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2 **Focus on the Essentials: Tryptophan Metabolism and the Microbiome-Gut-Brain Axis**

3
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ABSTRACT

The gut-brain axis is a bidirectional communication system between the central nervous system and the gastrointestinal tract, in which serotonin (5-HT) functions as a key neurotransmitter. Recent research has increasingly concentrated on tryptophan, the precursor to 5-HT and on the microbial regulation of tryptophan metabolism, with an emphasis on host-microbe control over kynurenine pathway metabolism and microbial-specific pathways that generate bioactive tryptophan metabolites. Here, we critically assess recent progress made towards a mechanistic understanding of the microbial regulation of tryptophan metabolism and microbiota-gut-brain axis homeostasis highlighting the role tryptophan metabolism plays in preclinical and clinical neuroscience and in the challenge to improve our understanding of how perturbed tryptophan metabolism contributes to stress-related psychiatric disorders.

Abbreviations:

5-HT: 5-hydroxytryptamine (serotonin)
5-HTP: 5-hydroxytryptophan
AAD: Aromatic amino Acid Decarboxylase
AANAT: Arylalkylamine N-acetyltransferase
AHR: Aryl Hydrocarbon receptor
ASD: Autism Spectrum Disorder
ASMT: Acetyl-Serotonin O-Methyltransferase
CA: Cholic Acid
CNS: Central Nervous System
DCA: Deoxycholic Acid
EC cells: Enterochromaffin cells
ENS: Enteric Nervous System
GF: Germ-Free
GI tract: Gastrointestinal tract
GPCR: G-Protein-Coupled Receptor
IBD: Inflammatory Bowel Disease
IBS: Irritable Bowel Syndrome
IDO: Indoleamine dioxygenase
KAT: Kynurenine aminotransferase
KYNA: Kynurenic Acid
L-KYN: L-Kynurenine
MDD: Major Depressive Disorder
QUIN: Quinolinic Acid
SCFA: Short Chain Fatty Acid
SERT: Serotonin Transporter
SPF: Specific Pathogen-Free
SSRI: Selective Serotonin Reuptake Inhibitors
TDC: Tryptophan Decarboxylase
TDO: Tryptophan 2,3-dioxygenase
TnaA: Tryptophanase
TPH: Tryptophan 5-hydroxylase

INTRODUCTION

Host-microbe interactions are now more routinely considered in the context of brain function and behavior. Establishing the mechanistic basis for this fascinating dialogue between the gut microbiome and the gut-brain axis has proved more challenging. As the field transitions beyond compositional assessments of the gut microbiome, tryptophan has come under increasing scrutiny as a pivotal essential amino acid in the lexicon of host-microbial crosstalk. Recent advances in this field continue to demarcate the indirect means through which our gut microbes influence host metabolic pathways [1,2]. Direct microbial metabolism of tryptophan also yields microbial metabolites and candidate interkingdom signaling molecules acting as an interface between the host and its resident microorganisms with important physiological implications both in the gut and the brain [3,4]. Support continues to accumulate from studies of a broad swathe of gut-brain axis disorders that the metabolism of tryptophan is perturbed and associated with alterations in the composition or function of the gut microbiome [2]. In this review, we critically evaluate the recent advances in this area as we strive towards a mechanistic understanding of the microbial regulation of gut-brain axis homeostasis and the implications for neuroscience.

TRYPTOPHAN METABOLISM

Tryptophan metabolites have a huge impact both in the central nervous system (CNS) and in the periphery (see fig 1). Once absorbed from the gut they become available in the circulation for distribution to target sites both peripherally and in the CNS. Tryptophan can also be metabolized directly by the gut microbiota and generate a range of indoles with diverse biological activity [5]. The combination of microbial and host gastrointestinal metabolism of tryptophan is thus likely an important factor in the systemic availability of tryptophan, as well as indoles, kynurenine and serotonin (5-HT) produced locally [3]. Much work has been done to better understand the impact of aberrant host tryptophan metabolism in psychiatric disorders and to identify the extent to which these molecular mechanisms dictate the impact of the gut microbiota on host physiology, brain function and behavior.

-- Insert Figure 1 here --

TRYPTOPHAN METABOLISM & GUT-BRAIN AXIS DISORDERS

The importance of 5-HT in the gastrointestinal tract is consistent with the fact that ~95% of 5-HT is produced endogenously by enterochromaffin cells in the gut where it is involved in functions such as motility and secretion. Disruption in central and peripheral serotonergic signaling pathways are reported in GI disorders, such as inflammatory bowel disease (IBD) [6] and irritable bowel syndrome (IBS) – a functional gastrointestinal disorder with significant psychiatric comorbidity - and in pathologies like autism spectrum disorder (ASD), a central nervous system disorder with comorbid gastrointestinal symptoms. For instance, activation of the kynurenine pathway has been reported in patients with IBD compared to controls. A sex-difference in tryptophan metabolism has been observed in both controls and patients with IBD characterised by lower serum tryptophan levels in female compared to males. The authors suggested this sex-difference could have important implications for understanding the increased female prevalence for some inflammatory phenotypes [7]. Differences in microbial subnetworks have been demonstrated in IBS patients compared to controls with respect to functional connectivity of brain regions in the somatosensory network and GI sensorimotor function, pointing to alterations in interactions within the brain-gut-microbiome axis [8]. The

120 authors also pointed out the importance of members of the order *Clostridiales* in modulating
121 host 5-HT biosynthesis and release. A recent study working with BTBR mice – a mouse-based
122 model of ASD-like behaviors – exhibited microbiota-related impairments in 5-HT production
123 in the intestine [9]. ASD is frequently associated with GI symptoms that can plausibly be linked
124 to dysregulation of tryptophan metabolism in the gut [11,12]. In a study of children with autism,
125 the authors demonstrated elevated concentrations in urine of xanthurenic acid and quinolinic
126 acid suggesting preferential transformation from tryptophan at the expense of kynurenic acid
127 [12].

128

129 **THE GUT MICROBIOME, STRESS RELATED PSYCHIATRIC DISORDERS AND** 130 **TRYPTOPHAN METABOLISM**

131

132 An increasing number of studies report the impact of the intestinal microbiota on the fate and
133 metabolism of tryptophan (see fig 2). Importantly, the immuno- and stress- sensitive enzymes
134 responsible for the initial conversion of L-tryptophan to L-kynurenine – indoleamine-2,3-
135 deoxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) – may also be regulated directly or
136 indirectly by the gut microbiome. Indeed, experiments have revealed that germ-free (GF) mice
137 (i.e. mice devoid of microorganisms, raised in a sterile environment) have reductions in
138 kynurenine pathway metabolism that could be restored by colonization post-weaning [13].
139 Although the precise mechanisms are unclear, there are several potential routes through which
140 the intestinal microbiota could regulate the expression and activity of kynurenine pathway
141 enzymes. Examples include the production of hydrogen peroxide, microbial priming of the host
142 immune system, activation of the aryl hydrocarbon receptor, the secretion of microbial
143 metabolites influencing gut barrier integrity or via TLRs (see also figure 3) [14]. Intestinal
144 microbes are thought to be involved in stress-related disorders as exemplified by the study of
145 Valles-Colomer et al. [15*] where differences in gut microbial composition were associated
146 with lower quality of life (QoL) and depression status compared to healthy controls. In fact,
147 certain strains of bacteria in the gut are able to directly utilize tryptophan consequently changing
148 its availability to the host [16**,18]. Kelly et al. [18*] performed fecal microbiota transplants
149 from depressed patients to rats depleted of intestinal microbiota and demonstrated that the
150 depressive phenotype is transmitted via the transfer of the intestinal microbiota as is the
151 physiological hallmark of depression in terms of increased tryptophan metabolism along the
152 kynurenine pathway.

153

154

-- Insert Figure 2 here --

155

156

156 **TRYPTOPHAN & SEROTONIN**

157

158 Early studies in this field helped establish the principle that the gut microbiome regulated
159 tryptophan availability and onward metabolism into 5-HT, not just locally in the gut but also in
160 the CNS [14,20,20*]. Acute tryptophan depletion (ATD) leads to increased depressive-like
161 behavior and a stronger reduction of tryptophan, 5-HT and 5-hydroxyindoleacetic acid in the
162 medial prefrontal cortex and hippocampus of GF than in SPF mice [21*]. Interestingly,
163 following ATD, GF mice behave more similarly to SPF mice under basal conditions. The
164 authors concluded that the serotonergic system of GF mice, which is abnormal at baseline, is
165 more vulnerable to ATD. Administration of prebiotics (i.e. substrates that are selectively
166 utilized by, and promotes the growth and/or activity of, beneficial host microorganisms
167 compared to probiotics, which are live microorganisms consumed to produce a health benefit)
168 in mice has shown antidepressant and anti-anxiolytic effects which underlines the possibility of
169 exerting beneficial effects on the serotonergic system by therapeutic targeting of the gut

170 microbiome, an appealing strategy, and one that can be expedited with an enhanced knowledge
171 of the mechanisms underpinning this important emerging aspect of host-microbe dialogue [22].
172

173 Since 5-HT is mainly synthesized in the gut, it is not surprising that the intestinal microbiota
174 can have a significant impact on its availability. Kwon et al. [23] demonstrated a considerable
175 difference in the composition of the intestinal microbiota depending on whether or not the TPH-
176 1 gene – the rate-limiting enzyme of 5-HT synthesis – was knocked out and whether the
177 progenitors were heterozygous or homozygous for this gene. They also provided evidence that
178 5-HT directly modulated the growth of commensal bacteria *in vitro* in a concentration-
179 dependent and species-specific manner. It has also been demonstrated that mice with a TPH2
180 gene mutation, which leads to lower 5-HT biosynthesis in both enteric and CNS serotonergic
181 neurons specifically, exhibit both brain and intestinal dysfunction and a slow release 5-HTP
182 formulation was able to restore ENS-mediated GI function [24**].
183

184 Another proposed mechanism [16**] is by microbial biotransformation of cholic acid (CA) -
185 secreted by the liver – into deoxycholic acid (DCA). Raising luminal concentrations of DCA in
186 the colon of GF mice to levels seen in specific-pathogen free (SPF) mice sufficiently increases
187 colon and serum 5-HT compared to vehicle-injected controls. This restoration of peripheral 5-
188 HT correlates with elevations in colonic TPH1 expression. Sun et al. [25] further showed that
189 the elevation of 5-HT seen in high fat diet rats can be restored to a conventional-like level by
190 use of fecal microbiota transplantation from control animals which may imply that elevated
191 levels of DCA and CA could lead to the upregulation of TPH1 expression in the small intestine.
192

193 By colonization of previously GF mice with a complex microbiota, De Vadder et al. [26*]
194 demonstrated that the gut microbiota stimulates neuronal and mucosal 5-HT release and that
195 maturation of the adult ENS in GF mice requires 5-HT_{4R}-specific signaling. Moreover, the
196 microbiota likely affects 5-HT₃ receptor expression to modulate colonic secretion [27]. This
197 study also addressed the importance of short-chain fatty acids (SCFAs: microbial metabolites
198 produced by bacterial fermentation of dietary fibers by the intestinal microbiota) in 5-HT
199 colonic secretion and hypothesized that this effect could be mediated via acetate production by
200 the gut microbiota. Another study confirmed this result *in vitro* by exposing BON cells (human
201 EC cell model) to microbiota-derived SCFAs which significantly increased TPH1 mRNA
202 expression [28]. There is thus growing evidence, including mechanistic insights, that the
203 intestinal microbiota is a contributor to the colonic secretion of 5-HT. A very elegant study by
204 Yano et al. [16**] introduced the concept that spore-forming bacteria could regulate host 5-HT
205 synthesis in colonic enterochromaffin cells in mice. Indeed Mandić et al. [29] examined the
206 specific involvement of the bacterium *Clostridium Ramosum* in colonic secretion of 5-HT in
207 the gut and suggested it could be due to an induced expansion of enterochromaffin cells.
208

209 5-HT availability - in both the brain and intestine - depends on 5-HT transporter (SERT)
210 function. Recently Singhal et al.[30] emphasized differences in cecal and fecal microbiota
211 composition of SERT^{-/-} or SERT^{+/+} mice, concluding that SERT plays an important role in
212 maintaining the homeostasis of the gut microbiota and that deficiency leads to loss of bacterial
213 niches and altered microbial metabolic capabilities. In addition to being able to impact 5-HT
214 production by acting on enterochromaffin cells, there are 5-HT-producing bacterial strains [14].
215 Lyte et al.[31] provided evidence that there could be a biogenic amine transport system in the
216 biofilm of certain bacteria, particularly the genus *Lactobacillus*, demonstrating that bacteria are
217 capable of modifying host availability of 5-HT. Since intestinal bacteria have an impact on 5-
218 HT availability, bacteria may be indirectly involved in psychiatric diseases. It is also of
219 considerable interest whether or not intestinal bacteria are reciprocally affected by the use of

220 psychotropic drugs with serotonergic mechanisms of action. To address this question, Cussotto
221 et al. [32] showed *in vitro* that two SSRI drugs, escitalopram and fluoxetine, modulate the
222 growth of resident gut bacteria. The importance of these results were confirmed in a recent
223 study which documented changes in microbial communities after chronic administration of
224 fluoxetine [33].

225
226 One of the most understudied mechanisms by which the gut microbiota could influence the
227 level of 5-HT in the gut lumen is deconjugation of 5-HT-O-glucuronide - produced by the liver
228 - by β -glucuronidase, a bacterial enzyme. Ex-GF mice have the majority of 5-HT in an
229 unconjugated form whereas GF mice have approximately 50% of the 5-HT in a conjugated
230 form. This leads to the possibility that the intestinal microbiota could have a specific role in
231 liberating biologically active free 5-HT [34]. Taken together, there is now evidence to postulate
232 a role of microbiota in 5-HT production from EC cells and change in 5-HT availability in the
233 host (see fig 3).

234
235 -- Insert Figure 3 here --

236 237 **TRYPTOPHAN & KYNURENINE**

238
239 The available recent evidence suggests that the gut microbiota can exert an impact on important
240 kynurenine pathway enzymes at multiple levels of the gut-brain axis. By comparing GF,
241 colonized GF and conventionally colonized animals, Moloney et al. [35] highlighted the role
242 of the intestinal microbiota in modulating the expression of miRNAs associated with the
243 kynurenine pathway in the mouse hippocampus. Evidence shows that the microbial
244 composition of chronically stressed mice changes compared to controls in a way that is
245 associated with the development of depression-like behavior. A *Lactobacillus* strain, possibly
246 by the production of H₂O₂ [36], exerted a protective role against stress-induced depression-like
247 behavior associated with inhibition of intestinal IDO1 activity and a decreased circulating level
248 of kynurenine. Another study focusing on kynurenine in MDD patients [37] supports those
249 results as it showed that administration of *Lactobacillus plantarum* leads to a decrease in
250 kynurenine concentrations and improved cognitive function. Kazemi et al. [38] also
251 demonstrated the benefit of an 8-week probiotic treatment - *Lactobacillus helveticus* and
252 *Bifidobacterium longum* supplementation - in MDD patients. This treatment resulted in a
253 significant decrease in kynurenine/tryptophan ratio (used here as a marker of IDO activity) in
254 serum samples compared to placebo. Furthermore, REGA3 has recently been identified [39] as
255 an antimicrobial protein within the GI tract able to affect the composition of the gut microbiota
256 towards an increase in *Lactobacillus*. Interestingly, REG3A-associated increases in
257 *Lactobacillus* promotes production of kynurenine in gut epithelial cells in mice. By working
258 with mice with an IDO-1 gene knockout in the context of obesity, Laurans et al.[40] found an
259 increase of IL-22 target genes such as the antimicrobial proteins (Reg3g and Reg3b) in the
260 intestine of High Fat Diet fed *Ido1* *-/-* mice compared to high fat diet wild type mice
261 highlighting that obesity may be associated with a microbiota-associated shift in tryptophan
262 metabolism towards kynurenine production. Since the flow of kynurenine across the blood
263 brain barrier is considered critical to its role in CNS pathology, harnessing the gut microbiota
264 as a control point for kynurenine generation could have important therapeutic implications.

265 266 **TRYPTOPHAN & MELATONIN**

267
268 Melatonin is a hormone synthesized from 5-HT and mostly secreted by the pineal gland in
269 mammals, but it can also act locally and be synthesized by several organs including the sites

270 within the gastrointestinal tract. Its best known role is the regulation of the circadian rhythm
271 but has also been shown to affect multiple molecular pathways including immune function,
272 apoptosis, proliferation, angiogenesis and oxidative stress [41]. Sleep deprivation is a common
273 burden that must be considered seriously as it can impact the autonomic nervous system,
274 endocrine system and immune function, and that can be a trigger factor of metabolic or mental
275 diseases. Gao et al. [42] investigated the effect of melatonin in a mouse model of sleep
276 deprivation and found melatonin mediated sleep-deprivation induced mucosal injury and
277 altered gut microbiota composition. Intriguingly, they show that sleep deprivation negatively
278 impacts the diversity and richness of colonic microbiota and that melatonin supplementation
279 greatly improves this state. In the context of weaning stress, melatonin supplementation was
280 able to improve body weight gain and intestinal morphology and to increase the richness indices
281 of intestinal microbiota and shape the composition of intestinal microbiota in conventionally
282 colonized mice [43]. However, in both antibiotic-treated and GF mice, melatonin failed to affect
283 intestinal morphology suggesting that there could be an involvement of intestinal microbiota in
284 the regulatory functions of melatonin in intestinal physiology. Interestingly, a third study [44]
285 focused on lipid metabolism found that melatonin supplementation in high fat diet fed mice
286 alleviated the lipid accumulation and was able to reverse gut microbiota dysbiosis. They also
287 showed results that suggest that melatonin can act on the intestinal microbiota by increasing the
288 number of acetic acid-producing strains. These recent studies suggest that melatonin acts on the
289 intestinal microbiota in several very different contexts, which implies that its role is essential
290 in many physiological conditions and that its impact should not to be neglected in future studies.

291 292 **TRYPTOPHAN & INDOLE**

293
294 Indole is produced from tryptophan via the enzyme tryptophanase by multiple indole-producing
295 bacteria [45]. This metabolite plays a significant role for their survival and controls diverse
296 physiological processes such as antimicrobial response, biofilm formation, motility and a range
297 of other functions. Importantly, animal cells cannot synthesize indole. However, indole can be
298 oxidized by non-indole-producing bacteria or eukaryotes into several biologically active
299 derivatives [46]. Understanding how these tryptophan derivatives, synthesized by certain
300 bacteria, can impact the host is an important research objective. There is growing evidence that
301 these molecules have an impact at both peripheral and cerebral level, in particular through the
302 binding to certain receptors such as the aryl hydrocarbon receptor (AHR) [4,47], that promotes
303 the expression of inflammation associated genes. Indole has been detected in the human gut at
304 concentrations of 250-1100 μM [4] and indole derivatives synthesized by gut bacteria have been
305 found in blood, peripheral tissues, urine and brain tissues which suggests an important role of
306 those bacterial compounds. Some indole-derivatives are characterized by neurodepressive
307 properties - namely oxindole and isatin - and excessive production of indole by the gut
308 microbiota may adversely affect behavior in rats [47*].

309
310 An increasing number of studies are focusing on the activation of the AHR as it has shown to
311 have profound effects upon immunological status of the GI tract. However, the range of ligands
312 responsible for AHR-activation within the gut continues to expand [48]. Recently, indole and
313 some of these derivatives have been shown to be potent activators or stimulators of AHR and
314 thus to influence the transcription of important factors of the immune system. This discovery is
315 potentially of major importance because it highlights activation of the host's immune system
316 through metabolites produced by the intestinal microbiota. Koper et al.[49] studied the kinetics
317 of tryptophan-derived AHR-ligands by using a Simulator of the Human Intestinal Microbial
318 Ecosystem (SHIME) and were able to simulate the ascending, transverse and descending colon
319 from fresh human fecal sample. Some kynurenine derivatives showed a constant concentration

320 through the colon, while other metabolites showed increased or decreased concentrations
321 through different regions, although the implications of these region-specific variations are
322 unclear. Table 1 lists some key indoles thought to activate the AHR and their potential
323 physiological impact.

324 **TRYPTOPHAN & TRYPTAMINE**

325
326
327 *Clostridium sporogenes* and *Ruminococcus gnavus* are strains present in the gut microbiota
328 capable of decarboxylating tryptophan to tryptamine through the specific enzyme tryptophan
329 decarboxylase [50]. Tryptamine can play several roles in the gut such as signaling and has been
330 shown to induce the release of 5-HT by enterochromaffin cells. Indeed, enteric neurons are able
331 to take up tryptamine, which displaces 5-HT in intracellular synaptic vesicles, causing 5-HT
332 release therefore might affect gastrointestinal motility[24**]. Bhattarai et al. [51**] uncovered
333 a specific mechanism by which tryptamine-producing bacteria could accelerate gastrointestinal
334 transit by activating the epithelial GPCR 5-HT4 receptor. To date, there are very few studies
335 investigating the synthesis of tryptamine [50] by intestinal bacteria and the effect of this
336 molecule in the body, but these promising initial studies indicate that there are some interesting
337 discoveries to be made.

338 **CONCLUDING SECTION**

339
340
341 The essential role of tryptophan as a precursor to a range of bioactives important for signaling
342 along the microbiome-gut-brain axis is increasingly appreciated in the context of psychological
343 wellbeing and symptom generation. These tryptophan derivatives may facilitate both interorgan
344 and interkingdom crosstalk and systemic availability of tryptophan, indoles, kynurenine, 5-HT
345 and melatonin, each have an essential and unique aspect in maintaining signaling homeostasis
346 along the microbiome-gut-brain axis. Microbial regulation of tryptophan availability and
347 metabolism has important implications for many gut-brain axis disorders including GI disorders
348 with psychiatric comorbidity, such as IBS, IBD and other CNS pathologies with GI dysfunction
349 like ASD. These observations are likely missing pieces of the puzzle in understanding the origin
350 and consequences of aberrant host tryptophan metabolism in many psychiatric disorders as
351 well. Future research should look to clarify the importance of lifestyle choices such as diet,
352 sleep, daily activity and exercise participation for tryptophan metabolism in health and disease.
353 It remains to be seen if this fast accumulating information can be rationally integrated within a
354 framework that enables mechanistically-oriented therapeutic targeting of the gut microbiome.

355 **CONFLICT OF INTEREST STATEMENT**

356
357
358 APC Microbiome Ireland collaborates with a number of industry partners including Dupont
359 Nutrition Biosciences APS, Cremo SA, Alkermes Inc., 4D Pharma PLC, Mead Johnson
360 Nutrition, Nutricia Danone and Suntory Wellness. TGD has been an invited speaker at meetings
361 organized by Servier, Lundbeck, Janssen and AstraZeneca and has received research funding
362 from Mead Johnson, Cremo, Suntory Wellness, Nutricia and 4D Pharma. JFC has been an
363 invited speaker at meetings organized by Mead Johnson, Yakult, Alkermes and Janssen and has
364 received research funding from Mead Johnson, Cremo, Suntory Wellness, Nutricia, Dupont and
365 4D Pharma. GC has spoken at meetings sponsored by food and pharmaceutical companies
366 including Janssen Ireland and Probi. This neither influenced nor constrained the content of this
367 review.

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377

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380

* of special interest

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** of outstanding interest

382

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660 **Figure Legends**

661

662 **Figure 1: Tryptophan metabolism and the Microbiome-gut-brain axis**

663

664 An essential amino acid obtained from dietary proteins, tryptophan, serves as a precursor to a
665 variety of imperative bioactive molecules, some generated by the host and some fabricated by
666 gut microbes (indicated by blue arrows). The most widely known fate of tryptophan is
667 conversion into 5-HT and melatonin downstream. Nevertheless, a large majority of tryptophan
668 is metabolized along the kynurenine pathway giving rise to molecules often collectively
669 referred to as “kynurenines”. The availability of tryptophan is also altered by gut microbes
670 generating either indole and its derivatives, tryptamine or even 5-HT which can impact on
671 gastrointestinal function via GPCR activation. An increasing number of studies highlight the
672 importance of this pathway in metabolic and psychiatric disorders.

673

674 **Figure 2: Tryptophan metabolism pathways and stress related Gut / Brain Interactions**

675

676 Aberrant tryptophan metabolism can occur in response to stress and inflammation in both the
677 gut and the brain. An imbalance in the concentration of the different molecules that these
678 pathways generates has consequences upon gut-brain signaling. In the gut, following immune
679 activation or during the stress response, tryptophan is preferentially converted to kynurenine
680 rather than 5-HT. Decreased 5-HT conversion from tryptophan – synthesized primarily by
681 enterochromaffin cells - impacts on gastrointestinal motility and function. In the brain,
682 tryptophan is metabolized along the kynurenine pathway by microglia and astrocytes leading
683 to the formation of either kynurenic acid or quinolinic acid (by Astrocyte or Microglia,
684 respectively). The majority of CNS kynurenine is derived from the periphery and once in the
685 CNS, it can also participate in onwards metabolism. The balance between kynurenic acid and
686 quinolinic acid is important for health and disease. Excessive activation of kynurenine
687 metabolism may have neurotoxic consequences in clinical psychiatric and neurological
688 disorders, such as depression.

689

690 **Figure 3: Candidate mechanisms for microbial regulation of tryptophan and serotonin**
691 **release.**

692

693 The availability and metabolism of tryptophan is under the influence of various intrinsic and
694 extrinsic factors. There are a number of potential mechanisms through which the gut
695 microbiome can influence tryptophan metabolism and the production of 5-HT or other
696 metabolites. 5-HT can be synthesized both in the brain and in the gut by two different rate-

697 limiting isoenzymes of tryptophan hydroxylase (TPH) - TPH1 and TPH2, respectively. It has
698 been shown recently that some bacteria found in the gut microbiota, *in vitro*, are able to
699 synthesize 5-HT. The microbiota has several ways to modulate 5-HT availability by regulating
700 5-HT secretion from enterochromaffin cells with short chain fatty acids (SCFA) increasing
701 TPH1 mRNA expression. Microbial enzymes often biotransform metabolites produced by the
702 liver, including the conversion of hepatic-derived cholic acid into deoxycholic acid leading to
703 increased 5-HT in the colon and blood serum or by cleaving 5-HT-O-glucuronide, secreted into
704 the gut lumen from the liver, into free 5-HT.

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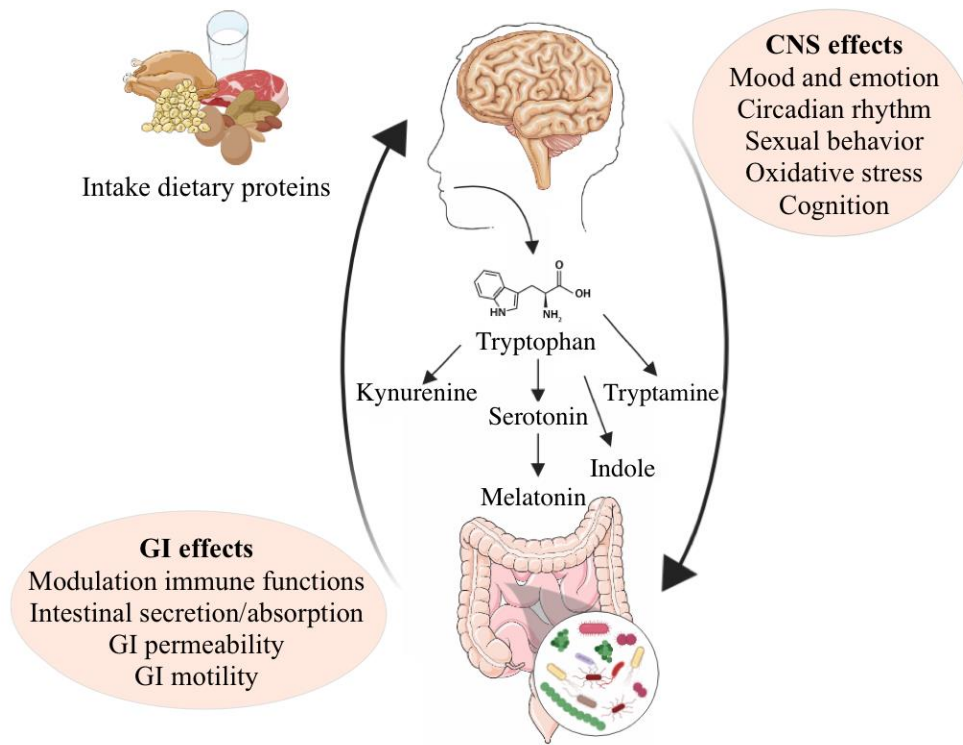
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Table 1. AHR ligands and their physiological impact on host metabolism

AHR ligands	Model	Potential physiological impact	Ref
Indole, 3-methyl indole, 2-oxindole	In vitro ligand binding, ligand structure activity analyses	Influence the transcription of important factors of the immune system.	[52]
Indoxyl-3-sulfate (IS)	Mouse model of multiple sclerosis	Regulation of genes in neuroinflammation.	[53*]
Skatole/3-methylindole	Human colon cancer cell line Caco-2	Acts on the intestinal epithelial cells by AHR-dependent or -independent activation pathways regulating the amount of IEC death.	[54]
Indole-3-propionic acid (IPA)	Model of high-fat diet mice	Might be reducing intestinal permeability and plasma LPS.	[55]
Indole-3-propionic acid (IPA)	Tryptophan-rich diet in rats	Contributes to changes in body weight gain.	[56]
Indole, Skatole and Indoleacetic Acid	Humans	Influence of indoles derivatives on hedonic food intake and obesity by acting on the extended reward network.	[57]
Indoleacrylic Acid (IA)	Model of colitis in mice	Indoleacrylic acid (IA) has a beneficial effect on intestinal epithelial barrier function and mitigates inflammatory responses by immune cells.	[58*]
AHR ligands	Fecal microbiota transplant (FMT) from CARD ^{-/-} mice into WT or GF mice <i>CARD9 is one of the IBD susceptibility genes</i>	The FMT resulted in an increase sensitivity to colitis observed in mice depleted of CARD9 gene. These alterations might be due to an impaired ability of the microbiota of CARD9 ^{-/-} mice to catabolize tryptophan into AHR ligands.	[59**]

709



Graphical Abstract

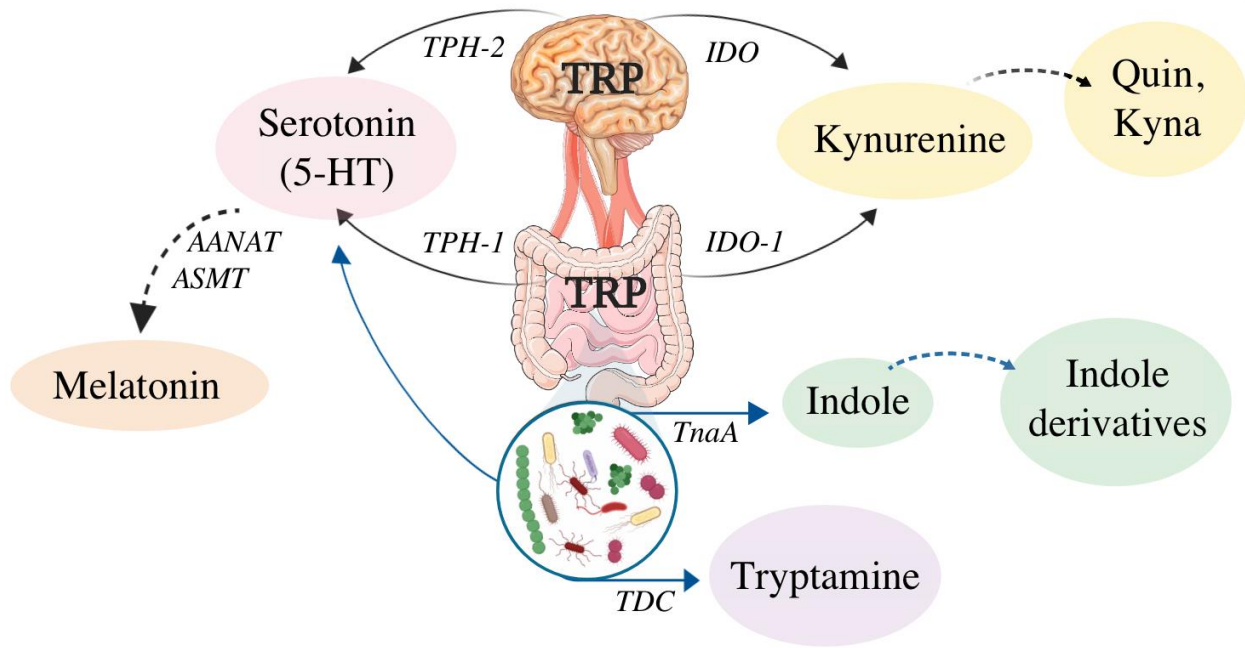


Figure 1

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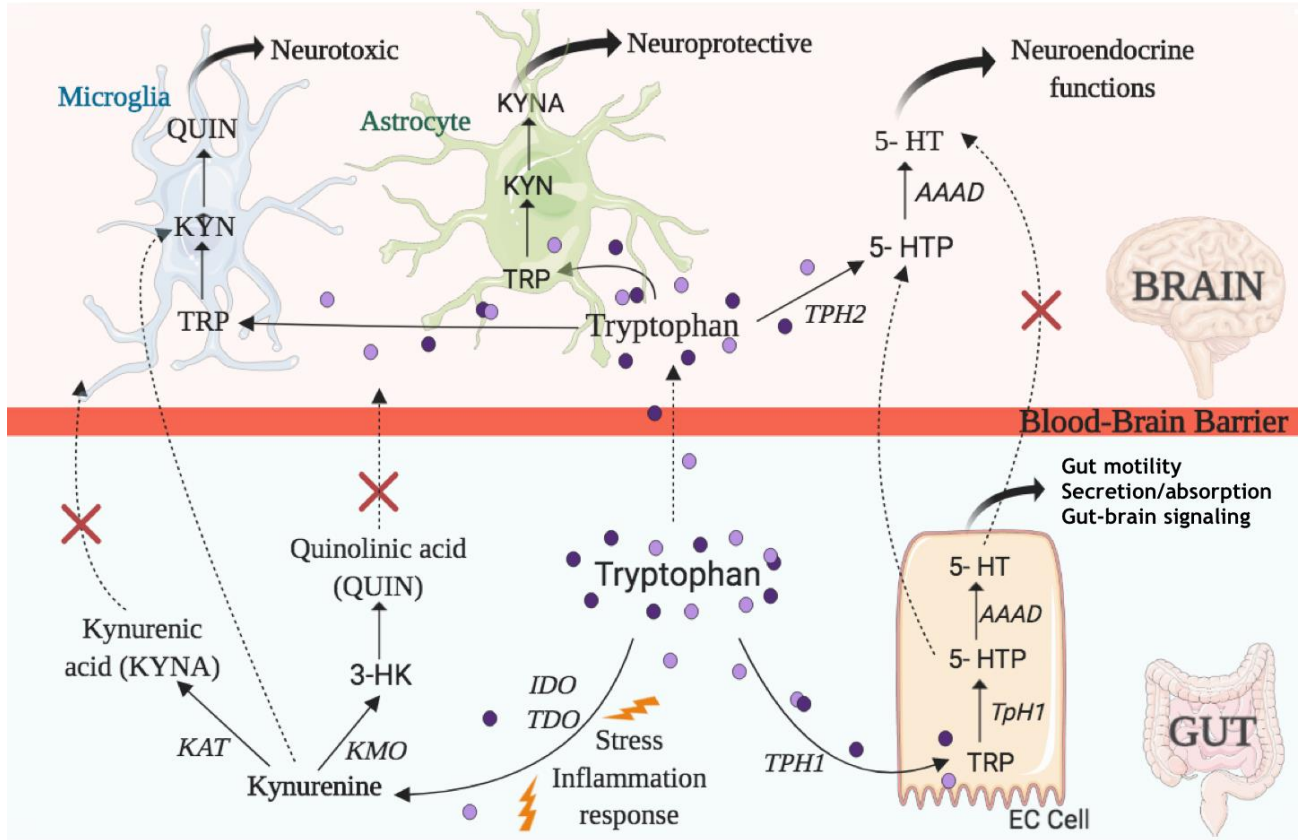


Figure 2

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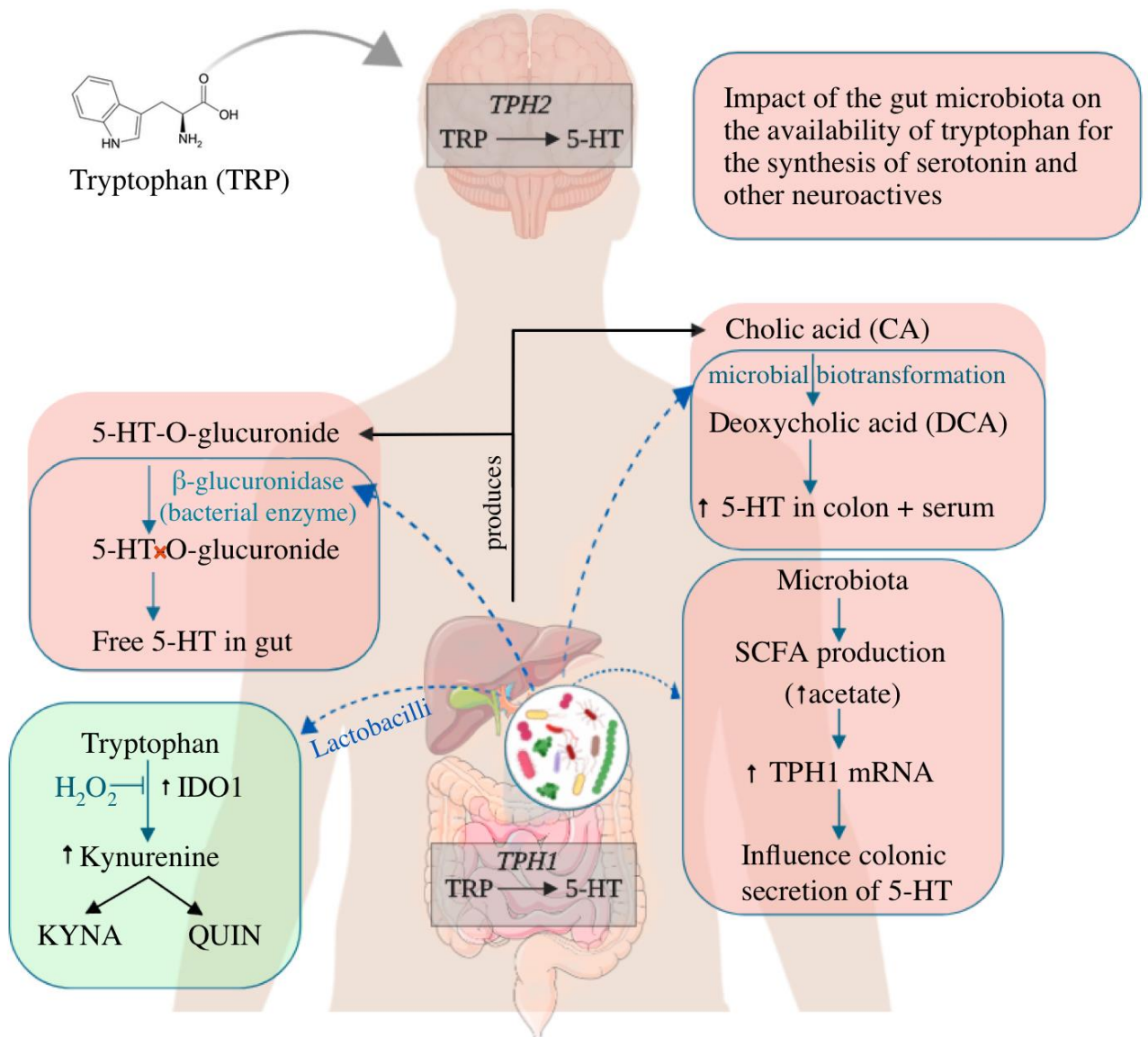


Figure 3

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