Host–microbiome interactions: the aryl hydrocarbon receptor as a critical node in tryptophan metabolites to brain signaling

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ABSTRACT

Tryptophan (Trp) is not only a nutrient enhancer but also has systemic effects. Trp metabolites signaling through the well-known aryl hydrocarbon receptor (AhR) constitute the interface of microbiome-gut-brain axis. However, the pathway through which Trp metabolites affect central nervous system (CNS) function have not been fully elucidated. AhR participates in a broad variety of physiological and pathological processes that also highly relevant to intestinal homeostasis and CNS diseases. Via the AhR-dependent mechanism, Trp metabolites connect bidirectional signaling between the gut microbiome and the brain, mediated via immune, metabolic, and neural (vagal) signaling mechanisms, with downstream effects on behavior and CNS function. These findings shed light on the complex Trp regulation of microbiome-gut-brain axis and add another facet to our understanding that dietary Trp is expected to be a promising noninvasive approach for alleviating systemic diseases.

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Introduction

Tryptophan (Trp) is not only a nutritional enhancer but also serves as a key prerequisite that aligns gastrointestinal physiology and central nervous system (CNS) function. This process is achieved through the regulation of indole pathway, kynurenine (Kyn) pathway and serotonin (5-hydroxytryptamine, 5-HT) synthesis.¹² Being metabolized into numerous bioactive metabolites³ (Table 1), Trp metabolism has become part of the cellular and organismal communication strategies. These intermediates can serve as ligands for aryl hydrocarbon receptor (AhR)¹²,¹³ (Table 2). In recent years, the focus on AhR has shifted to its mode of action in response to physiological ligands. After activation, AhR has been shown to participate in a broad variety of physiological and pathological processes, which not only focus on intestinal homeostasis, but are also highly to the autoimmune and neoplastic diseases of CNS.²⁸ Recent research has shown that AhR can suppress proinflammatory cytokines in astrocytes²⁹ and microglia³⁰ that has potential to be a novel factor of interest for several brain diseases such as plasticity,³¹ alzheimer’s disease (AD)³² and epilepsy³³ in “gut-brain” axis.

Gut microbiota and CNS are connected via multiple bidirectional pathways, including neural (vagus), metabolism, and immune signaling.³⁴ Microbe-derived neuroactive metabolites include Trp precursors and metabolites, which are secreted into the circulation and traffic to the CNS.³⁵ In turn, CNS is capable of shaping microbial function and composition by regulating neurotransmitters to achieve bidirectional communication.

In this article, we review the most recent insights regarding the Trp metabolism in “microbiome-gut-brain” axis, in which, AhR serves as a critical node in microbiota to brain signaling. In the gut, under the direct or indirect regulation of the microbiota, the three major Trp metabolism pathways lead to serotonin, Kyn, and indole derivatives, some of which are ligands for AhR.³⁶,³⁷ These derivatives involved in immune, metabolic, and neural (vagal) communication mechanisms in “microbiome-gut-brain” axis under AhR regulation is reinforced discussed, with a focus on the consequences on both physiology and diseases.
The basic recognition of AhR

AhR belongs to xenobiotic receptors (XRs). It has functionally evolved into cellular sensor for both endogenous and exogenous stimuli^38^ to regulate the clearance and detoxification of xenobiotics.\(^25\) Unlike membrane-bound receptors, most XRs shuttle between the cytoplasm and nucleus. They modulate the expression of target genes involved in cell proliferation, metabolism, and immune responses.\(^38^\) XR transcriptional activity is regulated by binding to diverse and low-affinity small molecules through a highly conserved ligand-binding domain (LBD).\(^40^\) AhR individually and/or interactively influences cellular metabolism and their activation also play an important role in “gut-brain” axis. Thus, understanding its basic feature is a key prerequisite for exploring the role of AhR in regulating host homeostasis via “microbiota-gut-brain” connection (Figure 1).

Structures and main features of AhR

AhR is a ligand-controlled transcription factor with a basic helix-loop-helix (bHLH) and per-AhR nuclear translocator (ARNT)-Sim domains, which are highly conserved during vertebrate evolution. A wide range of compounds, such as endogenous amino acid derivatives have been shown to regulate the expression of target genes by acting as AhR agonists or inhibitors.\(^25,41^\) As a nucleocytoplasmic shuttling protein, AhR is mainly located in the cytoplasm as a complex in the absence of AhR ligands. This complex contains a 90-kDa heat shock protein (Hsp90), the Hsp90-interacting protein p23 and AIP.
Also known as XAP2 and ARA9. When exposed to ligands, AhR immediately binds to these chemicals. The translocation of AhR from the cytoplasm into the nucleus is then initiated. In the nucleus, AhR dissociates from Hsp90, p23, and AIP and forms a heterodimer with ARNT. The AhR-ARNT dimer then binds to the promoters of AhR target genes to induce gene expression. Meanwhile, AhR activation is linked to the expression of inflammatory cytokines, including IL-6, IL-10, and IL-22, and production of CYP genes such as CYP1 and CYP3A, all of which play important roles in modulating host homeostasis.

**AhR involved in the signaling from gut to brain**

AhR: AhR participates in a broad variety of physiological and pathological processes that are highly relevant to intestinal homeostasis, autoimmune, and neoplastic diseases of CNS. The reduced level of AhR agonists that derived from intestinal microbiota has been reported in multiple conditions, including IBD, metabolic syndrome, and CNS diseases. AhR has involved in the regulation of multiple organ functions but its mRNA expression differs between tissues, its abundant expression in the gut indicates its important roles in regulating intestinal function. As reported, AhR regulates intestinal epithelial cell (IEC) regeneration, preventing malignant outgrowth, while deficits in the levels of AhR or its ligands significantly decrease the number of intestinal IELs and increases epithelial damage. With a special focus on the immune system, AhR activation has multiple effects in dendritic cells (DCs) and T cells, which inhibits induction of cytokines that promote polarization of pathogenic T cell subsets and reduces the expression of MHC class II in DCs.

AhR has been regarded as a key inducer of CYPs. CYP1 gene expression can be induced by AhR upon exposure to intra- and/or extracellular ligands. The microbiota-derived metabolite indoxyl sulfate (IS) is a potent endogenous AhR ligand that is reported to regulate the transcription of various genes, including CYP1A1, CYP1B1, CYP1A2, and IL-6. Meanwhile, CYP1 enzymes also play key roles in attenuating intracellular AhR activation by oxidizing AhR ligands such as 6-formylindolo[3,2-b]carbazole (FICZ). However, excessive CYP1A1-induced metabolic clearance of AhR agonists resulted in an impaired AhR-dependent intestinal immune system, such as...
as the loss of type 3 innate lymphocytes in the small intestine and colon as well as increased susceptibility to gut pathologies. In CYP1 enzyme-deficiency (Cyp1a1/1a2/1b1-/-) Th17 cells, AhR-dependent IL-22 production was increased, which suggested that disruption of CYP1 function may modify AhR-orchestrated immune response.

As the cognition of “microbiome-gut-brain” axis grows, AhR activation offers a therapeutic avenue for the regulation of CNS inflammation. In astrocytes and microglia, AhR suppresses pro-inflammatory nuclear factor-κB (NF-κB) signaling. On the basis of the potential function of some microbial metabolites on CNS through AhR-dependent mechanisms, the role of AhR in the modulation of inflammation-promoting activities of microglia and astrocytes by the commensal microbiota has been investigated recently.

**Trp metabolites act as ligands of AhR**

**AhR ligands generated in the kynurenine pathway**

The Kyn pathway is the dominant Trp metabolic pathway. Approximately 90% of ingested Trp is degraded along this pathway in both immune and epithelial cells. N-formylkynurenine, which is generated through Trp degradation by Trp 2,3-dioxygenase (TDO), indoleamine 2,3-dioxygenase 1 (IDO1) and IDO2, is further catabolized into Kyn by Kyn formamidase. Kyn and one of its downstream products, kynurenic acid (KA), have been demonstrated to play an important role in cancer and the immune system by serving as an AhR agonist. To date, only one experimental study has shown that xanthurenic acid, a Kyn catabolite, can activate human AhR in a TDO-dependent manner. Excess xanthurenic acid and over-expressed TDO can facilitate the migration of tumor cells, but these cells are inoperative when treated with AhR inhibitors. Another downstream metabolite of Kyn, 3-hydroxyanthranilic acid, which is oxidized into cinnabarinic acid, is also an endogenous AhR ligand and can protect cells against apoptosis that is induced by oxidative stress in an AhR-dependent manner. However, in addition to Kyn and KA, there are no published studies investigating the role of other AhR ligands derived from the Kyn pathway on CNS function (Figure 2).

**AhR ligands produced in the serotonin pathway**

Serotonin is a pivotal neurotransmitter that is present in the gut (~95%) and CNS (~5%). It is produced in enterochromaffin (EC) cells via Trp hydroxylase 1 (Tph1). Moreover, it has also been reported that indigenous spore-forming bacteria present in mouse and human microbiota could accelerate serotonin generation in colonic EC cells. These cells carry Tph1, an enzyme that is responsible for the degradation of Trp into 5-hydroxytryptophan, a short-lived metabolite that is further decarboxylated to serotonin by aromatic amino acid decarboxylase (AAAD). Moreover, certain microbiota can directly utilize Trp to synthesize serotonin in vitro. The serotonin can be further degraded along two metabolic pathways by different enzymes, whereby monoamine oxidase (MAO) is responsible for the metabolic conversion of most serotonin to 5-hydroxyindoleacetic acid (5-HIAA). In another serotonin catabolism route, melatonin can be produced through the decomposition of serotonin in the pineal gland (Figure 3).

Serotonin is an endogenous agonist of human AhR. Abnormal serotonin metabolism within the gut correlates to gastrointestinal diseases, such as irritable bowel syndrome. In addition to serotonin itself, its catabolites, such as 5-HIAA, are potential AhR ligands. Melatonin has been reported to modulate a number of physiological functions, notably circadian rhythm, free radical scavenging, and oxidation resistance. However, whether melatonin can directly act as an AhR ligand remains to be elucidated.

**AhR ligands derived from the indole pathway**

**Indole and its derivatives generated by gut microorganisms**

Gut microbiota expressing tryptophanase can catabolize Trp into indoles, which are important signaling molecules that modulate intestinal health. Numerous studies have shown that indole and
indole-containing chemicals can activate AhR.\textsuperscript{25,65}

IAA is a natural AhR ligand derived from Trp fermentation by gut bacteria; its generation can be divided into the following three major pathways: the indole-3-pyruvic acid (IPyA), tryptamine, and indole-3-acetamide (IAM) pathways.\textsuperscript{66}

In the context of Trp, aminotransferases can increase AhR activity via the metabolic formation of IPyA, a compound that can be converted into a number of AhR activators, such as FICZ, IAA, 3-methylindole (skatole), and IAld. Tryptamine generated through the degradation of Trp by decarboxylase is also a bacteria-derived AhR ligand.\textsuperscript{67} Moreover, an uremic toxin, IS is produced by the microbial metabolism of indoles and is also a potent endogenous ligand that can activate human AhR directly.\textsuperscript{33} (Figure 4).

**Trp photoproducts**

Trp is the most powerful near-ultraviolet (UV) absorbing amino acid. Upon exposure to visible or UV light, Trp can be converted to photoproducts, including FICZ and 1-(1 H-indol-3-yl)-9 H-pyrido[3,4-b]indole (IPI), both of which have been reported for their AhR-inducing properties.\textsuperscript{68} AhR activated by FICZ could protect the intestinal epithelial barrier from the destruction caused by tumor necrosis factor-alpha (TNF-\(\alpha\))/IFN-\(\gamma\),\textsuperscript{15,69} demonstrating that FICZ may be developed as a potent drug for resistance to intestinal diseases. Recent studies also show that FICZ can be formed through novel light-independent pathways\textsuperscript{16} (Figure 4). In the absence of light, the oxidant hydrogen peroxide (H\(_2\)O\(_2\)) is capable of converting Trp to FICZ. During the enzymatic hydrolysis of Trp, one of the Trp catabolites, indole-3-pyruvate (I3P), is spontaneously decarboxylated to generate indole-3-acetaldehyde (I3A), which subsequently dimerized to form FICZ and its oxidation product, indolo[3,2-b]carbazole-6-carboxylic acid (CICZ).\textsuperscript{16} Moreover, another Trp downstream compound, tryptamine, can also be converted into I3A by monoamine oxidase.\textsuperscript{16} This suggests that an endogenous FICZ production pathway exists in the absence of light. Cellular FICZ can be cleared by CYP1A enzymes, which is an important part of the negative

\begin{figure}
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\caption{Key Trp metabolites and enzymes in the kynurenine (Kyn) pathway. Tryptophan (Trp) is first catabolized into N-formylkynurenine, a precursor of kynurenine, by tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase 1/2 (IDO1/2). Gut bacteria (such as Ruminococcus gnavus) and inflammatory stimuli (such as IFN-\(\gamma\)) can induce IDO expression, thus impacting Trp metabolism along the Kyn pathway. So far, the identified aryl hydrocarbon receptor (AhR) ligands derived from the Kyn metabolic pathway, including Kyn, kynurenic acid, xanthurenic acid, and cinnabarinic acid, are highlighted with a red outline.}
\end{figure}
feedback loop to inhibit excessive and/or prolonged AhR activation. Thus, FICZ is a transient AhR activator in the cell system. However, some I3P derivatives produced during FICZ formation process can inhibit CYP1A1, thereby enhancing the potency of FICZ and thereby increased its power as an AhR activator.

Additionally, IPI has an equivalent CYP1A-inducing efficacy to FICZ. IPI-induced 7-ethoxyresorufln demethylase (EROD) activity notably decreased in AhR-defective c35 cells, supporting that the IPI response depends on AhR. However, the AhR-activating efficacy of IPI in vivo and its mechanism are unclear. Additionally, the function of the IPI-AhR pathway remains unclear.

**The AhR as a critical node in Trp metabolites to brain signaling**

It is well established that gut-brain axis is a fundamental component underlying health and diseases. The effects of the microbiota are not limited to the intestine but also signal to the brain influencing CNS inflammation and being involved in neuropsychiatric disorders. The maintenance of a mutualistic state between them is actually in the action of Trp metabolites through AhR.

**Trp metabolites in the intestine regulates “microbiome-brain” axis via AhR-dependent immunity pathway**

The three major pathways of Trp metabolism in the gut produces serotonin, Kyn, and indole derivatives are under the direct or indirect regulation of the microbiota, which is involved in the regulation of host immunity by activating AhR. AhR expressed in many host cell types including leukocytes and brain-resident cell types. Stimulation of AhR by Trp metabolites has become a focal point in this regard, with dual
emphasis on promoting anti-inflammatory responses, ameliorating CNS inflammation and maintaining host homeostasis.\textsuperscript{72,73} (Figure 5).

The connection of Kynurenine-TDO/IDO-AhR mitigates inflammation and autoimmune diseases

Kyn and its metabolites 3-hydroxykynurenine (3HK) can cross the blood-brain barrier whereas their high selection and significant implications for pathogenic activities of neurological disorders and the metabolism of neurotransmitters.\textsuperscript{74,75} After taken up by astrocytes, microglia, and neurons, the neuroprotective KA can be generated by astrocytes whereas neurotoxic KP metabolites such as quinolinic acid (QA) is produced by microglia.\textsuperscript{75-77}

The realization of this neuroactive function not only depends on downstream products of the Kyn pathway via AhR, but is also associated with the coevolution of IDO1, TDO2, and AhR.\textsuperscript{3} Trp catalolism via the Kyn pathway is mediated by IDO and TDO, which are considered as rate-limiting enzymes and produce Kyn as an AhR agonist.\textsuperscript{78,79} Considering the close interaction between AhR and IDO/TDO, their coevolution is indeed vital in immunological regulation.

The expression of IDO1 is regulated by AhR\textsuperscript{80} via an autocrine AhR-IL6-STAT3 signaling loop.\textsuperscript{81} As reported, IDO1 contributes to intestinal homeostasis.\textsuperscript{82} In the absence of AhR ligands, IDO1 activity is inhibited, together with stimulating immune tolerance\textsuperscript{83} and suppressing antigen-specific T lymphocyte activation.\textsuperscript{84} The stimulating effect of intestinal bacteria in IDO1 activity has been clearly demonstrated.\textsuperscript{85} Additionally, the c-SRC-dependent phosphorylation of IDO1 regulated by Kyn is realized by AhR activation, which further inhibits immunopathology triggered by gut microbes, including Salmonella typhimurium and group B Streptococcus,\textsuperscript{86} and elicits the generation of transforming growth factor (TGF)-β1 by dendritic cells.\textsuperscript{85} Recently, emerging evidence implicates the AhR-IDO1 pathway in autism spectrum
disorder (ASD) as well. As reported, the pathogenesis of ASD is related to high IDO1 activity. Considering the facilitating effect of ARNT on AhR, the association between ARNT and ASD severity may partially prove the involvement of AhR in this cerebral process. In addition to IDO1, the expression of TDO2 can also be detected in the brain, and activated in gliomas. Recently, lipopolysaccharide has been shown to stimulate the expression of TDO2, which subsequently produces Kyn. Via activating AhR-dependent pathway, the promotion of tumor cell motility and survival, the prevention of endotoxin tolerance, and the inhibition of anti-tumor immune responses are demonstrated.

**Indole derivatives-AhR pathway regulates CNS inflammation in "microbiome-gut-brain" axis**

In the action of certain microbiota, metabolite molecules, such as IAA, IS, IPA, I3A, and IAlD, derived from dietary Trp activate microglia, which transfer signaling through the AhR in astrocyte cells to mediate responses to CNS inflammation and reduce CNS autoimmunity.

Glia, consisting of not only microglia but also astrocytes, serves as the switch that participates in regulating the immune microenvironment of the brain. In addition to the abundance of cell populations, diverse functions ensure astrocytes to exert vital roles in CNS during health and diseases. As reported, their involved functions ranging from regulating synaptic and neuronal transmission to regulating CNS development, repair, cell metabolism, and immunoregulation. IFN-I signaling in astrocytes in combination with Trp microbial metabolites activate AhR. The activated AhR subsequently inhibits NF-κB activation via inducing the expression of suppressor of cytokine signaling 2 (Socs2). Moreover, effective anti-inflammatory and neurodegeneration-arresting characters of interferon-alpha receptor-1 (IFNAR-1) are demonstrated to be mediated by AhR. Thus, this IFN-I-AhR-Socs2-NF-κB pathway suggests that targeting IFNAR1 signaling may be a therapeutic approach of CNS inflammation and also demonstrates a molecular mechanism for the protective effect of AhR ligands against CNS autoimmunity.

In addition to astrocytes, microglia is also a kind of immune cells of CNS and is reported to express AhR. Some certain astrocytes are instructed by microglia and these two cell types communicate on a molecular level to mediate responses to CNS inflammation.
metabolites of Trp regulate the activation of microglia, which is accompanied by the generation of TGFα and Vascular endothelial growth factor B (VEGF-B), regulating CNS associated diseases and the transcriptional program of astrocytes via AhR.30 In-depth research has shown that microglia-derived TGFα acts via the ErbB1 receptor in astrocytes to exert neuroprotective functions and promote beneficial astrocyte activities.103,104 Conversely, the production of VEGF-B triggers Vascular endothelial growth factor receptor 1 (FLT-1) signaling in astrocytes exacerbates their pathogenic activities and worsens experimental allergicercephalomyelitis (EAE) development.105 Additionally, VEGF-B and TGFα also participate in the formation of multiple sclerosis (MS) lesion stage30 in CD14+ cells and involve in microglial control of astrocytes in humans, suggesting but not enough to prove implications of TGF-α and VEGF-B for humans.

Gut microbial Trp metabolism connects with extended central reward network via AhR-based metabolic pathway

Gut microbiota has taken the limelight as a key regulator of brain-gut axis signaling, which influence extends beyond the gut and is involved in many aspects of human health and disease, including hedonic food intake, ingestive behavior,106,107 and obesity.73,108 Microbiota-derived Trp metabolites are associated with connectivity in key regions of the brain’s extended reward network.73 Supporting this concept is associations between increased weight and changed brain activity and connectivity, highlighting the possible role of the brain in the pathophysiology of obesity.109,110

Microbe-derived Trp metabolites are associated with connectivity of key regions of the brain’s extended reward network, in which the amygdala-nucleus accumbens (NAcc) circuit and the amygdala-anterior insula (aINS) circuit are vital to microbial-gut-brain signaling influencing non-homeostatic food intake.111 Based on IAA signal, the activated AhR may explain the positive association between indoles, the amygdala-aINS circuit, and food addiction scores.73 After activated, AhR can act as a transcription factor and regulate the rate-limiting enzymes in Trp metabolism along the Kyn pathway.85

Meanwhile, with the involvement of AhR, microbial-derived indole derivatives bi-directionally regulate the release of the anorectic hormone glucagon-likepeptide1 (GLP-1).112 Specifically, GLP-1 secretion is increased in colonic enteroendocrine L cells when being exposed to physiological levels of indole, whereas prolonged exposure causes adverse effect.112 It is noteworthy that interacting with the intestinal enteroendocrine L cells and GLP-1 is a potential mechanism that indole affects the reward circuit.73 As reported, GLP-1 is speculated to act locally on vagal afferent nerve terminals considering most GLP-1 is rapidly inactivated by dipeptidyl peptidase 4 prior to leaving the gut.113 Based on the vagal afferent, GLP-1 then signals to the brain circuits and nucleus tractus solitarius (NTS). The completion of this process plays an important role in regulating ingestive behavior.113 Consistently, another research on the GLP-1 agonist Exenatide also indicates that Exenatide can affect appetite control by regulating the functional connectivity of NTS-related reward regions.114 Considering AhR is involved in glucose and insulin-regulated metabolism,12 AhR activation results in reduced fasting glucose levels, increased glucose and insulin dysmetabolism, and improved GLP-1 secretion,12,72 which highlights how Trp metabolites target ingestive behavior via “gut-brain” axis.

Trp metabolism regulates “microbiome-brain” axis via AhR-based neural (vagal) pathway

Although the microbiome-gut-brain communication can be mediated by metabolic and immune pathways, hijacking vagus nerve signaling may still be the most direct and fastest way that gut microbiota regulates brain function.115 The vagus nerve, which contains a paired afferent and efferent fiber, links the viscera with the brain and innervates most of the gastrointestinal tract.116 The vagal afferent nerves transmit signals from the gastrointestinal tract to the CNS.34 Instead of directly contacting with gut microbiota, vagal afferents sense luminal signals of microbial metabolites or products through their diffusion across gut barrier.117 These microbiota-derived neuro-modulatory metabolites include short-chain fatty
acids (SCFA), branched-chain amino acids, peptidoglycans, GABA, catecholamines, and Trp precursors and metabolites, such as serotonin. The vagus nerve is involved in maintaining corporeal homeostasis by regulating hunger, satiety, neurotransmitter levels, and inflammation in the brain. As reported, oleylethanolamide belongs to a kind of fatty-acid derivatives. Its synthesis after fat digestion activates intestinal PPAR-α receptors, which in turn activates the vagal nerve and transfers signals from the gut to the brain to promote satiety. In the involvement of gut microbiota, Trp is actively metabolized into indole or serotonin that significantly affect host biosynthesis and modify host neurotransmitter pools. Considering c-Fos protein expression in the dorsal vagal complex can be an indicator of vagus nerve activation, the overexpressed c-Fos after indole treatment indicates an activation of the vagal afferent fibers in the intestinal mucosa induced by indole. Moreover, the production of serotonin by the intestinal EC cells can also be stimulated by SCFA accumulation. EC cells possess receptors for several bacteria metabolites, such as GPR35 and its ligand kynurenic acid. On adequate stimulation of these receptors, serotonin was released in a calcium-dependent fashion. In turn, the intimate, synapse-like contact of vagal afferent nerve establishes a pathway by which this local serotonin can regulate the activity of gut vagal afferents via serotonin type 3 receptors (5-HT3R) on unmyelinated vagal afferents in the gut mucosa resulting in altered vagal afferent input.

Conclusions

Trp is not only a nutritional enhancer but also plays a key role in modulating CNS homeostasis by being metabolized into numerous bioactive chemicals, most of which have far been identified as AhR ligands. These Trp metabolites activated AhR serve as chemical messengers that mediate the bidirectional crosstalk between the gut microbe and CNS and can regulate host homeostasis via different routes of immune, metabolic, and neural (vagal) communication.

However, there are still some existing questions that need to be addressed. First, AhR activation by certain Trp metabolites may be the result of the action of other compounds generated in Trp metabolic pathways. Second, dose–response experiments are required in future studies, as the optimal dosage of Trp metabolites in the human or animal diet remains to be elucidated, and this is pivotal for maintaining a healthy nervous system. Third, ligands and function of AhR are different between various species. Thus, many effects of Trp metabolites on AhR in mouse models need to be further confirmed in human cells. Finally, the exact mechanism of how Trp metabolites transmit signals to the brain through AhR still needs to be elucidated.

These metabolites serve as a kind of chemical language communicating in “gut-brain” axis and ultimately affect the outcomes of many disorders, including IBD, cancer, metabolic syndrome, autoimmune diseases, and neurodegenerative diseases. Efforts to identify the molecular mechanisms of how these Trp metabolites regulate host physiology will markedly provide new insights toward successful translation of microbiome-gut-brain axis research from bench to bedside and increase our understanding of developing therapeutic intervention that may alleviate the associated CNS diseases.

Abbreviations

| Abbreviation | Description                        |
|--------------|-----------------------------------|
| AAAD         | aromatic amino acid decarboxylase  |
| Aβ           | beta amyloid                       |
| AD           | alzheimer's disease                |
| AhR          | aryl hydrocarbon receptor          |
| aINS         | amygdala-anterior insula           |
| ARNT         | AhR nuclear translocator           |
| ASD          | autism spectrum disorder           |
| BBB          | blood–brain barrier                |
| BBDP         | BioBreeding diabetes-prone         |
| bHLH         | basic helix-loop-helix             |
| CAR          | constitutive androstan receptor    |
| CICZ         | indolo[3,2-b]carbazole-6-carboxylic acid |
| CNS          | central nervous system             |
| C. sporogenes| Clostridium sporogenes             |
| CYP          | cytochrome P450                     |
| DCs          | dendritic cells                    |
| DSS          | dextran sulfate sodium             |
| EAE          | experimental allergicencephalomyelitis |
| EC           | enterochromaffin                   |

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Abbreviations

| Abbreviation | Description                        |
|--------------|-----------------------------------|
| AAAD         | aromatic amino acid decarboxylase  |
| Aβ           | beta amyloid                       |
| AD           | alzheimer's disease                |
| AhR          | aryl hydrocarbon receptor          |
| aINS         | amygdala-anterior insula           |
| ARNT         | AhR nuclear translocator           |
| ASD          | autism spectrum disorder           |
| BBB          | blood–brain barrier                |
| BBDP         | BioBreeding diabetes-prone         |
| bHLH         | basic helix-loop-helix             |
| CAR          | constitutive androstan receptor    |
| CICZ         | indolo[3,2-b]carbazole-6-carboxylic acid |
| CNS          | central nervous system             |
| C. sporogenes| Clostridium sporogenes             |
| CYP          | cytochrome P450                     |
| DCs          | dendritic cells                    |
| DSS          | dextran sulfate sodium             |
| EAE          | experimental allergicencephalomyelitis |
| EC           | enterochromaffin                   |
Disclosure of potential conflicts of interest

The authors declare that they have no competing interests.

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Authors’ contributions

The review was mainly conceived and designed by XM. Literature was collected by NM. The manuscript was mainly written by NM and edited by TH, Lee J. J and XM. XM resourced the project. All authors contributed to, read, and approved the final manuscript.

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References

1. Sun M, Ma N, He T, Johnston LJ, Ma X. Tryptophan (Trp) modulates gut homeostasis via aryl hydrocarbon receptor (AhR). Crit Rev Food Sci Nutr. 2019;1–9. doi: 10.1080/10408398.2019.1598334.

2. Lee H, Lee Y, Kim J, An J, Lee S, Kong H, Song Y, Lee C-K, Kim K. Modulation of the gut microbiota by metformin improves metabolic profiles in aged obese mice. Gut Microbes. 2018;9(2):155–165. doi: 10.1080/19490976.2017.1405209.

3. Agus A, Plancais J, Sokol H. Gut microbiota regulation of Tryptophan metabolism in health and disease. Cell Host Microbe. 2018;23:716–724. doi: 10.1016/j.chom.2018.05.003.

4. Clarke G, McKernan DP, Gaszner G, Quigley EM, Cryan JF, Dinan TG. A distinct profile of tryptophan metabolism along the kynurenine pathway downstream of toll-like receptor activation in irritable bowel syndrome. Front Pharmacol. 2012;3:90. doi: 10.3389/fphar.2012.00090.

5. Lin HM, Barnett MP, Roy NC, Joyce NI, Zhu S, Armstrong K, Helsby NA, Ferguson LR, Rowan DD. Metabolomic analysis identifies inflammatory and noninflammatory metabolic effects of genetic modification in a mouse model of Crohn’s disease. J Proteome Res. 2010;9:1965–1975. doi: 10.1021/pr901130s.
6. DiNatale BC, Murray IA, Schroeder JC, Flavney CA, Lahoti TS, Laurenzana EM, Omiecinski CJ, Perdew GH. Kynurenine acid is a potent endogenous aryl hydrocarbon receptor ligand that synergistically induces interleukin-6 in the presence of inflammatory signaling. Toxicol Sci. 2010;115:89–97. doi:10.1093/toxsci/kfq024.

7. Keszthelyi D, Troost FJ, Jonkers DM, Kruimel JW, Leue C, Maslee AA. Decreased levels of kynurenine acid in the intestinal mucosa of IBS patients: relation to serotonin and psychological state. J Psychosom Res. 2013;74:501–504. doi:10.1016/j.jpsychores.2013.01.008.

8. Joshi AD, Carter DE, Harper TA Jr., Elferink CJ. Aryl hydrocarbon receptor-dependent stanniocalcin 2 induction by cinnamonic acid provides cytoprotection against endoplasmic reticulum and oxidative stress. J Pharmacol Exp Ther. 2015;353:201–212. doi:10.1124/jpet.141.1122265.

9. Lowe MM, Mold JE, Kanwar B, Huang Y, Louie A, Pollastri MP, Wang C, Patel G, Franks DG, Schlezinger J, et al. Identification of cinnamonic acid as a novel endogenous aryl hydrocarbon receptor ligand that drives IL-22 production. PLoS One. 2014;9:e87877. doi:10.1371/journal.pone.0087877.

10. Novikov O, Wang Z, Stanford EA, Parks AJ, Ramirez-Cardenas A, Landesman E, Lalkou I, Sarita-Reyes C, Guseinleitner D, Li A, et al. An aryl hydrocarbon receptor-mediated amplification loop that enforces cell migration in ER−/PR−/Her2− human breast cancer cells. Mol Pharmacol. 2016;90:674–688. doi:10.1124/mol.116.105361.

11. Lin HM, Edmunds SI, Helsby NA, Ferguson LR, Rowan DD. Nontargeted urinary metabolite profiling of a mouse model of Crohn’s disease. J Proteome Res. 2009;8:2045–2057. doi:10.1021/pr800999t.

12. Natividad JM, Agus A, Planchais I, Lamas B, Jarry AC, Martin R, Michel M-L, Chong-Nyuen C, Roussel R, Straube M, et al. Impaired aryl hydrocarbon receptor ligand production by the gut microbiota is a key factor in metabolic syndrome. Cell Metab. 2018;28:737–49.e4. doi:10.1016/j.cmet.2018.07.001.

13. Ma NMX. Dietary amino acids and the gut-microbiome-immune axis: physiological metabolism and therapeutic prospects. Compr Rev Food Sci Food Saf. 2019;18:221–242. doi:10.1111/1541-4337.12401.

14. Kiely CJ, Pavli P, O’Brien CL. The role of inflammation in temporal shifts in the inflammatory bowel disease mucosal microbiome. Gut Microbes. 2018;9:477–485. doi:10.1080/19490976.2018.1448742.

15. Yu M, Wang Q, Ma Y, Li L, Yu K, Zhang Z, Chen G, Li X, Xiao W, Xu P, et al. Aryl hydrocarbon receptor activation modulates intestinal epithelial barrier function by maintaining tight junction integrity. Int J Biol Sci. 2018;14:69–77. doi:10.7150/ijbs.22259.

16. Smirnova A, Wincent E, Vikstrom Bergander L, Alsberg T, Bergman J, Rannug A, Rannug U. Evidence for new light-independent pathways for generation of the endogenous aryl hydrocarbon receptor agonist FICZ. Chem Res Toxicol. 2016;29:75–86. doi:10.1021/acs.chemrestox.5b00416.

17. Ma Y, Wang Q, Yu K, Fan X, Xiao W, Cai Y, Xu P, Yu M, Yang H. 6-Formylindolo(3,2-b)carbazole induced aryl hydrocarbon receptor activation prevents intestinal barrier dysfunction through regulation of claudin-2 expression. Chem Biol Interact. 2018;288:83–90. doi:10.1016/j.cbi.2018.04.020.

18. Jennis M, Cavanaugh CR, Leo GC, Mabus JR, Lenhard J, Hornby PJ. Microbiota-derived tryptophan indoles increase after gastric bypass surgery and reduce intestinal permeability in vitro and in vivo. Neurogastroenterol Motil. 2018;30:e13178.

19. Cheng Y, Jin UH, Allred CD, Jayaraman A, Chapkin RS, Safe S. Aryl hydrocarbon receptor activity of tryptophan metabolites in young adult mouse colonocytes. Drug Metab Dispos. 2015;43:1536–1543. doi:10.1124/dmd.115.063677.

20. Zelante T, Ianniotti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, Zecchi R, D’Angelo C, Massi-Benedetti C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity. 2013;39:372–385. doi:10.1016/j.immuni.2013.08.003.

21. Dou L, Salle M, Cerini C, Poitevin S, Gondouin B, Jourde-Chiche N, Fallague K, Brunet P, Calaf R, et al. The cardiovascular effect of the uremic solute indole-3 acetic acid. J Am Soc Nephrol. 2015;26:876–887. doi:10.16181/ASN.2013121283.

22. Rasmussen MK, Balaguer P, Ekstrand B, Daujat-Chavanieu M, Gerbal-Chaloin S, Skatole (3-Methylindole) is a partial aryl hydrocarbon receptor agonist and induces CYP1A1/2 and CYP1B1 expression in primary human hepatocytes. PLoS One. 2016;11:e0154629. doi:10.1371/journal.pone.0154629.

23. Schroeder JC, Dinatale BC, Murray IA, Flavney CA, Liu Q, Laurenzana EM, Lin JM, Strom SC, Omiecinski CJ, Amin S, et al. The uremic toxin 3-indoxyl sulfate is a potent endogenous agonist for the human aryl hydrocarbon receptor. Biochemistry. 2010;49:393–400. doi:10.1021/bi901786x.

24. Cassani E, Barichella M, Cestaro B, Bianchi F, Cereda E, Bollici C, Zampella Maria P, Ficara F, Cestaro B, et al. Increased urinary indoxyl sulfate (indican): new insights into gut dysbiosis in Parkinson’s disease. J Parkinsonism Relat Disord. 2015;21:389–393. doi:10.1016/j.parkreldis.2015.02.004.

25. Kawai S, Iijima H, Shinzaki S, Hiyama S, Yamaguchi T, Araki M, Iwatai S, Shiraishi E, Mukai A, Inoue T, et al. Indigo naturalis ameliorates murine dextran sodium sulfate-induced colitis via aryl hydrocarbon receptor activation. J Gastroenterol. 2017;52:904–919. doi:10.1007/s00535-016-1292-z.

26. Kumagai T, Aratsu Y, Sugawara R, Sasaki T, Miyairi S, Nagata K. Indirubin, a component of Ban-Lan-Gen, activates CYP3A4 gene transcription through the human
pregnane X receptor. Drug Metab Pharmacokinet. 2016;31:139–145. doi:10.1016/j.dmpk.2016.01.002.

27. Sugimoto S, Naganuma M, Kanai T. Indole compounds may be promising medicines for ulcerative colitis. J Gastroenterol. 2016;51:853–861. doi:10.1007/s00535-016-1220-2.

28. Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. Nat Rev Immunol. 2019;19:184–197. doi:10.1038/s41577-019-0125-8.

29. Rothhammer V, Mascanfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao -C-C, Patel B, Yan R, Blain M, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. Nat Med. 2016;22:586–597. doi:10.1038/nm.4106.

30. Rothhammer V, Borucki DM, Tjon EC, Takenaka MC, Chao CC, Ardura-Fabregat A, de Lima KA, Gutiérrez-Vázquez C, Hewson P, Staszewski O, et al. Microglial control of astrocytes in response to microbial metabolites. Nature. 2018;557:724–728. doi:10.1038/s41586-018-0119-x.

31. Frye CA, Koonce CJ, Walf AA. The pregnane xenobiotic receptor, a prominent liver factor, has actions in the midbrain for neurosteroid synthesis and behavioral/ neural plasticity in female rats. Front Syst Neurosci. 2014;8:60. doi:10.3389/fnsys.2014.00060.

32. Jain S, Rathod V, Prajapati R, Nandeepar PK, Sangamwar AT. Pregnan X receptor and P-glycoprotein: a connexion for Alzheimer’s disease management. Mol Divers. 2014;18:895–909.

33. Yu N, Zhang YF, Zhang K, Cheng YF, Ma HY, Di Q. Pregnan X receptor not nuclear factor-kappa B up-regulates P-glycoprotein expression in the brain of chronic epileptic rats induced by kainic acid. Neurochem Res. 2017;42:2167–2177. doi:10.1007/s11064-017-2224-x.

34. Cox LM, Weiner HL. Microbiota signaling pathways that influence neurologic disease. Neurotherapeutics. 2018;15:135–145. doi:10.1007/s11684-017-0598-8.

35. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13:701–712. doi:10.1038/nrn3346.

36. Alexeev EE, Laniš JM, Kao DJ, Campbell EL, Kelly CJ, Battista KD, Gerich ME, Jenkins BR, Walk ST, Kominsky DJ, et al. Microbiota-derived indole metabolites promote human and Murine intestinal homeostasis through regulation of interleukin-10 receptor. Am J Pathol. 2018;188:1183–1194. doi:10.1016/j.ajpath.2018.01.011.

37. Hubbard TD, Murray IA, Perdew GH. Indole and tryptophan metabolism: endogenous and dietary routes to Ah receptor activation. Drug Metab Dispos. 2015;43:1522–1535. doi:10.1124/dmd.115.064246.

38. Mackowiak B, Wang H. Mechanisms of xenobiotic receptor activation: direct vs indirect. Biochim Biophys Acta. 2016;1859:1130–1140. doi:10.1016/j.bbabmb.2016.02.006.

39. Li H, Wang H. Activation of xenobiotic receptors: driving into the nucleus. Expert Opin Drug Metab Toxicol. 2010;6:409–426. doi:10.1517/17425251003598886.

40. Furue M, Takahara M, Nakahara T, Uchi H. Role of Ahr/ARNT system in skin homeostasis. Arch Dermatol Res. 2014;306:769–779. doi:10.1007/s00403-014-1481-7.

41. Seok SH, Ma ZK, Feltenberger JB, Chen H, Chen H, Scarlett C, Lin Z, Satyshur KA, Cortopassi M, Jefcoate CR, et al. Trace derivatives of kynurenine potently activate the aryl hydrocarbon receptor (AHR). J Biol Chem. 2018;293:1994–2005. doi:10.1074/jbc.RA117.00631.

42. Denison MS, Soshilov AA, He G, DeGroot DE, Zhao B. Exactly the same but different: promiscuity and diversity in the molecular mechanisms of action of the aryl hydrocarbon (dioxin) receptor. Toxicol Sci. 2011;124:1–22. doi:10.1093/toxsci/kfr218.

43. Schiering C, Vonk A, Das S, Stockinger B, Wincent E. Cytochrome P4501-inhibiting chemicals amplify aryl hydrocarbon receptor activation and IL-22 production in T helper 17 cells. Biochem Pharmacol. 2018;151:47–58. doi:10.1016/j.bcp.2018.02.031.

44. Wincent E, Bengtsson J, Mohammadi Bardbori A, Alasberg T, Luecke S, Rannug U, Rannug A. Inhibition of cytochrome P4501-dependent clearance of the endogenous agonist FICZ as a mechanism for activation of the aryl hydrocarbon receptor. Proc Natl Acad Sci USA. 2012;109:4479–4484. doi:10.1073/pnas.1118467109.

45. Lamas B, Richard ML, Leduq V, Pham HP. CAR9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. Nat Med. 2016;22:598–605.

46. Rothhammer V, Borucki DM, Garcia Sanchez MI, Mazzola MA, Hemond CC, Regev K, Paul A, Kivisäkk P, Bakshi R, Izquierdo G, et al. Dynamic regulation of serum aryl hydrocarbon receptor agonists in MS. Neuro Immunol Neuroinflamm. 2017;4: e359. doi:10.1212/XXI.0000000000000359.

47. Esser C, Rannug A. The aryl hydrocarbon receptor in barrier organ physiology, immunology, and toxicity. Pharmacol Rev. 2015;67:259–279. doi:10.1124/pr.114.009001.

48. Ikuta T, Kurosumi M, Yatsuoka T, Nishimura Y. Tissue distribution of aryl hydrocarbon receptor in the intestine: implication of putative roles in tumor suppression. Exp Cell Res. 2016;343:126–134. doi:10.1016/j.yexcr.2016.03.012.

49. Li Y, Innocent S, Withers DR, Roberts NA, Gallagher AR, Grigorieva EF, Wilhelm C, Veldhoen M. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor
activation. Cell. 2011;147:629–640. doi:10.1016/j.cell.2011.09.025.

50. Hauben E, Gregori S, Draghici E, Migliavacca B, Olivieri S, Woisetschlager M, Roncarolo MG. Activation of the aryl hydrocarbon receptor promotes allograft-specific tolerance through direct and dendritic cell-mediated effects on regulatory T cells. Blood. 2008;112:1214–1222. doi:10.1182/blood-2007-08-109843.

51. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138:103–141. doi:10.1016/j.pharmthera.2012.12.007.

52. McBerry C, Gonzalez RM, Shryock N, Dias A, Aliberti J. SOCS2-induced proteasome-dependent TRAF6 degradation: a common anti-inflammatory pathway for control of innate immune responses. PLoS One. 2012;7:e38384. doi:10.1371/journal.pone.0038384.

53. Clarke G, Grencham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF. The microbiome-gut-brain axis during early life regulates the hippocampal serotonin system in a sex-dependent manner. Mol Psychiatry. 2013;18:666–673. doi:10.1038/mp.2012.77.

54. Vecsei L, Szalardy L, Fulop F, Toldi J. Kynurenines in the CNS: recent advances and new questions. Nat Rev Drug Discov. 2013;12:64–82. doi:10.1038/nrd3793.

55. Pantouris G, Serys M, Yuasa HJ, Ball HJ, Mowat CG. Human indoleamine 2,3-dioxygenase-2 has substrate specificity and inhibition characteristics distinct from those of indoleamine 2,3-dioxygenase-1. Amino Acids. 2014;46:2155–2163. doi:10.1007/s00726-014-1766-3.

56. Liu Y, Liang X, Dong W, Fang Y, Lv J, Zhang T, Fiskesund R, Xie J, Liu J, Yin X, et al. Tumor-repopulating cells induce PD-1 expression in CD8 (+) T cells by transferring kynurenine and AhR activation. Cancer Cell. 2018;33:480–94 e7. doi:10.1016/j.ccell.2018.02.005.

57. Le Floch N, Otten W, Merlot E. Tryptophan metabolism, from nutrition to potential therapeutic applications. Amino Acids. 2011;41:1195–1205. doi:10.1007/s00726-010-0752-7.

58. Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, Nagler C, Ismagilov R, Mazmanian S, Hsieh E, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015;161:264–276. doi:10.1016/j.cell.2015.02.047.

59. Ma N, Guo P, Zhang J, He T, Kim SW, Zhang G, Ma X. Nutrients mediate intestinal bacteria-mucosal immune crosstalk. Front Immunol. 2018;9:5. doi:10.3389/fimmu.2018.00005.

60. O’Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behav Brain Res. 2015;277:32–48. doi:10.1016/j.bbr.2014.07.027.

61. Manzella C, Singhal M, Alrefai WA, Saksena S, Dudeja PK, Gill RK. Serotonin is an endogenous regulator of intestinal CYP1A1 via AhR. Sci Rep. 2018;8:6103. doi:10.1038/s41598-018-24213-5.

62. Jin DC, Cao HL, Xu MQ, Wang SN, Wang YM, Yan F, Wang B-M. Regulation of the serotonin transporter in the pathogenesis of irritable bowel syndrome. World J Gastroenterol. 2016;22:8137–8148. doi:10.3748/wjg.v22.i36.8137.

63. Zhao L, Xiao HT, Mu HX, Huang T, Lin ZS, Zhong LLD, Zeng G-Z, Fan B-M, Lin C-Y, Bian Z-X, et al. Magnolol, a natural polyphenol, attenuates dextran sulfate sodium-induced colitis in mice. Molecules. 2017;22. doi:10.3390/molecules22071218.

64. Ma N, Zhang J, Reiter RJ, Ma X. Melatonin mediates mucosal immune cells, microbial metabolism, and rhythm crosstalk: a therapeutic target to reduce intestinal inflammation. Med Res Rev. 2019;40. doi:10.1002.med.21628.

65. Whittfield-Cargile CM, Cohen ND, Chapkin RS, Weeks BR, Davidson LA, Goldsby JS, Hunt CL, Steinmeyer SH, Menon R, Suchodolski JS, et al. The microbiota-derived metabolite indole decreases mucosal inflammation and injury in a murine model of NSAID enteropathy. Gut Microbes. 2016;7:246–261. doi:10.1080/19490976.2016.1156827.

66. Patten CL, Blakney AJ, Coulson TJ. Activity, distribution and function of indole-3-acetic acid biosynthetic pathways in bacteria. Crit Rev Microbiol. 2013;39:395–415. doi:10.3109/1040841X.2012.716819.

67. Jin UH, Cheng Y, Park H, Davidson LA, Callaway ES, Chapkin RS, Jayaraman A, Asante A, Allred C, Weaver EA, et al. Short chain fatty acids enhance aryl hydrocarbon (Ah) responsiveness in mouse colonocytes and Caco-2 human colon cancer cells. Sci Rep. 2017;7:10163. doi:10.1038/s41598-017-10824-x.

68. Dianio-Moore S, Ma Y, Labitzke E, Tao H, David Warren J, Anderson J, Chen Q, Gross SS, Rikfink AD. Discovery and biological characterization of 1-(1H-indol-3-yl)-9H-pyrido[3,4-b]indole as an aryl hydrocarbon receptor activator generated by photocatalysis of tryptophan by sunlight. Chem Biol Interact. 2011;193:119–128. doi:10.1016/j.cbi.2011.05.010.

69. Liu Z, Li L, Chen W, Wang Q, Xiao W, Ma Y, Sheng B, Li X, Sun L, Yu M, et al. Aryl hydrocarbon receptor activation maintained the intestinal epithelial barrier function through Notch1 dependent signaling pathway. Int J Mol Med. 2018;41:1560–1572. doi:10.3892/ijmm.2017.3341.

70. Dalton A, Mermier C, Zuhl M. Exercise influence on the microbiome-gut-brain axis. Gut Microbes. 2019;10:1–14.

71. Bagda D, Reichert JL, Koschutnig K, Aigner CS, Holzer P, Koskenen K, Moisll-Eichern C, Schöpf V. Probiotics drive gut microbiome triggering emotional brain signatures. Gut Microbes. 2018;9:486–496. doi:10.1080/19490976.2018.1460015.

72. Nicolas GR, Chang PV. Deciphering the chemical lexicon of host-gut microbiota interactions. Trends
73. Osadchiy V, Labus JS, Gupta A, Jacobs J, Ashley-McNally C, Hsiao EY, Mayer EA. Correlation of tryptophan metabolites with connectivity of extended central reward network in healthy subjects. PLoS One. 2018;13:e0201772. doi:10.1371/journal.pone.0201772.

74. Garrison AM, Parrott JM, Tunon A, Delgado J, Redus L, O’Connor JC. Kynurenine pathway metabolic balance influences microglia activity: targeting kynurenine monoxygenase to dampen neuroinflammation. Psychoneuroendocrinology. 2018;94:1–10. doi:10.1016/j.psyneuen.2018.04.019.

75. Platten M, Nollen EAA, Rohrig UF. Tryptophan metabolism as a common therapeutic target in cancer, neurodegeneration and beyond. Nat Rev Drug Discovery. 2019;18:379–401.

76. Espey MG, Chernyshev ON, Reinhard JF Jr., Namboodiri MA, Colton CA. Activated human microglia produce the excitotoxin quinolinic acid. Neuronoreport. 1997;8:431–434. doi:10.1007/s0001756-199701200-00011.

77. Guillemin GJ, Smythe G, Takikawa O, Brew BJ. Expression of indoleamine 2,3-dioxygenase and production of quinolinic acid by human microglia, astrocytes, and neurons. Glia. 2005;49:15–23. doi:10.1002/glia.20090.

78. Cervenka I, Agudelo LZ, Ruas JL. Kynurenines: tryptophan metabolites in exercise, inflammation, and mental health. Science. 2017;357. doi:10.1126/science.aaf9794.

79. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Kynurenine pathway metabolism and the microbiota-gut-brain axis. Neuropharmacology. 2017;122:399–412. doi:10.1016/j.neuropharm.2016.07.002.

80. Vogel CFA, Goth SR, Dong B, Pessah IN, Matsumura F. Aryl hydrocarbon receptor signaling mediates expression of indoleamine 2,3-dioxygenase. Biochem Biophys Res Commun. 2008;375:331–335. doi:10.1016/j.bbrc.2008.07.156.

81. Litzenburger UM, Opitz CA, Sahm F, Rauschenbach KJ, Trump S, Winter M, Ott M, Ochs K, Lutz C, Liu X, et al. Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR. Oncotarget. 2014;5:1038–1051. doi:10.18632/oncotarget.1637.

82. Alvarado DM, Chen B, Iticovici M, Thaker AI, Dai N, VanDussen KL, Shaikh N, Lim CK, Guillemin GJ, Tritschler I, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature. 2011;478:197–203. doi:10.1038/nature10491.

83. Sznurkowski JJ, Zawrocki A, Emerich J, Sznurkowska K, Biernat W. Expression of indoleamine 2,3-dioxygenase predicts shorter survival in patients with vulvar squamous cell carcinoma (vSCC) not influencing on the recruitment of FOXP3-expressing regulatory T cells in cancer nests. Gynecol Oncol. 2011;122:307–312. doi:10.1016/j.ygyno.2011.04.050.

84. Platten M, Ho PP, Youssef S, Fontoura P, Garren H, Hur EM, Gupta R, Lee LY, Kidd BA, Robinson WH, et al. Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. Science. 2015;310:850–855. doi:10.1126/science.1117634.

85. Jaronen M, Quintana FJ. Immunological relevance of the coevolution of IDO1 and AHR. Front Immunol. 2014;5:521. doi:10.3389/fimmu.2014.00521.

86. Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Bicciato S, Mazza EMC, Macchiariulo A, Vacc A, et al. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. Nature. 2014;511:184+. doi:10.1038/nature13323.

87. Lim CK, Essa MM, de Paula Martins R, Lovejoy DB, Bilgin AA, Waly MI, Al-Farsi YM, Al-Sharbatli M, Al-Shaffae MA, Guillemin GJ, et al. Altered kynurenine pathway metabolism in autism: implication for immune-induced glutamatergic activity. Autism Res. 2016;9:621–631. doi:10.1002/aur.1565.

88. Fujisawa TX, Nishitani S, Iwanaga R, Matsuzaki J, Kawasaka C, Tochigi M, Sasaki T, Kato N, Shinohara K. Association of aryl hydrocarbon receptor-related Gene variants with the severity of autism spectrum disorders. Front Psychiatry. 2016;7:184. doi:10.3389/fpsyt.2016.00184.

89. Schwartz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurenines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 2012;13:465–477. doi:10.1038/nrn3257.

90. Haber R, Bessette D, Hulihangbllin B, Durcan MJ, Goldman D. Identification of tryptophan 2,3-dioxygenase Rna in rodent brain. J Neurochem. 1993;60:1159–1162. doi:10.1111/j.1471-4159.1993.tb03269.x.

91. Opitz CA, Litzenberger UM, Sahm F, Ott M, Tritschler I, Trump S, Schumacher T, Jestaedt L, Schrenk D, Weller M, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature. 2011;478:197–203. doi:10.1038/nature10491.

92. Salter MW, Stevens B. Microglia emerge as central players in brain disease. Nat Med. 2017;23:1018–1027. doi:10.1038/nm.4397.

93. Ben Haim L, Rowitch DH. Functional diversity of astrocytes in neural circuit regulation. Nat Rev Neurosci. 2017;18:31–41. doi:10.1038/nrn.2016.159.

94. Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci. 2015;18:942–952. doi:10.1038/nn.4043.

95. Sofroniew MV. Astrocyte barriers to neurotoxic inflammation. Nat Rev Neurosci. 2015;16:249. doi:10.1038/nrn3898.

96. Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ, Barres BA. Astrocyte
glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. Nature. 2012;486:410–412. doi: 10.1038/nature11059.

97. Alvarez JJ, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, Sabbagh M, Wosik K, Bourbonniere L, Bernard M, et al. The hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science. 2011;334:1727–1731. doi:10.1126/science.1206936.

98. Tsai HH, Li HL, Fuentealba LC, Molosky AV, Taveira-Marques R, Zhuang HL, Tenney A, Murnen AT, Fancy SPJ, Merkle F, et al. Regional astrocyte allocation regulates CNS synaptogenesis and repair. Science. 2012;337:358–362. doi:10.1126/science.1222381.

99. Marsland BJ. Regulating inflammation with microbial metabolites. Nat Med. 2016;22:581–583. doi:10.1038/nm.4117.

100. Buttgereit A, Lelios I, Yu XY, Vrohlings M, Krakoski NR, Gautier EL, Nishinakamura R, Becher B, Greter M. Sall1 is a transcriptional regulator defining microglia identity and function. Nat Immunol. 2016;17:1397–1406. doi:10.1038/ni.3585.

101. Lee YH, Lin CH, Hsu PC, Sun YY, Huang YJ, Zhuo JH, Wang C-Y, Gan Y-L, Hung -C-C, Kuan C-Y, et al. Aryl hydrocarbon receptor mediates both proinflammatory and Anti-inflammatory effects in lipopolysaccharide-activated microglia. Glia. 2015;63:1138–1154. doi:10.1002/glia.22805.

102. Liddelow SA, Guttenplan KA, Larke LEC, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung W-S, Peterson TC, et al. Neurotoxic reactive astrocytes are induced by activated microglia. Nature. 2017;541:481–487. doi:10.1038/nature21029.

103. White RE, Yin FQ, Jakeman LB. TGF-alpha increases astrocyte invasion and promotes axonal growth into the lesion following spinal cord injury in mice. Exp Neurol. 2008;214:10–24. doi:10.1016/j.expneuro.2008.06.012.

104. Anderson MA, Burda JE, Ren Y, Ao Y, O’Shea TM, Kawaguchi R, Coppola G, Khakh BS, Deming TJ, Sofroniew MV, et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature. 2016;532:195–200. doi:10.1038/nature17623.

105. Nag S, Eskandarian MR, Davis J, Eubanks JH. Differential expression of vascular endothelial growth factor-A (VEGF-A) and VEGF-B after brain injury. J Neuropathol Exp Neurol. 2002;61:778–788. doi:10.1093/jn/61.9.778.

106. Leitao-Goncalves R, Carvalho-Santos Z, Francisco AP, Fioreze GT, Anjos M, Baltazar C, Elias AP, Itskov PM, Piper MDW, Ribeiro C, et al. Commensal bacteria and essential amino acids control food choice behavior and reproduction. PLoS Biol. 2017;15:e2000862. doi:10.1371/journal.pbio.2000862.

107. Arora T, Loo RL, Anastasovska J, Gibson GR, Tuohy KM, Sharma RK, Swann JR, Deaville ER, Sleeth ML, Thomas EL, et al. Differential effects of two fermentable carbohydrates on central appetite regulation and body composition. PLoS One. 2012;7:e43263. doi:10.1371/journal.pone.0043263.

108. Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe. 2015;17:565–576. doi:10.1016/j.chom.2015.04.011.

109. Kilpatrick LA, Coveleskie K, Connolly L, Labus JS, Ebrat B, Stains J, Jiang Z, Suyenobu BY, Raybould HE, Tillisch K, et al. Influence of sucrose ingestion on brainstem and hypothalamic intrinsic oscillations in lean and obese women. Gastroenterology. 2014;146:1212–1221. doi:10.1053/j.gastro.2014.01.023.

110. Gupta A, Mayer EA, Sanmiguel CP, Van Horn JD, Woodworth D, Ellingson BM, Fling C, Love A, Tillisch K, Labus JS, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. Neuroimage Clin. 2015;7:506–517. doi:10.1016/j.nicl.2015.01.005.

111. Mayer EA. Gut feelings: the emerging biology of gut-brain communication. Nat Rev Neurosci. 2011;12:453–466. doi:10.1038/nrn3071.

112. Chimerel C, Emery E, Summers DK, Keyser U, Gribble FM, Reimann F. Bacterial metabolite indole modulates incretin secretion from intestinal enteroendocrine L cells. Cell Rep. 2014;9:1202–1208. doi:10.1016/j.celrep.2014.10.032.

113. van Bloemendaal L, Ten Kulve JS, la Fleur SE, Ijzerman RG, Diamant M. Effects of glucagon-like peptide 1 on appetite and body weight: focus on the CNS. J Endocrinol. 2014;221:T1–16. doi:10.1530/JOE-13-0414.

114. Coveleskie K, Kilpatrick LA, Gupta A, Stains J, Connolly L, Labus JS, Sanmiguel C, Mayer EA. The effect of the GLP-1 analogue Exenatide on functional connectivity within an NTS-based network in women with and without obesity. Obes Sci Pract. 2017;3:434–445. doi:10.1002/osp4.124.

115. Fulling C, Dinan TG, Cryan JF. Gut microbe to brain signaling: what happens in vagus. Neuron. 2019;101:998–1002. doi:10.1016/j.neuron.2019.02.008.

116. Dallie B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019;16:461–478.

117. Bonaz B, Bazin T, Pelissier S. The vagus nerve at the interface of the microbiota-gut-brain axis. Front Neurosci. 2018;12. doi:10.3389/fnins.2018.00049.

118. Horiiuchi M, Takeda T, Takahashi H, Ozaki-Masuzawa Y, Taguchi Y, Toyoshima Y, Otani L, Kato H, Sone-Yonezawa M, Hakuno F. Branched-chain amino acid supplementation restores reduced insulinotropic activity of a low-protein diet through the vagus nerve in rats. Nutr Metab (Lond). 2017;14:59. doi:10.1186/s12986-017-0215-1.

119. Buckley MM, O’Malley D. Development of an ex vivo method for multi-unit recording of
microbiota-colonic-neural signaling in real time. Front Neurosci. 2018;12:112. doi:10.3389/fnins.2018.00112.

Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA. 2011;108:16050–16055. doi:10.1073/pnas.1102999108.

Torres-Fuentes C, Schellekens H, Dinan TG, Cryan JF. The microbiota-gut-brain axis in obesity. Lancet Gastroenterol Hepatol. 2017;2:747–756. doi:10.1016/S2468-1253(17)30147-4.

Li Y, Hao YB, Zhu JX, Owyang C. Serotonin released from intestinal enterochromaffin cells mediates luminal non-cholecystokinin-stimulated pancreatic secretion in rats. Gastroenterology. 2000;118:1197–1207. doi:10.1016/S0016-5085(00)70373-8.

Ressler KJ, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. Nat Neurosci. 2007;10:1116–1124. doi:10.1038/nn1944.

Gaetani S, Oveisi F, Piomelli D. Modulation of meal pattern in the rat by the anorexic lipid mediator oleoylethanolamide. Neuropsychopharmacology. 2003;28:1311–1316. doi:10.1038/sj.npp.1300166.

Hankir MK, Seyfried F, Hintschich CA, Diep TA, Kleber K, Kranz M, Deuther-Conrad W, Tellez LA, Rullmann M, Patt M, et al. Gastric bypass surgery recruits a gut PPAR-alpha-striatal D1R pathway to reduce fat appetite in obese rats. Cell Metab. 2017;25:335–344. doi:10.1016/j.cmet.2016.12.006.

Williams BB, Van Benschoten AH, Gimermancic P, Donia MS, Zimmermann M, Takedani M, Ishihara A, Kashyap P, Fraser J, Fischbach M, et al. Discovery and characterization of gut microbiota decarboxylases that can produce the neurotransmitter tryptamine. Cell Host Microbe. 2014;16:495–503. doi:10.1016/j.chom.2014.09.001.

Covasa M, Ritter RC. Reduced CCK-induced Fos expression in the hindbrain, nodose ganglia, and enteric neurons of rats lacking CCK-1 receptors. Brain Res. 2005;1051:155–163. doi:10.1016/j.brainres.2005.06.003.

Jaglin M, Rhimi M, Philippe C, Pons N, Bruneau A, Goustard B, Daugé V, Maguin E, Naudon L, Rabot S, et al. Indole, a signaling molecule produced by the gut microbiota, negatively impacts emotional behaviors in rats. Front Neurosci. 2018;12. doi:10.3389/fnins.2018.00216.

Zubcevic J, Richards EM, Yang T, Kim S, Sumners C, Pepine CJ, Raizada MK. Impaired autonomic nervous system-microbiome circuit in hypertension A premise for hypertension therapy. Circ Res. 2019;125:104–116. doi:10.1161/CIRCRESAHA.119.313965.