



Microbial Indoles at the Gut-Immune-Brain Interface During Stress: Metabolism, Signaling, and Neuroimmune Effects

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Abstract

Microbial breakdown of dietary tryptophan is a key biochemical bridge connecting gut ecology, mucosal immunity, barrier integrity, and central nervous system function during stress. This narrative review synthesizes current evidence on microbial indole metabolites along the gut-immune-brain axis, separating direct experimental causality from taxonomic associations and non-stress disease models. Luminal substrate availability, fermentable dietary fibres, interspecies cross-feeding, and intestinal pH influence indole output. Upon formation, indole derivatives engage distinct host receptor systems – primarily the aryl hydrocarbon receptor, alongside the pregnane X receptor and peroxisome proliferator-activated receptor beta/delta. Biological outcomes shift considerably across specific chemical species, concentrations, target tissues, and underlying inflammatory states, demonstrating that microbial indoles cannot be generalized as uniformly protective postbiotics. Available evidence suggests that specific microbial indoles may influence sympathoadrenal stress responses, whereas direct links to classic hypothalamic-pituitary-adrenal reactivity remain limited. Highlighting critical methodological gaps, the review concludes that microbial indoles function as dynamic, situational signaling molecules during stress rather than intrinsically protective homeostatic mediators.

Keywords: gut microbiota; tryptophan metabolism; microbial indoles; stress; gut-immune-brain axis; neuroimmunity.

Abbreviations: AhR, aryl hydrocarbon receptor; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; IAA, indole-3-acetic acid; IAld, indole-3-aldehyde; ILA, indole-3-lactic acid; IPA, indole-3-propionic acid; PPAR- β/δ , peroxisome proliferator-activated receptor beta/delta; PXR, pregnane X receptor.

1. Introduction

Stress is a coordinated physiological response involving neural, endocrine, immune, metabolic, and gastrointestinal systems. Although acute stress can be adaptive, repeated or prolonged stress may alter gastrointestinal motility, secretion, epithelial function, immune activity, feeding behaviour, and the physicochemical environment of the intestinal lumen. These host-derived

changes can in turn modify microbial metabolism, including the transformation of dietary tryptophan into indole and related metabolites. The gut microbiota is therefore not simply altered by stress at the level of community composition; it may also change the chemical signals presented to epithelial, immune, endocrine, and neural systems (Mayer et al., 2015; Cryan et al., 2019; Roth et al., 2021; Tofani et al., 2025).

Tryptophan metabolism matters here specifically because the same dietary amino acid is processed by both host and microbial enzymes. Beyond the host's own kynurenine and serotonin pathways, gut microorganisms turn tryptophan into indole and a related family of metabolites, each with its own biological profile. These compounds can act locally in the gut, cross into circulation after the host modifies them, or shape systemic signaling indirectly through the intestinal barrier and immune system. Their effects vary a great deal – what happens depends on which metabolite it is, how much of it there is, which receptors are present, the cell type involved, and the wider physiological context (Roager and Licht 2018). In this review, “microbial indoles” is used as an umbrella term for indole and selected microbiota-associated tryptophan-derived indole metabolites. Unless otherwise stated, the evidence is interpreted at the level of the individual metabolite rather than the chemical class as a whole.

A handful of recent studies have started drawing a more direct line between stress and microbial tryptophan metabolism. Gheorghe et al. (2024) found that a single acute stressor was enough to alter gut tryptophan metabolism and barrier-related outcomes, with the effect depending on both the microbiota and the time of day. Wei et al. (2024) pushed this further mechanistically: psychological stress raised levels of the microbial metabolite indole-3-acetate (IAA), and this rise tracked with enrichment of *Lactobacillus murinus*, while IAA itself turned out to impair mitochondrial bioenergetics in intestinal stem cells and disrupt their commitment to secretory lineages. Together these two studies show not just that stress reshapes what the microbiota produces, but that at least one resulting metabolite can sit on a genuinely causal path to a host phenotype.

Still, the overall picture is patchy. A lot of gut-brain-axis research stops at bacterial composition and never measures metabolites directly, while much of the mechanistic work on indoles comes from inflammatory, metabolic, or neurodegenerative models rather than stress paradigms proper. Two caveats are worth keeping in mind throughout: not every circulating indole derivative is exclusively microbial, and not every biological effect of indoles goes through the aryl hydrocarbon receptor (AhR). Losing sight of either point makes it too easy to slide from association to mechanism without earning it.

This review examines microbial indole metabolites at the gut-immune-brain interface during stress. It considers how indoles are formed and ecologically regulated, how tryptophan metabolism changes under stress, and how these metabolites affect barrier, immune, neuroimmune, and neuroendocrine pathways. Mechanistic evidence is kept apart from indirect or disease-model evidence so that established findings remain distinct from open questions.

For this narrative review, PubMed and Google Scholar were searched for literature available up to August 2026, with no lower date limit. Search terms combined tryptophan or individual indole metabolites (indole, IAA, ILA, IPA, IAld, tryptamine) with gut microbiota, stress, AhR, PXR, PPAR, brain, neuroimmune, or HPA axis. Reference lists of relevant papers were also checked. Peer-reviewed English-language original studies were prioritized, while major reviews were used for background. Direct mechanistic evidence was defined as measurement or experimental manipulation of a specific metabolite linked to a host outcome. Association-only studies and inflammatory, metabolic, or neurodegenerative models not designed to study stress were treated as indirect evidence and are identified as such in the text and tables.

2. Microbial Metabolism of Tryptophan and Formation of Indole Derivatives

2.1. Tryptophan at the host-microbiota metabolic interface

Tryptophan is an essential aromatic amino acid that comes mainly from dietary protein. Most of it is absorbed in the small intestine and used for protein synthesis or other host metabolism, but a portion of unabsorbed dietary and host-derived protein reaches the large intestine, where the gut microbiota can make use of it (Roager and Licht 2018). From there, tryptophan feeds into several interconnected metabolic pools that host and microbial enzymes both draw on.

Three main routes are usually distinguished (Fig. 1). The host's kynurenine pathway breaks tryptophan down into kynurenine and its downstream products, some of which feed into nicotinamide adenine dinucleotide synthesis. The serotonin pathway converts tryptophan to 5-hydroxytryptophan and then serotonin, with further conversion to melatonin in some tissues. Intestinal microorganisms, meanwhile, transform luminal tryptophan into indole and a chemically diverse set of indole derivatives (Roth et al. 2021; Roager and Licht 2018). None of these three routes runs in isolation as a simple linear reaction – substrate availability and community-level microbial metabolism can redirect tryptophan between competing pathways at any point.

The best-studied microbial products include indole, indole-3-acetic acid (IAA), indole-3-lactic acid (ILA), indole-3-propionic acid (IPA), indole-3-aldehyde (IAld), indoleacrylic acid (IAcrA), and tryptamine. Which one forms depends on the taxon, and even the strain, and different enzymes can be involved starting from the same substrate (Roager and Licht 2018; Sinha et al. 2024). So finding a bacterial taxon with the genetic capacity to metabolize tryptophan says little by itself about how much of a given metabolite is actually produced in vivo, or which one it will be.

The label “microbiota-derived” also needs a closer look. A 2026 study using stable isotopes showed that mammalian cells can generate aryl-pyruvates, aryl-lactates, and aryl-acetates independently of microbial metabolism, whereas free indole and aryl-propionates remained largely dependent on bacterial activity (AbuSalim et al. 2026). Practically, that means circulating IAA or ILA cannot be assumed bacterial in origin, whereas free indole and IPA carry a stronger, more consistent microbiota-dependent signature.

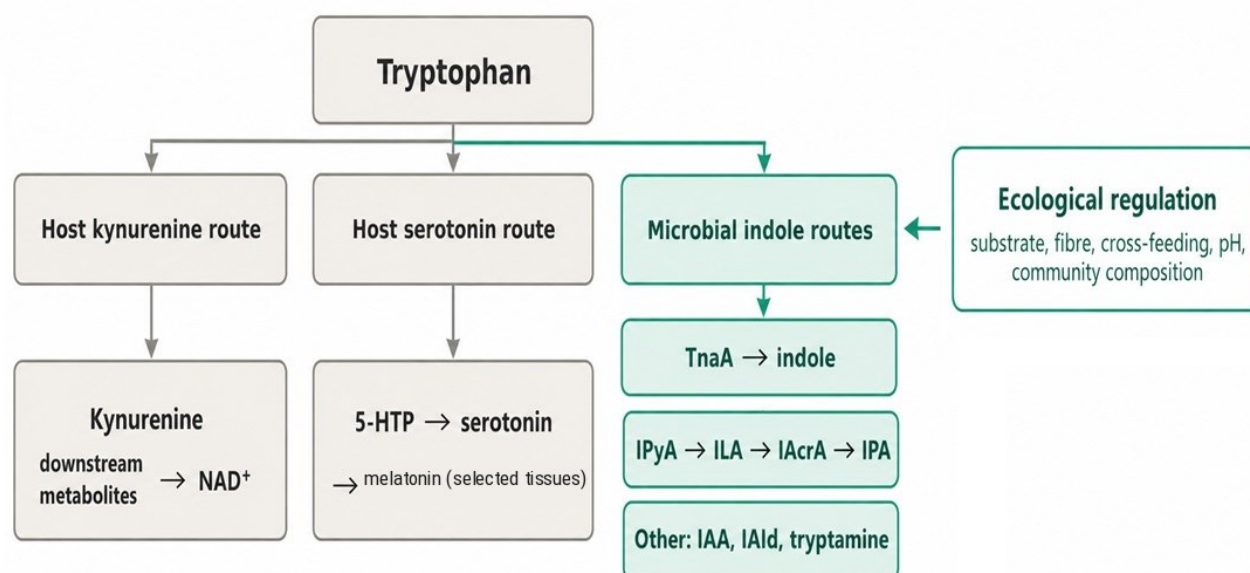


Fig. 1. Major host and microbial routes of tryptophan metabolism relevant to indole formation

Abbreviations: 5-HTP, 5-hydroxytryptophan; TnaA, tryptophanase; IPyA, indole-3-pyruvic acid; ILA, indole-3-lactic acid; IAcrA, indoleacrylic acid; IPA, indole-3-propionic acid; IAA, indole-3-acetic acid; IAld, indole-3-aldehyde; NAD⁺, nicotinamide adenine dinucleotide (oxidized form).

2.2. Major microbial pathways and indole metabolites

The most direct and best-understood microbial route to indole is bacterial tryptophanase activity. Tryptophanase (TnaA), encoded by *tnaA*, converts L-tryptophan into indole, pyruvate, and ammonia. This reaction occurs in numerous indole-producing bacteria and is particularly well characterized in *Escherichia coli* (Li and Young 2013, 2015). Genetic evidence further supports the central role of TnaA: disruption of *tnaA* abolishes detectable indole production, while supplementation with exogenous indole restores indole-dependent transcriptional responses in *E. coli* (Wang et al. 2001).

A more complex reductive pathway operates in several anaerobic gut bacteria. Working with *Clostridium sporogenes*, Dodd et al. (2017) combined genetic analysis, metabolic profiling, and gnotobiotic mouse experiments to characterize a pathway that processes aromatic amino acids, including tryptophan. Along this pathway, tryptophan is converted through a series of reductive reactions into indole-3-lactate (ILA), indole-3-acrylate (IAcrA), and ultimately indole-3-propionate (IPA). Genetic and metabolic analyses, together with experiments in gnotobiotic mice, demonstrated that disrupting the pathway alters both the production of these metabolites and their levels in the host circulation. Thus, this bacterial pathway represents an important route by which gut microbes transform aromatic amino acids into circulating metabolites that can affect host physiology (Dodd et al. 2017).

Indoleacrylic acid (IAcrA) can also be produced by other members of the gut microbiota. Wlodarska et al. (2017) demonstrated that several commensal *Peptostreptococcus* species, including *P. russellii*, possess the metabolic capacity to convert tryptophan into IAcrA. The study further showed that microbially produced IAcrA can influence intestinal epithelial barrier function and attenuate inflammatory responses, linking this microbial pathway to host intestinal physiology (Wlodarska et al. 2017).

ILA is not restricted to Stickland-fermenting clostridia. Breastfeeding-associated *Bifidobacterium* species, including *B. longum*, *B. breve* and *B. bifidum*, can convert tryptophan to ILA through a dedicated aromatic lactate dehydrogenase (ALDH), encoded by *aldh* (originally annotated as type 4 *ldh*). Laursen et al. (2021) demonstrated ILA production in bacterial cultures, identified the enzyme responsible, and confirmed its role through genetic disruption, complementation, and monocolonization of germ-free mice. These findings also illustrate why metabolic functions should not be assigned solely at the genus level, as the capacity to produce aromatic lactic acids differs substantially among *Bifidobacterium* species.

Other indole derivatives follow distinct, often strain-specific metabolic routes. Indole-3-aldehyde (IAld) is produced during tryptophan catabolism by selected lactobacilli. Zelante et al. (2013) showed that tryptophan utilization by lactobacilli leads to the production of IAld, which acts as an aryl hydrocarbon receptor (AhR) ligand and promotes AhR-dependent IL-22 production. This pathway contributes to mucosal protection from inflammation and enhances colonization resistance against *Candida albicans* (Zelante et al. 2013).

IAA has a more heterogeneous origin than free indole or IPA. Although it is produced by several gut microorganisms, recent evidence shows that mammalian metabolism can also contribute substantially to the circulating IAA pool. Using stable-isotope approaches in cells and animal models, AbuSalim et al. (2026) demonstrated host production of indole-3-acetate independently of the microbiome. Therefore, circulating IAA should not be interpreted as an exclusively microbiota-derived metabolite (AbuSalim et al. 2026).

Tryptamine represents another distinct route of microbial tryptophan metabolism and is formed by direct decarboxylation of tryptophan by bacterial tryptophan decarboxylase. This pathway has been experimentally demonstrated in selected gut bacteria, including *Clostridium sporogenes* and *Ruminococcus gnavus* (Williams et al. 2014). Tryptamine has been shown to influence intestinal

function and, more recently, to modulate intestinal and blood-brain barrier properties in vitro (Bhattarai et al. 2018; Rosell-Cardona et al. 2026). Although its role in stress-related models remains poorly characterized, these findings support its potential relevance to gut-brain communication.

The major tryptophan-derived microbial metabolites discussed above, together with their representative producers, key metabolic pathways, and relevant experimental evidence, are summarized in Table 1.

Table 1. Major tryptophan-derived indole metabolites discussed in this review

Metabolite	Representative microbial producers	Key pathway / enzyme	Evidence relevant to this section (Study)
Indole	<i>Escherichia coli</i> and other tryptophanase (<i>tnaA</i>)-positive gut bacteria	Tryptophanase (TnaA): L-tryptophan → indole + pyruvate + ammonia	Genetic disruption of <i>tnaA</i> abolishes detectable indole production; exogenous indole restores indole-dependent transcriptional responses in <i>Escherichia coli</i> (Wang et al. 2001; Li and Young 2013, 2015).
ILA	<i>Bifidobacterium longum</i> , <i>Bifidobacterium breve</i> , <i>Bifidobacterium bifidum</i> ; <i>Clostridium sporogenes</i>	In bifidobacteria, aromatic lactate dehydrogenase (ALDH), encoded by <i>aldh</i> ; in <i>Clostridium sporogenes</i> , part of the reductive aromatic amino-acid pathway	Experimental ILA production has been confirmed by genetic and gnotobiotic approaches; ILA is an intermediate in the reductive pathway leading to IPA (Dodd et al. 2017; Laursen et al. 2021).
IACrA	<i>Clostridium sporogenes</i> ; <i>Peptostreptococcus russellii</i> and other selected <i>Peptostreptococcus</i> species	Intermediate of the reductive tryptophan pathway leading to IPA; also produced during tryptophan metabolism by selected <i>Peptostreptococcus</i> species	Microbially produced IACrA has been linked to intestinal epithelial barrier regulation and attenuation of inflammatory responses (Dodd et al. 2017; Wlodarska et al. 2017).
IPA	<i>Clostridium sporogenes</i>	End product of the reductive aromatic amino-acid pathway through ILA and IACrA	Genetic and gnotobiotic evidence shows that bacterial metabolism contributes to circulating IPA; aryl-propionates remain strongly microbiota-dependent (Dodd et al. 2017; AbuSalim et al. 2026).
IAA	Multiple gut microbial taxa; mammalian cells also contribute	Heterogeneous microbial and host-associated pathways; no single universal microbial route	Circulating IAA should not be interpreted as exclusively microbiota-derived because host metabolism can also contribute to its production (AbuSalim et al. 2026).
IAlD	<i>Lactobacillus reuteri</i> and selected lactobacilli	Tryptophan catabolism leading to indole-3-aldehyde formation	IAlD acts as an AhR ligand and promotes IL-22-dependent mucosal protection and colonization resistance against <i>Candida albicans</i> (Zelante et al. 2013).
Tryptamine	<i>Clostridium sporogenes</i> ; <i>Ruminococcus gnavus</i>	Direct decarboxylation of tryptophan by bacterial tryptophan decarboxylase	Tryptamine influences intestinal function and can modulate intestinal and blood-brain barrier properties in vitro; its role in stress-related models remains poorly characterized (Williams et al. 2014; Bhattarai et al. 2018; Rosell-Cardona et al. 2026).

Abbreviations: AhR, aryl hydrocarbon receptor; ALDH, aromatic lactate dehydrogenase; IAA, indole-3-acetic acid; IACrA, indoleacrylic acid; IAlD, indole-3-aldehyde; IL-22, interleukin-22; ILA, indole-3-lactic acid; IPA, indole-3-propionic acid; TnaA, tryptophanase.

2.3. Dietary and ecological regulation of microbial indole production

The production of microbial indole metabolites depends not only on the presence of particular bacterial species but also on the physicochemical and nutritional conditions within the intestinal environment. Substrate availability, dietary fibre, luminal pH, and interactions between microbial

species can all influence the fate of tryptophan. Roager and Licht (2018) summarized evidence that proteolytic fermentation is promoted by increased protein availability, depletion of fermentable carbohydrates, higher colonic pH, and prolonged intestinal transit. More recent studies have shown that dietary fibre and pH can redirect tryptophan metabolism between competing microbial pathways, even without major changes in the abundance of the bacteria involved (Sinha et al. 2024; Brinck et al. 2026).

Sinha et al. (2024) set up a competition for tryptophan – in a defined three-species community, in complex human faecal cultures, and in gnotobiotic mice colonized with human microbiota. Indole-producing *E. coli* and ILA/IPA-producing *C. sporogenes* were competing for the same pool of tryptophan. A fibre-degrading bacterium, *Bacteroides thetaiotaomicron*, released monosaccharides from pectin that *E. coli* could then use. That extra carbohydrate supplies repressed *tnaA* expression through carbon catabolite repression, which cut indole production and left more tryptophan for *C. sporogenes* – shifting output toward ILA and IPA instead. The metabolite profile tracked this substrate-dependent regulation far more closely than it tracked how abundant the tryptophan-metabolizing organisms actually were (Sinha et al. 2024).

A related study points to cross-feeding as another piece of the fibre story. Zünd et al. (2025) cultured faecal microbiota from 16 healthy adults with tryptophan and various dietary fibres. Pectin boosted IPA production, though how much varied a great deal from one donor to the next. *Lachnospira eligens* turned out to make ILA, while *Enterocloster aldenensis* made IPA from that ILA rather than from tryptophan directly. Co-culture experiments confirmed the cross-feeding step, which makes the point that a metabolite's final concentration can be the product of a relay between community members rather than the output of any one species.

pH is another major lever on this ecology. Brinck et al. (2026) found, across two human cohorts, that faecal pH correlated positively with indole and negatively with ILA or IPA. In vitro, pH 5.5 suppressed *E. coli tnaA* expression and indole production, leaving more tryptophan for *C. sporogenes* and favouring the alternative metabolites; human faecal cultures showed the same pH-dependent drop in *tnaA* expression and indole formation. Faecal indole concentration, notably, was not explained by *tnaA* gene abundance alone: genetic potential and actual metabolic activity are, once again, two different things.

These observations, taken together, favour a functional view of microbial tryptophan metabolism over a purely taxonomic one. The intestinal indole profile reflects substrate availability, gene regulation, community interactions, and physicochemical conditions, all acting at once. Sequencing the microbiome, on its own, cannot reliably predict how much of a given indole metabolite will actually be made. Working out how dietary, physiological, or stress-related shifts in the gut environment change the chemical signals reaching the host requires direct metabolite measurements, ideally paired with functional genomic or transcriptomic data.

3. Stress-Related Changes in Gut Microbiota and Indole Metabolism

3.1. Stress reshapes the intestinal metabolic environment

Stress can alter microbial function through several host-mediated pathways simultaneously. Activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis can affect gastrointestinal motility, secretion, epithelial physiology, immune activity, and feeding behaviour, thereby reshaping the physicochemical environment in which microbial metabolism occurs (Mayer et al. 2015; Cryan et al. 2019; Tofani et al. 2025). Consequently, a stress-associated change in an indole metabolite does not require a major shift in the abundance of its producer: the same microbial community may generate a different metabolic output when substrate availability, luminal conditions, or microbial gene expression changes. This interpretation is consistent with the ecological framework of indole regulation described in Section 2.

Circadian timing adds another layer of complexity. Tofani et al. (2025) showed that the gut microbiota regulates the circadian organization of stress responsivity and is required for appropriate adaptation to psychological stressors across the day. Microbiota depletion disrupted diurnal patterns of HPA-axis activity and produced time-of-day-dependent changes in stress responses, while microbiota transplantation restored key features of these rhythms. The study did not identify a specific indole metabolite responsible for the effect; therefore, it should not be used as direct evidence for an indole-mediated mechanism. It is nevertheless highly relevant to metabolomic study design because both stress responsivity and microbial activity vary with sampling time. Time of day is therefore a biological variable in this field, not merely a technical covariate (Tofani et al. 2025).

3.2. Direct evidence linking stress to microbial tryptophan metabolism

A particularly informative study by Gheorghe et al. (2024) examined tryptophan metabolism in the stressed gut using metabolomic and microbiome-based approaches. The acute restraint stressor lasted 15 min; cecal indole increased overall, whereas cecal IAA did not show the same stress effect across the day. Acute stress was sufficient to alter intestinal tryptophan metabolism and gut-barrier-related outcomes, while the microbiota was required for the normal diurnal organization of several tryptophan-related signals. The study is important because it moves beyond taxonomic description and shows that the microbial contribution to tryptophan metabolism is dynamic and sensitive to stress and circadian context. However, its results do not justify treating every stress-associated change in a tryptophan metabolite as evidence of an established causal mediator: a pathway-level alteration and the causal role of an individual metabolite are distinct questions (Gheorghe et al. 2024).

Wei et al. (2024) provide more direct causal evidence for one specific indole metabolite. In their mouse model, psychological stress increased sympathetic signaling, enriched the gut commensal *Lactobacillus murinus*, and increased intestinal indole-3-acetate (IAA). Direct manipulation of IAA showed that the metabolite impaired mitochondrial bioenergetics in intestinal stem cells and disrupted their commitment to secretory epithelial lineages. The study is particularly informative because it connects stress-related host signaling to a microbial metabolite and then to a defined host-cell phenotype. It also challenges the assumption that microbial indoles are uniformly beneficial: in this model, increased IAA was associated with impaired epithelial function rather than improved barrier homeostasis (Wei et al. 2024).

3.3. Evidence gaps and interpretive limitations

Even with this progress, studies that measure stress exposure, microbiota function, and specific indole metabolites all together, within a single experimental design, are still uncommon. A shift in 16S ribosomal RNA (16S rRNA)-based community composition can hint at altered metabolic potential, but it does not prove that indole production actually changed. The reverse problem exists too: a change in plasma or faecal IAA or ILA cannot automatically be credited to bacterial synthesis, since host metabolism contributes to the same pools. The strongest causal designs pair direct metabolite quantification with microbial or genetic manipulation, germ-free or gnotobiotic approaches, targeted supplementation or depletion, and functional host readouts.

Several factors help explain why results look inconsistent from one stress study to the next. Acute and chronic paradigms engage different physiological responses; diet and luminal pH shift microbial tryptophan metabolism independently of stress; sampling time captures different circadian states; and faecal concentrations do not necessarily track what is actually circulating. Sex, meanwhile, remains an underexamined variable across most of this preclinical literature. All of which argues for caution before generalizing a metabolite signature from one stress model to another, or from rodents to humans. The key experimental studies discussed in this section, together

with the type of metabolic evidence and their main interpretive limitations, are summarized in Table 2.

Table 2. Selected experimental evidence linking stress, microbiota, and tryptophan-related metabolism

Study	Experimental model	Indole / metabolic evidence	Main finding	Main limitation
Gheorghe et al. (2024)	Acute-stress mouse experiments comparing microbiota-intact and microbiota-depleted animals across the day	Intestinal/cecal tryptophan-related metabolomics integrated with microbiome analyses	Acute stress altered gut tryptophan metabolism and barrier-related outcomes, and the normal diurnal organization of these signals depended on the microbiota.	Demonstrates stress sensitivity of the pathway but does not identify a specific indole as the causal mediator.
Wei et al. (2024)	Mouse model of psychological stress; sympathetic brain-to-gut signaling; enrichment of <i>Lactobacillus murinus</i>	IAA directly measured and experimentally manipulated	Psychological stress increased intestinal IAA; direct IAA manipulation showed impaired mitochondrial bioenergetics in intestinal stem cells and disrupted secretory-lineage commitment.	Provides strong metabolite-level causality for an intestinal phenotype but does not establish a brain-directed indole mechanism.
Tofani et al. (2025)	Microbiota depletion/transplantation and time-of-day-dependent stress-response experiments in mice	Microbiome and circadian stress-response profiling; no indole-specific metabolite manipulation	The microbiota regulated circadian organization of stress responsivity and adaptation, highlighting time of day as a biological variable.	Supports the framework but does not identify a specific indole mediator.

Abbreviations: IAA, indole-3-acetic acid.

4. Indole Signaling at the Gut-Immune Interface

4.1. AhR is a major, but not exclusive, indole-sensing pathway

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor and an important sensor of dietary, host-derived, microbial, and environmental molecules (Safe et al. 2013; Bahman et al. 2024). In the canonical pathway, ligand binding promotes AhR translocation to the nucleus, where AhR heterodimerizes with the AhR nuclear translocator (ARNT) and binds xenobiotic response elements (XREs) in target genes. Cytochrome P450 family 1 subfamily A member 1 (CYP1A1) is one of the best-known AhR-responsive genes (Safe et al. 2013; Bahman et al. 2024). However, changes in CYP1A1 expression should be interpreted as a downstream pathway readout rather than, by themselves, definitive proof of a particular ligand–receptor interaction.

Microbial tryptophan catabolites can engage this pathway in the intestinal mucosa. Zelante et al. (2013) provided seminal evidence that tryptophan catabolites produced by *Lactobacillus reuteri*, particularly indole-3-aldehyde, activate AhR and drive interleukin-22 (IL-22)-dependent mucosal protection. This study established a mechanistic link between bacterial tryptophan metabolism, AhR signaling, and mucosal immune protection. However, ligand potency and biological effects vary substantially among indole derivatives and target cell types; therefore, the term “indole–AhR axis” should not be interpreted as implying a single uniform response (Zelante et al. 2013).

AhR is not the only host receptor system relevant to indole signaling. Venkatesh et al. (2014) showed that indole-3-propionic acid (IPA) regulates intestinal barrier function through the xenobiotic sensor pregnane X receptor (PXR). Their results further implicated Toll-like receptor 4 (TLR4) signaling downstream of PXR-mediated effects on inflammatory and junctional gene expression; TLR4 was not presented as the primary indole receptor. More recently, Li et al. (2025) reported that IPA reprograms CD4⁺ T-cell energy metabolism through peroxisome proliferator-

activated receptor beta/delta (PPAR- β/δ), increasing mitochondrial fatty-acid and amino-acid oxidation, reducing glycolytic capacity, and suppressing T helper 1 (Th1) and T helper 17 (Th17) differentiation. These effects were independent of AhR signaling, including in AhR-deficient CD4⁺ T cells, providing evidence that a biologically meaningful effect of an indole metabolite can occur through a non-AhR pathway (Venkatesh et al. 2014; Li et al. 2025).

4.2. Intestinal epithelial barrier and epithelial renewal

The intestinal barrier is built from mucus, a continuous epithelial layer, junctional complexes between cells, antimicrobial products, and immune cells sitting close by and indole signaling can reach several of these at once. In an epithelial-cell model, Bansal et al. (2010) showed that bacterial indole raised transepithelial resistance and changed the expression of genes involved in epithelial junctions and inflammation. Findings like this support a barrier-modulating role for indole, but a molecular-marker change is not the same thing as functional permeability.

Recent work also explains why barrier effects need to be treated as dose- and context-dependent, not as fixed properties of a given metabolite. Rosell-Cardona et al. (2026) compared several microbial tryptophan metabolites across in vitro intestinal and blood-brain barrier models and found the response changed with the metabolite, the concentration, and the barrier cell type. A compound that strengthens one barrier under one set of conditions cannot be assumed to do the same somewhere else, or at a different dose.

Wei et al. (2024) stress study adds another dimension: indole signaling can shape epithelial cell fate, not just junctional proteins. Stress-associated IAA impaired mitochondrial bioenergetics in intestinal stem cells and reduced their commitment to secretory lineages – which suggests that chronic barrier dysfunction could come not only from acute changes in tight junctions, but from altered epithelial renewal and differentiation building up over time.

4.3. Mucosal immune programs: IL-22, T cells, and immunometabolism

AhR-dependent interleukin-22 production is among the most solidly established links between microbial tryptophan catabolites and mucosal immunity. IL-22 acts mainly on epithelial cells, supporting antimicrobial defence, tissue repair, and barrier function. Zelante et al. (2013) demonstrated this in the context of mucosal protection, and their work laid the groundwork for later studies of AhR-responsive innate lymphoid and T-cell populations.

Indole metabolites shape adaptive immunity too, though not in a way that fits a simple ‘anti-inflammatory versus pro-inflammatory’ label. Regulatory T cells and Th17 cells are distinct programs with context-dependent roles: Th17 responses help defend barrier surfaces but can sustain inflammation if excessive or prolonged, while regulatory T cells rein in overactive immune responses and support tolerance. Li et al.'s (2025) IPA study is a good illustration – IPA reduced Th1 and Th17 differentiation without a matching rise in regulatory T cells, and the mechanism ran through metabolic reprogramming via PPAR- β/δ rather than AhR, tying microbial chemistry directly to immunometabolism.

Altogether, the evidence points to a network of receptors rather than one dominant pathway. Different indole metabolites can act on epithelial and immune cells through AhR, PXR, PPAR-family signaling, and likely other targets not yet identified. Which way a given response goes depends on the metabolite's chemical identity and concentration, the cellular context, and the host's physiological state. This diversity matters for understanding how stress-related changes in indole production might travel from the intestinal lumen to systemic and neuroimmune signaling.

5. Neuroimmune and Gut-Brain Effects of Microbial Indoles

Most mechanistic studies discussed in this section were not designed as stress models. They are included to assess biological plausibility and are labeled by experimental context; stress-specific evidence is discussed separately in Sections 3 and 6.

5.1. Routes from the intestinal lumen to the brain

Gut-derived indole metabolites do not need one direct route from the intestinal lumen to neurons to influence the brain. Once the microbiota produces a metabolite, it might act locally on the epithelium and mucosal immune system, get biotransformed by the host, enter circulation, or modify neural and endocrine signaling from the gut (Cryan et al. 2019; Morais et al. 2021). Any given change in brain function could therefore reflect some mix of direct metabolite exposure and indirect effects through barrier integrity, cytokines, vagal afferents, or systemic metabolic signals – and how much each route contributes varies by metabolite and by experimental model.

The blood-brain barrier (BBB) is a plausible point of contact for circulating microbial metabolites. In an *in vitro* study using bEnd.3 brain endothelial cells, Rosell-Cardona et al. (2026) found that indole, IAA, IPA, and tryptamine each changed transendothelial electrical resistance and the response to lipopolysaccharide in a concentration-dependent way. The direction of the effect was not consistent across metabolites or assays – some concentrations improved electrical resistance, while permeability measurements sometimes told a different story, including a harmful interaction for IPA under lipopolysaccharide exposure. This is direct evidence that tryptophan-derived microbial metabolites can alter endothelial barrier properties, but it is also a warning against calling any single indole “barrier-protective” based on one concentration or one readout (Rosell-Cardona et al. 2026).

None of this proves the same concentrations reach an intact brain *in vivo*. Distinct biological compartments – including luminal production, portal uptake, hepatic biotransformation, plasma protein binding, and active endothelial transport – create steep concentration gradients between the gut lumen and brain tissue. For this reason, establishing a genuine gut-to-brain mechanism requires integrative experimental designs that simultaneously quantify specific indole metabolites across multiple compartments, including faeces, portal blood, systemic plasma, cerebrospinal fluid, and brain tissue, alongside functional *in vivo* assessments of barrier integrity and neuroimmune activity.

5.2. Microglia, astrocytes and AhR-dependent neuroimmune signaling

Some of the strongest mechanistic evidence for indole-related neuroimmune signaling actually comes from experimental autoimmune encephalomyelitis (EAE) – a widely established animal model of multiple sclerosis – rather than from stress models. Rothhammer et al. (2016) showed that dietary tryptophan metabolites produced by the gut microbiota can regulate astrocyte activity and central nervous system (CNS) inflammation through the aryl hydrocarbon receptor (AhR). This work linked microbial tryptophan metabolism directly to an astrocyte transcriptional program and demonstrated that the suppression of CNS inflammation was AhR-dependent. In short, it established that gut-derived microbial tryptophan products can reach and modulate a defined receptor system within the neuroimmune compartment (Rothhammer et al. 2016).

A follow-up study extended this pathway to microglia, the resident immune cells of the brain. Rothhammer et al. (2018) found that commensal tryptophan metabolites regulate microglial AhR signaling and, through that mechanism, modulate the production of transforming growth factor- α (TGF- α) and vascular endothelial growth factor B (VEGF-B). These microglial-derived signaling factors in turn suppress neurotoxic, pathogenic astrocyte programs during experimental autoimmune encephalomyelitis. Microglia, in other words, can act as intermediaries in a multicellular circuit between a metabolite-sensitive pathway and astrocyte function (Rothhammer et al. 2018). Together, these two studies establish biological plausibility for an indole-AhR-neuroimmune pathway, though neither one shows that the same mechanism directly underlies adaptation to psychological stress specifically.

Evidence from neurodegenerative models points in a broadly similar direction. In male amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice (a genetic model of Alzheimer's disease), Sun et al. (2022) administered a mixture of indole, indole-3-acetic acid (IAA), and indole-3-propionic

acid (IPA) and observed increased AhR-related signaling alongside reduced neuroinflammation driven by nuclear factor kappa B (NF- κ B) and the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, leading to lower levels of central pro-inflammatory cytokines. Because it was an Alzheimer's disease model and the metabolites were given as a mixture, the study cannot isolate any single indole's individual contribution and does not speak to stress specifically – but it does support the broader point that gut-derived indole metabolites can modify central inflammatory signaling in vivo (Sun et al. 2022).

5.3. Neurogenesis, neuronal excitability and emotional behavior

Individual microbial indole metabolites have also been linked to neural processes outside classical inflammatory pathways. Wei et al. (2021) showed that tryptophan-metabolizing gut microbes regulate adult hippocampal neurogenesis through AhR signaling – tying microbial tryptophan metabolism and indole availability to changes in adult neurogenesis, a case of a microbiota-derived chemical signal shaping neural plasticity rather than simply switching on immune cells (Wei et al. 2021).

The behavioural literature is especially telling here, because it shows an indole effect's direction is not fixed but depends on context. Jaglin et al. (2018) compared germ-free rats mono-associated with an indole-producing *Escherichia coli* strain against rats colonized by an isogenic *tnaA*-deficient strain. Chronic microbial indole production increased anxiety-like and helplessness-related behaviours. Acute intracecal indole exposure produced a very different phenotype instead – strong motor depression, accumulation of oxidized indole derivatives in the brain, and signs of vagal activation. Chronic indole production, notably, did not change basal or post-test plasma corticosterone relative to the non-producing group, so the behavioural phenotype cannot simply be explained by a stronger HPA-axis corticosterone response (Jaglin et al. 2018).

Yu et al. (2025) found the opposite pattern: germ-free male C57BL/6J mice showed increased anxiety-related behaviour and hyperexcitable basolateral amygdala pyramidal neurons, linked to reduced small-conductance calcium-activated potassium channel activity. Colonizing them with live microbes, or giving them microbial-derived indoles orally, restored channel activity and reduced the anxiety phenotype. That this runs opposite to Jaglin et al.'s (2018) chronic-overproduction model is itself the point – microbiota status, host strain, exposure pattern, and metabolite concentration all help decide which way the behavioural outcome goes (Yu et al. 2025). The two studies therefore support a role for indole signaling in emotional behavior, but not a reproducible direction of effect.

Table 3. Representative experimental studies linking microbial indoles to neuroimmune and gut-brain effects

Study	Experimental model	Indole / mechanistic target	Main finding	Main limitation
Rosell-Cardona et al. (2026)	bEnd.3 brain endothelial cells; in vitro BBB model	Indole, IAA, IPA and tryptamine; endothelial barrier function	The metabolites altered BBB-related measures in a concentration and metabolite-dependent manner; the direction of the response varied across assays.	In vitro evidence; effects varied across metabolites, concentrations and barrier readouts.
Rothhammer et al. (2016, 2018)	EAE mouse models; primary astrocyte and microglial cultures	Microbial tryptophan metabolites → AhR; microglial TGF- α /VEGF-B signaling	AhR-dependent modulation of astrocyte and microglial programs reduced pathogenic astrocyte activity and CNS inflammation.	Autoimmune neuroinflammation model; not a psychological stress model.

Wei et al. (2021)	Mouse microbiota / indole-neurogenesis experiments	Microbial indoles → AhR-dependent signaling in the brain	Microbial tryptophan metabolism and indole availability regulated adult hippocampal neurogenesis through AhR signaling.	Not designed as a stress study; direct behavioural relevance is limited.
Sun et al. (2022)	Male APP/PS1 transgenic mice; indole + IAA + IPA mixture	AhR signaling; NF-κB/NLRP3 inflammatory pathway	The indole mixture increased AhR-related signaling and reduced NF-κB/NLRP3-associated neuroinflammation and inflammatory cytokines.	Alzheimer's disease model; use of a metabolite mixture prevents attribution to an individual indole.
Jaglin et al. (2018)	Gnotobiotic rats colonized with WT vs. tnaA-deficient <i>E. coli</i> ; acute intracaecal indole exposure also tested	Direct microbial indole production; vagal/central signaling and oxidized indole derivatives	Chronic microbial indole production increased anxiety-like and helplessness-related behaviour; acute indole exposure caused marked motor depression. Corticosterone did not differ between colonization groups.	Artificial mono-association and rat model; outcomes depended strongly on exposure pattern.
Yu et al. (2025)	Germ-free male C57BL/6J mice; microbial colonization or oral microbe-derived indoles	Microbial indoles → small-conductance Ca ²⁺ -activated K ⁺ (SK) channels in the basolateral amygdala	Microbial indoles restored amygdala SK-channel activity and reduced the anxiety-related phenotype.	Germ-free, male and strain-specific context; direction differs from chronic indole-overproduction models.
Wang et al. (2026)	IBS patients and mouse model; <i>A. shahii</i> , indole or AhR manipulation	<i>A. shahii</i> -tryptophanase-indole-AhR pathway; ventral dentate gyrus	Restoring tryptophanase-producing microbiota, indole supplementation or AhR activation improved affective phenotypes.	IBS rather than stress model; relevance to stress-specific mechanisms remains indirect.

Abbreviations: AhR, aryl hydrocarbon receptor; APP/PS1, amyloid precursor protein/presenilin 1 transgenic model; BBB, blood-brain barrier; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; IAA, indole-3-acetic acid; IBS, irritable bowel syndrome; IPA, indole-3-propionic acid; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor family pyrin domain-containing 3; SK, small-conductance calcium-activated potassium channel; TGF-α, transforming growth factor-alpha; VEGF-B, vascular endothelial growth factor B; WT, wild-type.

A more recent study adds a more anatomically specific gut-brain mechanism. Wang et al. (2026) reported that reduced *Alistipes shahii* abundance and reduced bacterial tryptophanase-dependent indole production went along with affective symptoms in irritable bowel syndrome and in a matching mouse model. Restoring tryptophanase-producing microbiota, supplementing indole directly, or activating AhR each rescued the emotional phenotype, and the ventral dentate gyrus emerged as a relevant AhR-responsive brain region (Wang et al. 2026).

None of this evidence supports a simple model where 'more indole' is uniformly good, or uniformly bad, for the brain. Indole signaling instead seems to be shaped jointly by dose, duration, microbial context, host genotype, physiological state, brain region, and which receptor gets engaged. That context-dependence matters a great deal when carrying neuroimmune findings over from inflammatory or neurodegenerative models to stress-related conditions.

The key mechanistic studies connecting microbial indole metabolites to neuroimmune signaling, central plasticity, and behavioral phenotypes along with their specific experimental paradigms and interpretive constraints are summarized in Table 3.

6. Microbial Indoles and Neuroendocrine Stress Signaling: Current Evidence and Missing Links

6.1. The HPA axis as a microbiota-sensitive stress pathway

The hypothalamic-pituitary-adrenal (HPA) axis is the central endocrine coordinator of the stress response: hypothalamic signals trigger pituitary release of adrenocorticotrophic hormone, which downstream drives glucocorticoid secretion from the adrenal cortex. In a foundational experiment, Sudo et al. (2004) showed that germ-free mice mounted exaggerated plasma adrenocorticotrophic hormone and corticosterone responses to restraint stress compared with specific-pathogen-free mice, and that early microbial colonization could change this phenotype. This established that the microbiota plays a role in developing and regulating neuroendocrine stress responsivity – though it did not identify indole metabolites as the mediators responsible (Sudo et al. 2004).

That distinction still matters. Plenty of literature connects microbiota composition with HPA-axis activity, but far fewer studies manipulate a defined microbial metabolite while also measuring endocrine stress outcomes. General evidence that the microbiota regulates the HPA axis cannot substitute for direct evidence that indole, IAA, ILA, or IPA specifically regulate glucocorticoid signaling. Roth et al. (2021), reviewing this broader literature, note that early-life microbiota disruption is linked to altered HPA-axis reactivity and serotonergic signaling in maternal-separation models – which shows how solid the general microbiota-HPA relationship is in the wider field, even though what indole metabolites specifically contribute to it remains largely unmapped.

6.2. Direct evidence from indole-production models

Mir et al. (2020) is one of the clearest direct links in the available literature between microbial indole production and chronic stress. Germ-free male C3H/HeN mice were colonized with either an indole-producing *E. coli* strain or a non-producing mutant, then exposed to unpredictable chronic mild stress. Chronic indole production raised the overall emotionality score specifically in stressed mice and markedly increased phenylethanolamine N-methyltransferase (*Pnmt*) expression in the adrenal medulla – the enzyme behind the final step of epinephrine biosynthesis. At the same time, the authors found no major changes in systemic tryptophan availability, brain serotonin or dopamine, or expression of selected gut and brain genes tied to cytokine and host tryptophan pathways (Mir et al. 2020).

This result points to the sympathoadrenal side of stress adaptation rather than a canonical HPA-axis mechanism. In the earlier rat study by Jaglin et al. (2018), indole-producing and non-producing groups had similar plasma corticosterone both at baseline and after stressful behavioural testing, despite clear behavioural differences between them. Together, these studies suggest microbial indole can shift emotional or stress-related phenotypes without a matching rise in circulating corticosterone. Direct measurements of corticotropin-releasing hormone, adrenocorticotrophic hormone, glucocorticoid receptor activation, and tissue-specific glucocorticoid target genes are still sparse in indole-manipulation experiments.

6.3. AhR-glucocorticoid receptor crosstalk: a plausible but unproven bridge

At the molecular level, AhR and the glucocorticoid receptor (GR) have been shown to interact in cell systems. Stejskalova et al. (2013) reported that dexamethasone sped up AhR degradation and suppressed CYP1A1 induction in placental JEG-3 cells. Jin et al. (2017) went further, demonstrating ligand-dependent crosstalk between AhR and GR in human retinal pigment epithelial cells, with effects on nuclear signaling and target-gene regulation. Both studies confirm the two receptor systems can influence each other, though the direction and size of that interaction depends on cell type, ligand, and experimental conditions (Stejskalova et al. 2013; Jin et al. 2017).

Neither study, though, looked at microbiota-derived indoles in a stress model, so calling AhR-GR crosstalk an established mechanism linking microbial indoles with stress adaptation would be

premature. What can be said for now is that three separate pieces are individually well supported – some microbial indole metabolites can activate AhR, glucocorticoids signal through GR during stress, and AhR and GR can interact in select cellular contexts – while whether they actually form a physiologically meaningful indole-AhR-GR circuit in a stressed organism is still an open question.

Closing this gap needs experiments that measure the microbial metabolite and the endocrine response in the same system, along with receptor-level tests of causality. A suitable design would combine quantified indole exposure with stress paradigms, tissue-specific AhR and GR readouts, and gain- or loss-of-function approaches rather than leaning on CYP1A1 expression or a single corticosterone measurement alone.

Table 4. Experimental evidence relevant to microbial indoles and neuroendocrine stress signaling

Study	Experimental model	Neuroendocrine / receptor target	Main finding	Main limitation
Sudo et al. (2004)	Germ-free vs. specific-pathogen-free mice; restraint stress; postnatal microbial colonization	HPA axis; ACTH; corticosterone	Germ-free mice showed exaggerated ACTH and corticosterone responses to restraint stress; early microbial colonization modified the neuroendocrine stress phenotype.	Establishes microbiota-dependent HPA regulation but does not identify microbial indoles as mediators.
Jaglin et al. (2018)	Gnotobiotic rats colonized with indole-producing vs. <i>tnaA</i> -deficient <i>E. coli</i>	Corticosterone; emotional behavior; microbial indole production	Microbial indole altered emotional behavior, whereas basal and post-test plasma corticosterone did not differ between colonization groups.	Artificial mono-association and rat model; supports behavioral effects without demonstrating a canonical HPA mechanism.
Mir et al. (2020)	Gnotobiotic male C3H/HeN mice colonized with indole-producing vs. non-producing <i>E. coli</i> + unpredictable chronic mild stress	Adrenal medulla; PNMT; epinephrine synthesis	<i>Chronic microbial indole production increased emotional vulnerability during stress and markedly increased adrenal Pnmt expression.</i>	Points mainly to sympathoadrenal rather than canonical HPA signaling; direct GR-pathway evidence remains limited.
Stejskalova et al. (2013)	Placental JEG-3 cells exposed to dexamethasone	GR-AhR interaction; AhR degradation; CYP1A1	Dexamethasone accelerated AhR degradation and suppressed CYP1A1 induction, demonstrating glucocorticoid modulation of AhR signaling.	Cell model; no microbial indole and no whole-organism stress paradigm.
Jin et al. (2017)	Human retinal pigment epithelial cells; ligand-dependent receptor manipulation	AhR-GR crosstalk and target-gene regulation	Functional, ligand-dependent crosstalk between AhR and GR signaling was demonstrated at the level of nuclear signaling and gene regulation.	Cell-specific evidence; no microbial metabolite and no stress model.

Abbreviations: ACTH, adrenocorticotrophic hormone; AhR, aryl hydrocarbon receptor; CYP1A1, cytochrome P450 family 1 subfamily A member 1; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; PNMT, phenylethanolamine N-methyltransferase.

7. Conclusions and Future Perspectives

The evidence synthesized in this review supports microbial tryptophan metabolism as a dynamic and environmentally responsive component of gut-immune-brain communication during stress rather than a fixed or uniformly protective pathway (Fig. 2). The intestinal profile of indole metabolites is determined not only by microbial taxonomic composition but also by substrate availability, dietary fibre, interspecies cross-feeding, luminal pH, and regulation of microbial metabolic pathways. Consequently, changes in microbial community structure cannot by themselves predict the functional output of tryptophan metabolism. Recent experimental studies further indicate that stress can reshape this metabolic environment in a microbiota- and time-of-day-dependent manner. Importantly, stress-associated IAA provides direct evidence that alteration of a defined indole metabolite can participate in a causal brain-to-gut pathway affecting intestinal epithelial cell metabolism and differentiation (Gheorghe et al. 2024; Wei et al. 2024).

At the host interface, indole metabolites engage multiple receptor and cellular pathways rather than a single signaling axis. AhR is among the best-characterized sensors of microbial tryptophan-derived signals and contributes to epithelial, immune, and neuroimmune responses. However, PXR-dependent regulation of intestinal barrier function and PPAR- β/δ -dependent reprogramming of CD4⁺ T-cell metabolism demonstrate that biologically relevant effects of indole metabolites can also occur through AhR-independent mechanisms (Venkatesh et al. 2014; Li et al. 2025). Findings from barrier, neuroinflammatory, neurogenesis, and neuronal-excitability models further indicate that the direction of an indole response depends on the chemical identity of the metabolite, concentration, duration of exposure, target tissue, and physiological or inflammatory context. Thus, microbial indoles should not be considered collectively as intrinsically beneficial postbiotics. Across independent studies, context dependence is more consistent than the direction of effect. Specific indole-mediated stress mechanisms have rarely been replicated in a second model.

The connection between microbial indole signaling and neuroendocrine stress regulation is considerably less established. Experimental manipulation of microbial indole production has demonstrated effects on emotional behaviour and adrenal-medullary Pnmt expression during chronic stress, whereas indole-associated behavioural changes have also been observed without corresponding differences in circulating corticosterone. These findings suggest that microbial indoles can influence stress-related phenotypes without necessarily producing parallel changes in the classical HPA-axis response. At the same time, although molecular crosstalk between AhR and the glucocorticoid receptor has been demonstrated in selected cellular systems, current evidence is insufficient to establish a physiologically relevant microbial indole-AhR-GR pathway during stress. Accordingly, Fig. 2 should be interpreted as an integrated framework connecting experimentally supported pathways while also highlighting the still incomplete link between microbial indole signaling and classical neuroendocrine stress regulation.

These limitations define several priorities for future research. Studies should move beyond parallel measurements of microbiota composition and host phenotype toward experimental designs that directly connect microbial function, metabolite exposure, receptor engagement, and physiological outcome. Targeted metabolomics across intestinal contents, portal blood, systemic circulation, and, where biologically justified, cerebrospinal fluid or brain tissue would help determine whether metabolite concentrations used in experimental systems reflect actual host exposure. Stable-isotope tracing will be particularly important for distinguishing microbial from host contributions to circulating metabolites such as IAA and ILA. Receptor-level causality should be established using pharmacological or genetic gain- and loss-of-function approaches rather than inferred from individual transcriptional markers such as CYP1A1. Finally, biological sex, diet, circadian phase, stress duration, and baseline microbiota composition should be incorporated as experimental variables because each can modify either microbial metabolism or the host response.

Beyond stress-related conditions, the pathways discussed here may also be relevant to autoimmune neuroinflammation, neurodegenerative disorders, intestinal inflammation, irritable bowel syndrome, and conditions involving altered emotional behaviour. Experimental findings also point to several possible therapeutic directions, including modulation of microbial tryptophan metabolism, administration of selected indole metabolites, and targeting host receptors such as AhR, PXR, or PPAR- β/δ . However, these possibilities remain largely preclinical. Given the strong dependence of indole effects on the specific metabolite, dose, tissue, and physiological context, translation into therapeutic strategies will require careful validation rather than treating microbial indoles as a single functional or therapeutic class.

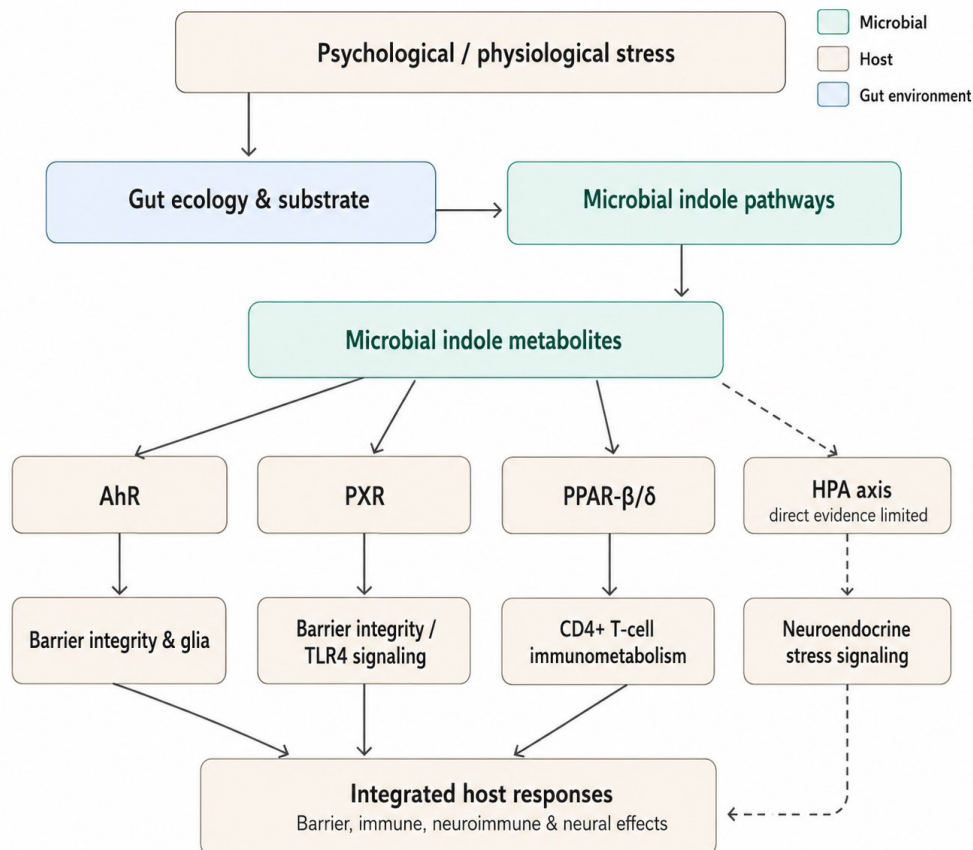


Fig. 2. Integrative schematic of microbial indole signaling at the gut-immune-brain interface during stress

Abbreviations: AhR, aryl hydrocarbon receptor; CD4, cluster of differentiation 4; HPA, hypothalamic-pituitary-adrenal; PPAR- β/δ , peroxisome proliferator-activated receptor-beta/delta; PXR, pregnane X receptor; TLR4, Toll-like receptor 4.

Source: original scheme developed by the author based on the evidence discussed in Sections 2-6. Solid arrows indicate experimentally supported relationships, whereas dashed arrows indicate proposed or insufficiently established links.

Overall, microbial indoles are best viewed as context-dependent chemical signals linking intestinal microbial metabolism with host physiology during stress. Their importance lies not in a universal protective effect but in their ability to modify epithelial, immune, neuroimmune, neural, and potentially neuroendocrine processes according to the metabolite and biological context. Establishing which indole metabolites are causal in specific stress conditions, determining the physiologically relevant concentrations at which they act, and identifying the receptor systems and target tissues responsible for their effects remain the key steps required before microbiota- or indole-targeted interventions can be considered mechanistically justified.

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Мікробні індоли на межі взаємодії кишечник-імунна система-мозок за умов стресу: метаболізм, сигнальні шляхи та нейроімунні ефекти

Мікробний метаболізм триптофану, що надходить із їжею, є однією з ключових біохімічних ланок, які поєднують кишкову екосистему, імунітет слизових оболонок, цілісність бар’єрів і функціонування центральної нервової системи за умов стресу. У цьому огляді узагальнено

сучасні дані про мікробні індольні метаболіти у межах осі кишечник-імунна система-мозок із чітким розмежуванням прямих причинно-наслідкових доказів, асоціативних спостережень та результатів, отриманих у моделях захворювань, не пов'язаних безпосередньо зі стресом. Утворення індольних метаболітів значною мірою визначається доступністю субстратів, харчовими волокнами, придатними до мікробної ферментації, обміном метаболітами між різними видами мікроорганізмів та рН кишкового вмісту, тоді як сам таксономічний склад мікробіоти не дає повного уявлення про її метаболічну активність. Після утворення індольні похідні взаємодіють із різними рецепторними системами хазяїна – насамперед з арил-вуглеводневим рецептором, а також із рецептором прегнану Х та рецептором, активованим проліфераторами пероксисом β/δ . Біологічні ефекти цих сполук істотно залежать від конкретного метаболіту, його концентрації, тканини-мішені та запального контексту, тому мікробні індולי не можна розглядати як універсально захисні постбіотики. Наявні дані дають підстави припускати, що окремі мікробні індולי можуть впливати на симпатoadреналову відповідь, тоді як прямі докази участі окремих індольних метаболітів у регуляції класичної гіпоталамо-гіпофізарно-надниркової осі поки що обмежені. Узагальнення наявних результатів і виявлених методологічних прогалин дає підстави розглядати мікробні індולי як динамічні й контекст-залежні сигнальні молекули, залучені до відповіді організму на стрес, а не як апріорі захисні чинники.

Ключові слова: кишкова мікробіота; метаболізм триптофану; мікробні індולי; стрес; вісь кишечник-імунна система-мозок; нейроімунітет.