activates the IDO1, more tryptophan is converted to kynurenine than serotonin, and depressive symptoms are observed.⁹² Desbonnet et al⁹³ reported that probiotic *Bifidobacterium infantis* can affect the tryptophan metabolism, and hence gut-brain axis communication. The inflammatory response decreased and serotonergic precursor increased when animal models were orally given *B. infantis*. Consequently, GI inflammation was attenuated, and depression was treated. However, this finding could not be generalized to all members of the genus *Bifidobacterium*, for example, *Bifidobacterium longum* did not alter tryptophan metabolism and KP in examined animal models.⁷⁹ In the absence of gut microbiota, an increase in the concentration of tryptophan in plasma leads to

a reduction in the kynurenine-to-tryptophan ratio, which can be attributed to the activities of IDO and TDO. Notably, administration of microbiota could restore the normal activity of these enzymes.⁷⁹

Among the metabolites produced in the KP, quinolinic acid and kynurenic acid are the most important compounds in neurogastroenterology studies. These metabolites target NMDA and $\alpha 7$ nicotinic acetylcholine receptors in the CNS and the enteric nervous system. The role of quinolinic acid and kynurenic acid in GI has been poorly understood. However, it seems that both of these compounds are immunoregulators. To date, the anti-inflammatory role of kynurenic acid in the GI and its inhibitory effect on colon cancer cells have been confirmed through the *in vitro* and *in vivo* studies.⁹⁴

Gut microbiota is able to metabolize the tryptophan directly and change the tryptophan availability in their host. About 4% to 6% of tryptophan is metabolized into indican, indole or indole acid derivatives, skatole, and tryptamine by the gut bacteria (Figure 3).⁹⁵ Although the definition of tryptophan metabolism by the gut bacteria is relatively easy at the molecular level, it is complicated to determine which type of metabolite gut bacteria produce. This is due to the diverse population of microbial community and their complex ecology.

The Role of Bacteria in Activation of IDO1

IDO1, the rate-limiting enzyme of KP, can influence the adaptive immunity of hosts.⁹⁶ Tissue damage causes overexpression of IDO1 by intestinal mononuclear cells. This enzyme can induce anti-inflammatory and immunosuppressive responses on the intestinal mucosa through regulation of the host immunomodulatory activities by kynurenine production, mucosal immune reactivity, and metabolism of gut microbes.^{97,98} In addition, IDO1 can exert its effect on T cells to establish the balance of anti-inflammatory and pro-inflammatory status in the gut. IDO1 can also regulate the host-microbiota relationships by affecting tryptophan metabolism.^{99,100} On the contrary, the gut microbiota can alter the tryptophan degradation rate as well as its availability, and hence influences the tryptophan metabolism through the KP in the host. *In vivo* studies have shown that in GF animals, KP activity and kynurenine-to-tryptophan ratio are reduced due to the lack of microbial population. However, this deficiency is eliminated after administration of normal microbiota in GF animals.⁸⁸ Importantly, in animal models with microbiota deficiency, the KP is not detected in the CNS. Infection of rodents with *Toxoplasma gondii* increased the metabolites of the KP in the brain, such as kynurenine, kynurenic acid, quinolinic acid, and 3-hydroxykynurenine.¹⁰¹ In contrast, transferring the *Bifidobacterium infantis* in rodents increased the tryptophan level and kynurenic acid-to-kynurenine ratio and reduced both the kynurenine-to-tryptophan ratio and IDO1 activity.⁹³ Colonization of *Lactobacillus johnsonii* in rats decreased the levels of IDO1 mRNA and kynurenine concentrations in serum. Similarly,

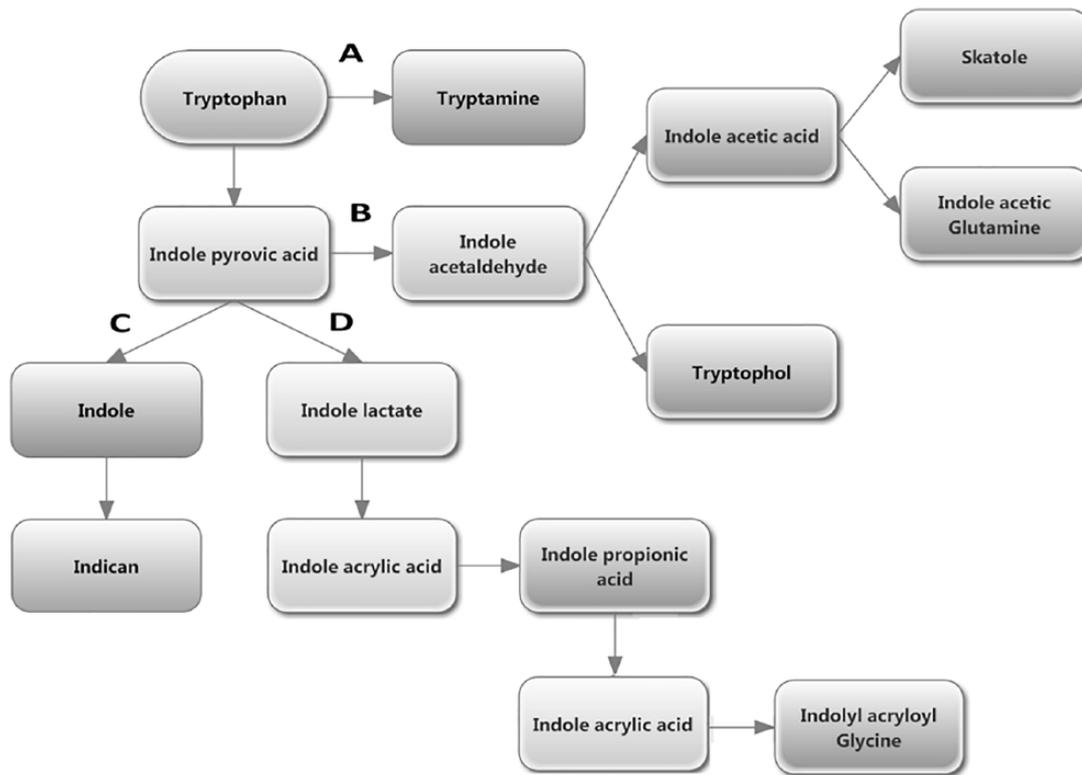


Figure 3. Tryptophan metabolism in the gastrointestinal tract by microbiota. (A) Decarboxylation of tryptophan to tryptamine by *Clostridium sporogenes* and *Ruminococcus gnavus*. (B) Conversion of tryptophan into indole pyruvic acid by tryptophanase followed by its pyruvic acid decarboxylation produces the precursor of tryptophol and indole acetic acid, that is, indole acetaldehyde. Indole acetic acid is converted to skatole by *Lactobacillus*, *Clostridium*, *Bacteroides*, and others.⁹⁵ (C) Production of indole and indican from indole pyruvic acid. (D) Catabolism of indole pyruvic acid into indole acrylic acid and its further conversion into indolyl acryloyl glycine after incorporation of glycine molecule.

cell-free suspension of *L. johnsonii* decreased the IDO1 activity by 47% in HT-29 intestinal epithelial cells.^{102,103} The main mechanism for the decrease in IDO1 activity after colonization with *L. johnsonii* is the production enhancement of H₂O₂ in ileum lumen. H₂O₂ acts as a signalling molecule and inhibits the activity of IDO1 via affecting the host-microbiota symbiotic interactions.⁹⁵

The high activity of KP enzymes contributes to increasing the kynurenine-to-tryptophan ratio, which may be considered as a biomarker for irritable bowel syndrome.¹⁰⁴ In addition, the high ratio of kynurenine to tryptophan has been reported in other inflammatory diseases and cancers in which the concentration of IFN- γ is higher than the normal status. The inflammatory process that causes IDO1 activation and subsequent larger kynurenine-to-tryptophan ratio may have a microbial origin. Brottveit et al¹⁰⁵ reported an increase of IFN- γ in duodenal biopsies of gluten-sensitive patients with no coeliac disease after eating gluten-containing bread. Gluten is a compound that is not completely digested by humans, so a high amount of intact gluten remains in the small intestinal cells, which can be toxic to human cells and has antimicrobial and immunomodulatory properties. Moreover, the undigested gluten can be used as a food source for gut microbes, leading to the activation of IFN- γ , followed by IDO1 activation.

Kynurenines have antimicrobial activity and can affect the microbial community of the GI tract. However, microbiota can influence the tryptophan metabolism via KP in the host in association with the immune system. Some investigations showed that GF animals possessed deficient immune systems and low rates of tryptophan metabolism through the KP. After administration of microbiota into the GF animals, tryptophan metabolism and KP were normalized.⁸⁸ Toll-like receptors (TLRs) act as important junctions for identification of the microbial components in the GI tract. In GF animals, the expression of TLRs decreases and KP metabolism increases, which can be in association with IFN- γ -mediated IDO1 activity elevation.¹⁰⁶ Aryl hydrocarbon receptor (AhR) is a cytosolic transcription factor that acts as an immunity and inflammation regulator and mediates intestinal homeostasis and carcinogenesis.¹⁰⁷ The KP metabolites such as kynurenic acid, xanthurenic acid, and cinnabarinic acid can attach to the AhR and induce the expression of AhR-dependent gene and lead to intestinal homeostasis. In addition, AhR itself can modulate the expression of IDO1 and TDO and is considered a main mediator of GI microbiota, KP, and the host immune system. Briefly, interactions between the gut microbiota, KP metabolites, and immune responses are complex and are controlled by various mechanisms. Gut microbiota has significant

roles in KP and its metabolites and controls the host's immunity through tryptophan metabolism adjustment.⁹⁵

Conclusion

Tryptophan is one of the essential amino acids for humans, which contributes to controlling emotional states, that is, happiness, well-being, as well as the cellular ageing process and energy production through its conversion into serotonin or NAD⁺. These compounds are the end products of the serotonin pathway and KP, respectively. Despite potential therapeutic effects of supplying excessive amounts of NAD⁺, KP can divert tryptophan away from serotonin pathways and cause depression. Moreover, enhanced activity of KP may lead to some neurodegenerative disorders through the production and accumulation of neurotoxic intermediates such as quinolinic acid. Generally, a large kynurenine-to-tryptophan ratio due to the overexpression of KP enzymes is observed in different human health complications, including irritable bowel syndrome, inflammatory diseases, cancer, and neurodegenerative disorders. Gut microbiota can also consume tryptophan and subsequently decrease its availability for both pathways because the human body can receive this amino acid from diet only. Moreover, the KP rate-limiting enzymes such as IDO1 and gut microbiota have mutual effects on each other. Some gut microbiota and gut pathogens can enhance IDO1 activity. In contrast, gut microbiota may produce some compounds such as H₂O₂ to suppress IDO1. On the contrary, IDO1 can make tryptophan unavailable for gut microbiota consumption and convert it into potential antimicrobial intermediates, such as kynurenine, resulting in killing some of the microbiota. In addition, the diversity, population, and ecology of gut microbiota are also determined by antibiotic intake, certain types of food ingredients (such as gluten), diseases, age, and stress, which influence tryptophan availability and KP rate. As the result of these interactions, a sophisticated and highly interconnected loop involving gut microbiota, KP, and tryptophan availability is drawn. Currently, our insight into this loop is very poor. By careful investigation, therapeutic or preventive use(s) of gut microbiota in some human diseases by regulating the tryptophan availability and/or the KP rate may be understood. Alternatively, gut microbiota may have the potential to reduce the concentration of some neurotoxic KP intermediates, lowering the severity/pathogenicity of neurodegenerative disorders.

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Author Contributions

Dr. Dehhahgi and M. Kazemi Shariat Panahi both wrote the manuscript and Prof Guillemin edited, approved and finalized it.

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