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Review

Serotonin, tryptophan metabolism and the brain-gut-microbiome axis

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h i g h l i g h t s

* Serotonin is a key neurotransmitter in the brain-gut axis.
* The gut microbiome is also critical to the normal functioning of the brain-gut axis.
* Behaviour linked to serotonergic neurotransmission is inﬂuenced by gut microbiota.
* Development of the gut microbiome overlaps the ontogeny of the serotonergic system.
* The gut microbiota is an appealing therapeutic target for brain-gut axis disorders.

a r t i c l e i n f o a b s t r a c t

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The brain-gut axis is a bidirectional communication system between the central nervous system and the gastrointestinal tract. Serotonin functions as a key neurotransmitter at both terminals of this network. Accumulating evidence points to a critical role for the gut microbiome in regulating normal functioning of this axis. In particular, it is becoming clear that the microbial inﬂuence on tryptophan metabolism and the serotonergic system may be an important node in such regulation. There is also substantial overlap between behaviours inﬂuenced by the gut microbiota and those which rely on intact serotoner- gic neurotransmission. The developing serotonergic system may be vulnerable to differential microbial colonisation patterns prior to the emergence of a stable adult-like gut microbiota. At the other extreme of life, the decreased diversity and stability of the gut microbiota may dictate serotonin-related health problems in the elderly. The mechanisms underpinning this crosstalk require further elaboration but may be related to the ability of the gut microbiota to control host tryptophan metabolism along the kynurenine pathway, thereby simultaneously reducing the fraction available for serotonin synthesis and increasing the production of neuroactive metabolites. The enzymes of this pathway are immune and stress-responsive, both systems which buttress the brain-gut axis. In addition, there are neural processes in the gastrointestinal tract which can be inﬂuenced by local alterations in serotonin concentrations with subsequent relay of signals along the scaffolding of the brain-gut axis to inﬂuence CNS neurotransmission. Therapeutic targeting of the gut microbiota might be a viable treatment strategy for serotonin-related brain-gut axis disorders.

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*Abbreviations:* CNS, central nervous system; ENS, enteric nervous system; BBB, blood-brain-barrier; 5-HTP, 5-hydroxytryptophan; TPH, tryptophan hydroxylase; TDO, tryptophan-2,3-dioxygenase; IDO, indoleamine-2,3-dioxygenase; AAAD, aromatic amino acid decarboxylase; NMDA, N-methyl-d-aspartate; ATD, acute tryptophan depletion; SSRIs, selective serotonin reuptake inhibitors; TLR, toll-like receptor; IBS, irritable bowel syndrome; IAA, indole 3-acetic acid; EC, enterochromafﬁn cell; ERK, extracellular signal-regulated kinase; GABA, gamma-aminobutyric acid; TCA, tricyclic antidepressant; HPA axis, hypothalamic pituitary adrenal axis; SHRP, stress hypo-responsive period; EPAN, extrinsic primary afferent neuron.

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# Introduction

Tryptophan and its metabolite serotonin have an expansive physiological repertoire, making them fundamental to health and there are numerous associations between alterations in this sys- tem and disease [[1–3].](#_bookmark14) A growing body of data is also pointing to the inﬂuence of this system far beyond the traditional focus on its signalling pathways in the central nervous system (CNS) (see Reviews in this Special Issue). Moreover, emerging data impli- cates the gut microbiome in the regulation of brain and behaviour in general with a speciﬁc emphasis on its impact on tryptophan metabolism and the serotonergic system.

Research in this area builds on the principles of the brain-gut axis concept (see [Fig. 1),](#_bookmark6) a bidirectional communication network between the brain and the gut with serotonin functioning as a key signalling molecule in both the enteric nervous system (ENS) and the CNS [[4–6].](#_bookmark17) Recently, it has become clear that the gut micro- biome is a critical component of this axis and one which exerts control at multiple levels, not just locally in the gastrointestinal tract [[7–10].](#_bookmark18) Using a variety of preclinical strategies, it has been established that manipulating the composition of the gut micro- biota across the lifespan or altering the trajectory of microbial colonisation of the gastrointestinal tract early in life inﬂuences the availability of tryptophan. In tandem and possibly related to this capacity, this research has also illuminated a role for the gut micro- biota in serotonergic signalling at the level of the CNS. There is also a substantial overlap between many of the behaviours under- pinned by serotonergic signalling and those which are inﬂuenced by alterations in the composition, diversity or stability of the micro- biota. Taken together, it seems plausible that the gut microbiota can either directly or indirectly recruit tryptophan metabolism and serotonergic signalling within the framework of the brain-gut axis to modulate host behaviour.

In this review, we evaluate the evidence supporting the ability

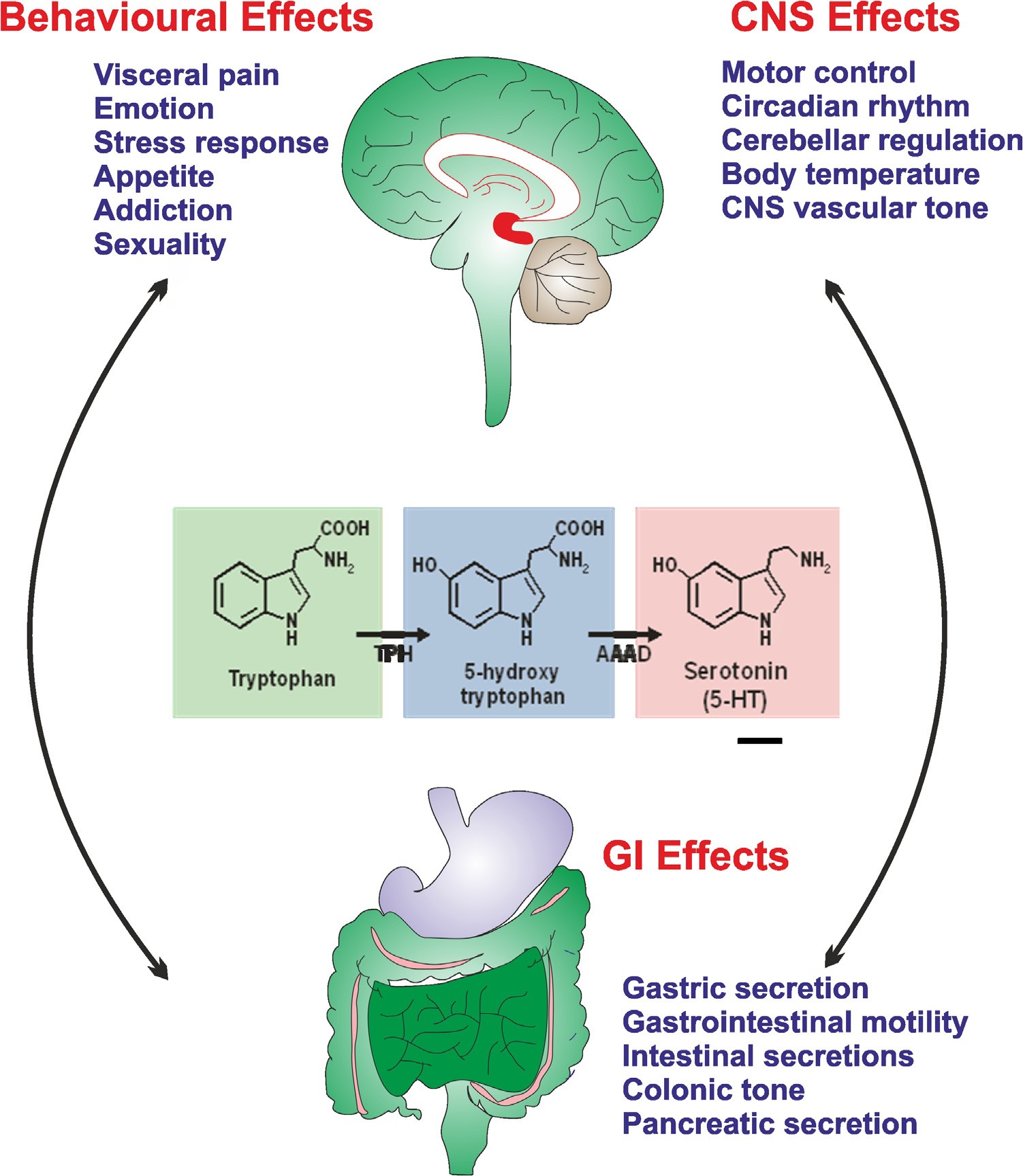
of the gut microbiota to impact on tryptophan metabolism and the serotonergic system. Potential mechanisms are explored including

the intriguing microbial faculty for tryptophan utilisation and sero- tonin synthesis. The parallel but overlapping developmental course of both the serotonergic system and the gut microbiota are charted and the implications of a microbial dysbiosis at critical neurode- velopmental time windows discussed. The potential consequences across a number of relevant behavioural domains, including pain, depression, anxiety and cognition, are emphasised and we also con- sider the potential for therapeutic targeting of the gut microbiota. We conclude by providing some perspectives on future directions in this area. Firstly, we brieﬂy outline some features of tryptophan metabolism and serotonin synthesis which although well known to this readership, form the basis for aspects of our discussion below.

# Serotonin synthesis and tryptophan metabolism

A detailed description of serotonin synthesis from tryptophan and the myriad other synthetic pathways beholden to the availabil- ity of tryptophan as a precursor are beyond the scope of this review and readers are referred to more detailed descriptions for further information [[11].](#_bookmark19) Tryptophan is an essential amino acid which must be supplied in the diet [[3].](#_bookmark15) This is normally as a constituent of pro- tein [[12]](#_bookmark20) but in the infant, for example, breast milk also contains a more immediately accessible non-protein portion which may be important for postnatal development [[13].](#_bookmark21) Once absorbed from the gut and made available in the circulation, where it exists in both a free and albumin-bound fraction [[14],](#_bookmark22) it can cross the blood-brain- barrier (BBB) via the large amino acid transporter to participate in serotonin synthesis in the CNS [[11].](#_bookmark19) However, the vast major- ity of serotonin is located in the gut where it is synthesised from tryptophan in the enterochromafﬁn cells (ECs) of the gastrointesti- nal tract and is also present in enteric nerves [[6,15,16].](#_bookmark23)

Irrespective of the location in the gut-brain axis, the syn- thetic cascade is similar. Tryptophan is ﬁrst converted to 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme, tryp- tophan hydroxylase (TPH), which is not saturated at normal tryptophan concentrations. Consequently, increased tryptophan

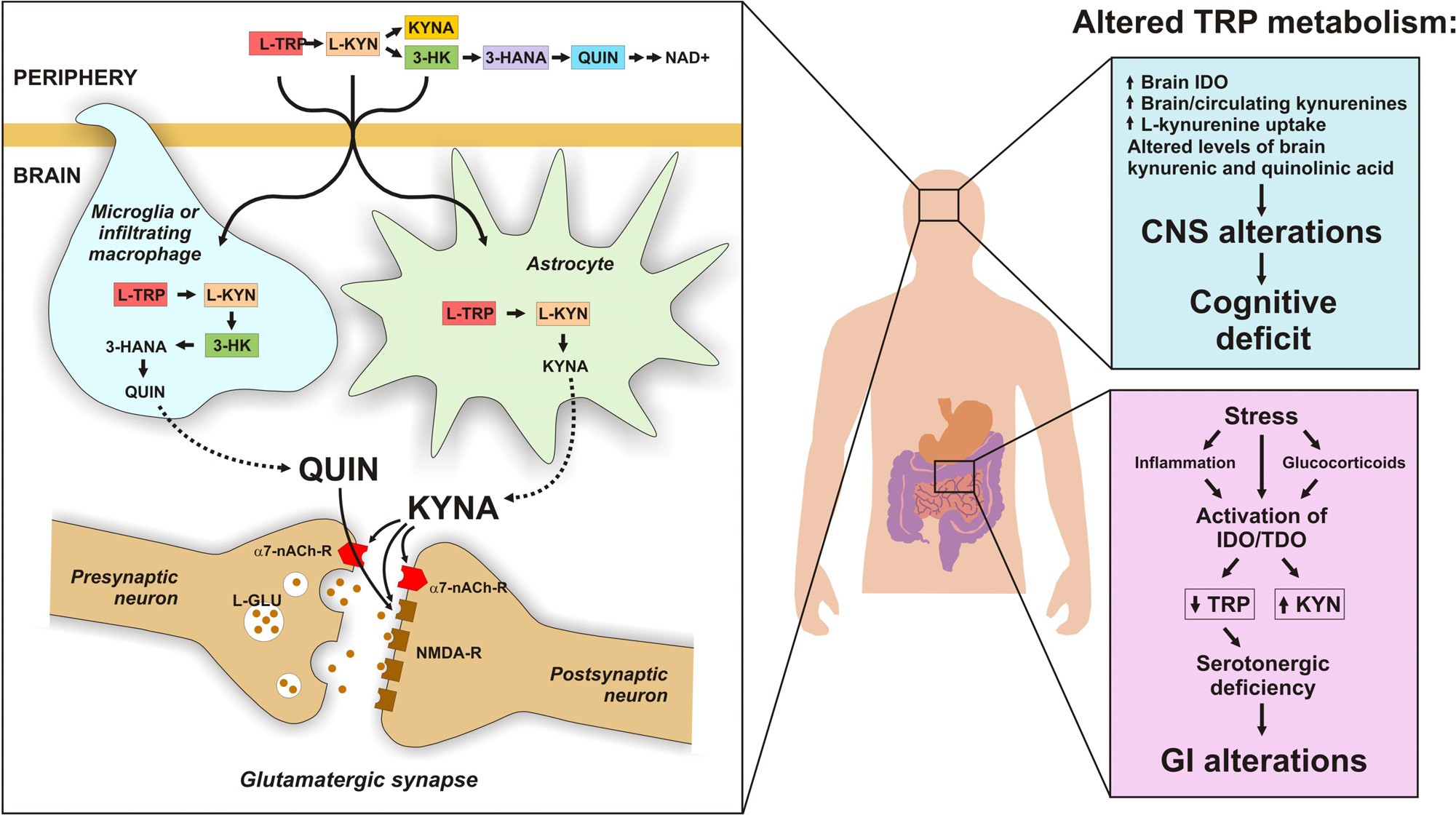


**Fig. 1.** The brain-gut axis and serotonergic metabolism. A bi-directional communication network exists between the brain and the gut and the 5-HT system plays an essential role in the functions and actions that occur in these two major organs. For example, 5-HT is a key neurotransmitter in the regulation of mood at the level of the CNS and has been implicated in visceral hypersensitivity in the gastrointestinal tract. Tryptophan is converted to 5-hydoxytryptophan (5-HTP) by tryptophan hydroxylase (TPH) and this is the rate limiting step in the pathway. Aromatic amino acid decarboxylase (AAAD) subsequently converts 5-HTP into serotonin (5-HT). These reactions occur both in the CNS and in the enteric nervous system where 5-HT regulates a myriad of functions including gastrointestinal motility and intestinal secretions. Alterations in the 5-HT system are evident in disorders of the brain-gut axis which present with dysfunctional communication between the brain and the gut and related symptoms as seen here.

concentrations can, at least theoretically, result in increased metabolic output. Onward metabolism of the short-lived 5-HTP intermediate product to 5-HT is via aromatic amino acid decarbox- ylase (AAAD) (see [Fig. 1)](#_bookmark6) [[1].](#_bookmark14) However, the dominant physiological pathway for tryptophan is actually along the kynurenine pathway (see [Fig. 2)](#_bookmark7) [[2,17].](#_bookmark16) Kynurenine is produced from tryptophan by the action of the largely hepatic based enzyme, tryptophan-2,3- dioxygenase (TDO) or the ubiquitous indoleamine-2,3-dioxygenase (IDO) [[18].](#_bookmark24) TDO can be induced by glucocorticoids or indeed tryp- tophan itself whereas IDO is inﬂuenced by certain inﬂammatory stimuli, IFN-μ being the most potent inducer [[11].](#_bookmark19) Once kynurenine is produced, it is further metabolised along two distinct arms of the pathway with one leading to the production of the neuroprotective kynurenic acid (a7 nicotinic acetylcholine receptor antagonist and N-methyl-d-aspartate (NMDA) receptor antagonist at glycine site) and the other to the neurotoxic quinolinic acid (a NMDA receptor agonist) [[2,19].](#_bookmark16) Moreover, kynurenic acid, which can be neuro- protective against quinolinic acid induced excitotoxicity, can also induce cognitive impairment when abnormally elevated. This is

likely due to its effects on the a7-nicotinic acetylcholine receptor [[20].](#_bookmark32) However, this is likely a complex process and one where some controversy remains due to the fact that some investigators have failed to observe inhibition of this particular receptor by kynurenic acid [[21].](#_bookmark33) Recently, kynurenic acid has also been identiﬁed as a ligand for previously orphan receptors in the gastrointestinal tract with agonist action at the G-protein coupled GPR35 receptor [[22].](#_bookmark34) Kynurenine itself can cross the BBB to participate in CNS synthesis of these neuroactive metabolites and indeed, the majority of CNS kynurenine is derived from the periphery [[11].](#_bookmark19) Plasma kynurenine increases are thought to be a reliably reﬂected in the CNS [[23].](#_bookmark35)

The impact of increased tryptophan metabolism along the kynurenine pathway can then be viewed through the dual lens of reduced availability for serotonin synthesis and increased produc- tion of neuroactive kynurenine pathway metabolites with respect to the impact in the CNS and ENS [[24].](#_bookmark36) We should point out that circulating tryptophan concentrations do not solely determine CNS availability as it competes with other large neutral amino acids for transport across the BBB [[25]](#_bookmark37) and with exercise, for example, also



**Fig. 2.** The kynurenine pathway of tryptophan metabolism. The vast majority of available tryptophan (L-TRP) is metabolised along the kynurenine pathway. Once kynurenine (L-KYN) is formed, it proceeds along two different arm of the pathway leading either to the formation of kynurenic acid (KYNA) or quinolinic acid (QUIN). KYNA is an a7 nicotinic acetylcholine receptor antagonist and N-methyl-d-aspartate (NMDA) receptor antagonist at the glycine site. QUIN is a NMDA receptor agonist. The balance between these two metabolites is important in health and disease. KYNA, which can be neuroprotective against QUIN induced excitotoxicity, can also induce cognitive impairment when abnormally elevated [[17,20].](#_bookmark25) Kynurenine formed in the periphery can cross the blood-brain-barrier and is the main source of CNS kynurenine. The enzymes responsible for the initial conversion of L-TRP to L-KYN, indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO), are immuno- and stress responsive, respectively. Activation of either enzyme can have a dual impact by limiting the availability of tryptophan for serotonin synthesis and increasing the downstream production of neurotoxic/neuroprotective metabolites. Accumulating evidence implicates the gut microbiota in the regulation of kynurenine pathway metabolism. This is thus a humoral route through which the gut microbiota can inﬂuence mood and cognition at the level of the CNS as well as local gastrointestinal (GI) function. (*N*-Methyl-d-aspartate receptors: NMDA-R; a7-nicotinic acetylcholine receptors: a7-nACh-R; Glutamate: L-GLU; 3-hydroxykynurenine: 3-HK; 3-hydroxyanthranilic acid; 3-HAA; Nicotinamide adenine dinucleotide: NAD+).

inﬂuencing CNS distribution and utilisation [[14].](#_bookmark22) Nevertheless, the acute tryptophan depletion (ATD) protocol demonstrates that at least in vulnerable populations, reducing the circulating concentra- tions of tryptophan can impact functionally on mood, reinstating, as ATD does, depressive symptoms in patients who have success- fully responded to selective serotonin reuptake inhibitors (SSRIs) [[26–28].](#_bookmark38)

# The gut microbiome

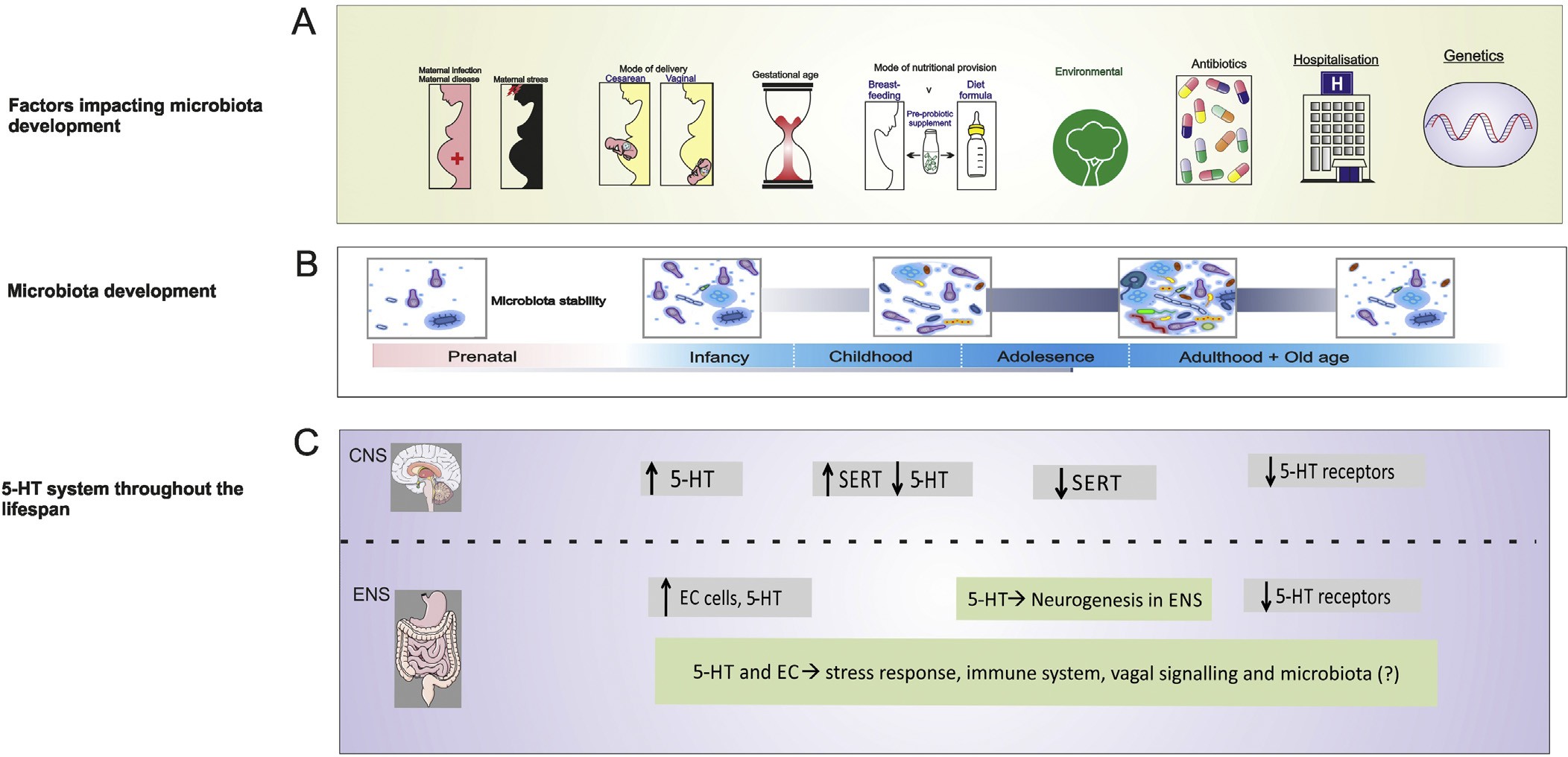
The gut microbiome refers to the collection of microorganisms and their genomes in the gut habitat which are now regarded as a critical node in the brain-gut axis [[5,9].](#_bookmark26) One outcome of the recent intense focus on this ‘virtual organ’ using metagenomic approaches is the realisation that microorganisms in our gastroin- testinal tract outnumbers the human cells in our bodies by a factor of 10 and contains 150 times as many genes as our genome (see below for developmental features and health implications) [[10,29].](#_bookmark27) The complex role of the gut microbiota within the brain-gut axis is just beginning to be charted, in contrast to a well-developed understanding of the reciprocal communication between the ENS and the CNS. A number of strategies are available to researchers in this area to help mark out the impact of the gut microbiota on brain and behaviour, including the use of microbiota deﬁcient germ-free animals, probiotic supplementation, antibiotic admin- istration, faecal transplantation studies and deliberate infections [[8].](#_bookmark28)

# The gut microbiome across the lifespan

A stable and diverse microbiota is considered important to health during adulthood and advances in our understanding of the precise composition of the gut microbiota has been reviewed extensively elsewhere [[30,31].](#_bookmark43) This compositional stability and diversity is bookended at either extreme of life by more chaotic gut microbiota patterns. In particular, during the period follow- ing birth until the attainment of a stable adult-like microbiota at approximately 3 years of age, there is considerable ﬂux which may prime for healthy in later life [[32,33].](#_bookmark45) The normal trajectory of gut microbiota development during this phase, as it is established, develops and stabilises, is vulnerable to a variety of inﬂuences (see [Fig. 3).](#_bookmark10) Initial microbial community composition is determined by delivery mode with the microbiota proﬁle of infants born vaginally initially dominated by the species (e.g. *Lactobacillus* spp) of their mother’s vaginal and faecal microbiota [[34,35].](#_bookmark48) In contrast, infants born by caesarean section (C-section) have a distinct microbiota more akin to the skin microbiota of their mothers, including *Staphy- lococcus*, *Corynebacterium* and *Propionibacterium* spp [[34]](#_bookmark48) with a low representation of *Biﬁdobacteria* spp [[36].](#_bookmark51) Meanwhile, preterm infants have a different microbiota (dominated by Proteobacteria initially and a lack of detectable Biﬁdobacterium and Lactobacillus genera) compared to that of healthy term infants, conﬁrming the importance of gestational age in shaping the microbiota [[37].](#_bookmark53)

Nutritional factors are also an important determinant of the

early-life gut microbial signature and there is an increased abun- dance of certain *Biﬁdobacterium* spp in exclusively breast-fed



**Fig. 3.** Neurodevelopmental sequence of events. The development and maturation of the gastrointestinal microbiota depends on and is inﬂuenced by many predictable and random events as shown here. Changes in both the gut microbiota and the 5-HT system occur across the lifespan and have substantial periods of developmental overlap during which a reciprocal inﬂuence is possible. The infant gut microbiota tends not to reach a stable adult-like conﬁguration until approximately 1-3 years of age and this early period coincides with many aspects of serotonergic system development. The gut microbiota remains amenable to manipulation during adulthood and could potentially be targeted therapeutically to modulate the serotonergic system. Old age is also characterised by alterations in the composition and diversity of the gut microbiota which could impact on tryptophan metabolism/serotonergic neurotransmission and have health implications.

infants. This dominance wanes and diversity increases following weaning to solid foods [[38].](#_bookmark55) The gut microbiota of formula-fed infants typically displays a lower prevalence of *Biﬁdobacteria* and a higher abundance of coliforms, *Bacteroides* and *Clostridium dif- ﬁcile* [[39].](#_bookmark56) In addition to predictable life events such as mode of birth, mode of early nutrition, weaning and introduction of solid food, other factors also inﬂuence the microbial composition. This includes host genotype [[34],](#_bookmark48) geographical and cultural factors [[40],](#_bookmark58) infections and antibiotic usage [[41]](#_bookmark60) and consumption of probiotics and prebiotics (see [Fig. 3)](#_bookmark10) [[42].](#_bookmark61)

Thus, each infant has a unique microbial experience dur- ing this early unstable phase with the implication that mental health beneﬁts might accrue with normal developmental patterns and increased risk for psychopathology arises from detrimental colonisation patterns [[32,33,43].](#_bookmark45) It remains to be established if these differential gut microbiota patterns mediate their beneﬁcial or adverse effects through regulation of tryptophan metabolism and/or serotonin synthesis (see Section [2).](#_bookmark5) However, if different microbiota compositions early in life do translate into different local and circulating concentrations of tryptophan and serotonin, the developing serotonergic system may be particularly susceptible to such alterations.

Studies in adult populations indicate that although there is a high inter-individual gut microbiota variability, an adult individ- ual’s intestinal microbial community is relatively stable over time in the absence of any major ecological trauma [[7,44].](#_bookmark18) In addition, there may be a core microbiome at the functional level despite this variation in community structure [[45]](#_bookmark63) and deviations from this functional capacity has been linked to metabolic disorders [[46].](#_bookmark65) However, the gut microbiota also exhibits plasticity dur- ing adulthood and is heavily inﬂuenced by nutritional factors and indeed potentially subject to rapid compositional shifts following alterations in diet [[47].](#_bookmark66) The response to disturbance of this micro- bial ecosystem by antibiotics is immediate and substantive and although there is evidence of resilience in its recovery, repeated

antibiotic administration can induce permanent alterations from its initial state [[48,49].](#_bookmark67)

The core microbiota of elderly subjects is distinct from that of younger adults with a larger between-subject variability and an enhanced abundance of *Bacteroides* species and altered patterns of *Clostridium* clusters [[50].](#_bookmark68) Age-related shifts in gut microbiota com- position are inﬂuenced by diet, residence location (community, day hospital or long-term residential care) and have also been linked to adverse health outcomes. For example, the loss of community- associated microbiota may correlate with increased frailty [[51].](#_bookmark70) As in the infant and adolescent, this later stage of life is also character- ized by more pronounced CNS changes in key brain structures than during adulthood, such as the amygdala, hippocampus and frontal cortex [[52]](#_bookmark72) and the function of these regions is heavily dependent on serotonergic neurotransmission [[1].](#_bookmark14) This would be consistent with changes in behaviours, such as sleep, sexual behaviour and mood in the elderly. Age-related changes in serotonin systems have also been implicated in prevalent disorders among this demo- graphic such as diabetes, faecal incontinence and cardiovascular diseases [[53].](#_bookmark73)

# Indirect microbial regulation of tryptophan metabolism and serotonin synthesis

Germ-free animals are microbiota-deﬁcient and are raised in a sterile environment [[54].](#_bookmark76) These animals can offer unique insights into the components of the gut-brain axis which are under the inﬂuence of the microbiota. Recently, they have been used to determine that the gut microbiota (see Section [3)](#_bookmark9) is essential for normal brain development and behaviour and can impinge on tryptophan and serotonin. For example, it has been demon- strated that the germ-free condition is characterised by increased plasma tryptophan concentrations which can be normalised fol- lowing colonisation of the mice immediately post-weaning [[55].](#_bookmark77) Interestingly, male germ-free mice showed the most robust CNS

changes, exhibiting increased hippocampal 5-HT concentrations, an alteration that proved resistant to the subsequent normalisation of circulating tryptophan concentrations following the introduc- tion of a gut microbiota immediately post-weaning. Increased 5-HT turnover, as indicated by the 5-HIAA/5HT ratio, is also evident in the striatum of germ-free mice [[56].](#_bookmark79)

Other investigators have also reported elevations in plasma lev- els of both tryptophan and 5-HT in germ-free mice compared to conventional animals [[57].](#_bookmark38) Plasma 5-HT levels are thought to arise mainly from the ECs of the gut [[58].](#_bookmark39) Interestingly, there may be a temporal effect of the colonisation process with, for example, one study reporting that the elevated tryptophan concentrations in germ-free mice were reduced four days following the introduc- tion of a microbiota but not at day 30 [[59].](#_bookmark40) Also of note is a recent study showing that germ-free rats have decreased hippocampal 5- HT concentrations but show a similar stress-induced elevation in both 5-HT and 5-HIAA to their conventional counterparts [[60].](#_bookmark42) The reasons for this divergence between germ-free mice and rats are currently unclear and not yet investigated as the study in rats is a very recent addition to the literature. However, it is notable that the stress response, in terms of corticosterone output, also diverges in germ-free rats and mice. The extensive cross talk between the serotonergic system and the HPA axis at the level of the CNS might explain these differences.

The impact of the gut microbiota on the CNS serotonergic system is not limited solely to microbiota-deﬁcient animals as adminis- tration of the probiotic *Biﬁdobacterium infantis* to rats resulted in reduced 5-HIAA concentrations in the frontal cortex [[61].](#_bookmark44) Further- more, there was also a marked increase in plasma concentrations of tryptophan and kynurenic acid in these animals [[61].](#_bookmark44) Further work remains to explore the impact of the use of different mouse strains, the sex-dependent character of the alterations as well as potential species-speciﬁc serotonergic proﬁles. Nevertheless, taken together, these studies conﬁrm the ability of the gut microbiota to profoundly inﬂuence the CNS serotonergic system.

Indirect mechanisms sustaining the inﬂuence of the microbiota on tryptophan availability and serotonin synthesis via the enzymes responsible for tryptophan degradation along the kynurenine path- way are possible. Studies in germ-free mice have implicated this pathway with a decrease in the ratio of kynurenine:tryptophan (used as an index of IDO or TDO activity) reported compared to con- ventional animals which normalises following introduction of a gut microbiota immediately post-weaning [[55].](#_bookmark77) Others have reported similar increases in both plasma kynurenine concentrations and the kynurenine:tryptophan ratio at both day 4 and day 30 follow- ing colonisation [[59].](#_bookmark40) Moreover, an increase in this ratio was also apparent following infection with *Trichuris muris* [[62].](#_bookmark46) Administra- tion of a lactobacillus strain, *Lactobacillus johnsonii*, to rats resulted in a reduction in serum kynurenine concentrations. Interestingly,

*L. johnsonii* also reduced IDO activity *in vitro* in HT-29 intestinal epithelial cells in this study. The authors linked this effect to the fact that these animals also showed an increase in hydrogen peroxide (H2O2) production in the ileum lumen and that H2O2 produced by

*L. johnsonii* abolished *in vitro* IDO activity [[63].](#_bookmark49) This is in agreement with studies which have demonstrated that H2O2 activates the per- oxidase function of IDO, thereby inducing protein oxidation and inhibiting enzyme activity [[64].](#_bookmark50) Given the fact that the production of H2O2 is a common feature of many lactic acid bacteria [[65],](#_bookmark52) this is a plausible mechanism through which the gut microbiota can inﬂu- ence host tryptophan metabolism. Interestingly, IDO activation has an antimicrobial function through both depletion of tryptophan and the generation of toxic kynurenine pathway metabolites (see [Fig. 2)](#_bookmark7) [[66].](#_bookmark54)

Clinically, alterations in the activity of IDO or TDO also seems relevant to a variety of disease states (see also Section [2).](#_bookmark5) Irritable bowel syndrome (IBS), a functional gastrointestinal disorder, is

regarded as a prototypical brain-gut axis disorder with alterations in the stability and diversity of the microbiota frequently noted coupled with alterations in serotonergic system in both the brain and gut [[15,67].](#_bookmark29) Increased IDO activity has been demonstrated in both male and female IBS populations which may be related to low- grade immune changes in this disorder [[68–70].](#_bookmark57) Interestingly, the expression of Toll-like receptors (TLRs) is altered in both clinical IBS populations [[71,72]](#_bookmark62) and animal models of the disorder [[73].](#_bookmark64) The immune consequences of these alterations, in terms of the low grade inﬂammation which has been reported in IBS, could arise as a consequence of aberrant microbiota-host interactions and poten- tially drive the IDO activation which has been reported. In this context, it is also interesting to note that once TLR receptors are engaged by their cognate ligands, degradation of tryptophan along the kynurenine pathway can ensue in general [[69,74,75]](#_bookmark59) and there appears to be a differential pattern of kynurenine production in IBS depending on which TLR receptor is activated [[69].](#_bookmark59)

The majority of the literature reports to date focus on kynurenine concentrations rather than those of the downstream metabolites. This is logical on the basis that kynurenine crosses the BBB whereas kynurenic acid and quinolinic acid do not but does mean that the relationship between the gut microbiome and these downstream kynurenine pathway metabolites remains unclear. Future studies would beneﬁt from a more complete proﬁle of these crucial kynurenine pathway metabolites, both in the periphery and in the CNS.

# Direct microbial regulation of tryptophan availability and serotonin synthesis

The gut microbiota (see Section [3)](#_bookmark9) can also directly utilise tryp- tophan, thereby potentially limiting its availability to the host. In addition to the growth requirements for bacteria [[76],](#_bookmark69) certain bacterial strains harbour a tryptophanase enzyme that produces indole from tryptophan [[77,78].](#_bookmark71) *Bacteroides fragilis*, for example, has this enzymatic capability which has recently been linked to gas- trointestinal abnormalities in autism spectrum disorders [[79].](#_bookmark74) The direct physiological signiﬁcance of indole 3-acetic acid (IAA) pro- duction from tryptophan for the host is not well understood but it is relevant to bacterial physiology and plant-microbe interactions where its effects can be both beneﬁcial and detrimental [[80]](#_bookmark75) Unlike eukaryotes, bacteria can also synthesise tryptophan via enzymes such as tryptophan synthase [[81,82].](#_bookmark78) Intriguingly, speciﬁc bacte- rial strains can also produce serotonin from tryptophan, at least *in vitro* (see [Table 1)](#_bookmark12) [[83–85].](#_bookmark80) Some microorganisms, mainly gram positive bacteria, are also susceptible to serotonergic drugs admin- istered to the host such as selective serotonin reuptake inhibitors (SSRIs) [[86].](#_bookmark84) The balance between bacterial tryptophan utilisation and metabolism, tryptophan synthesis, serotonin production and indeed the bacterial response to exogenous elevations in serotonin likely plays an important role in determining local gastrointestinal and circulating tryptophan availability for the host in addition to the dietary supply of this essential amino acid. Cumulatively, these

**Table 1**

Serotonin-producing bacterial strains.

|  |  |
| --- | --- |
| Bacterial strain | Reference |
| *Lactococcus lactis* subsp. *cremoris* (MG 1363) | [[244]](#_bookmark189) |
| *L. lactis* subsp. *lactis* (IL1403) | [[244]](#_bookmark189) |
| *Lactobacillus plantarum* (FI8595) | [[244]](#_bookmark189) |
| *Streptococcus thermophilus* (NCFB2392) | [[244]](#_bookmark189) |
| *Escherichia coli* K-12 | [[245]](#_bookmark190) |
| *Morganella morganii* (*NCIMB, 10466*) | [[246]](#_bookmark191) |
| *Klebsiella pneumoniae* (*NCIMB, 673*) | [[246]](#_bookmark191) |
| *Hafnia alvei* (NCIMB, 11999) | [[246]](#_bookmark191) |

**Table 2**

Receptor subtypes throughout the brain-gut axis (modiﬁed from [[142,247].](#_bookmark124)

Receptor subtype

CNS Location/Function GI Location/Function

5-HT1A Hippocampus, septum, dorsal raphe nuclei and amygdala; Autoreceptors, neuronal inhibition; Regulation of mood, cognition, pain, sleep, neuroendocrine function

ENS (submucosal and myenteric plexuses) Degranulation of enteric mast cells, release of mediators (e.g. Histamine)

5-HT1B Striatum, prefrontal cortex; Autoreceptor N/A

5-HT1D Raphe nuclei, Intracranial vessels; Autoreceptor, Contraction of vascular smooth muscle

N/A

5-HT1E Caudate, Putamen; Function unclear N/A

5-HT1F Neocortex; Integration of sensorimotor or afferent information associated with limbic functions

5-HT1-like Intracranial vessels; Inhibition of noradrenaline release, smooth muscle contraction

N/A N/A

5-HT1P N/A Jejunum; Excitatory action on vagal afferent ﬁbres

5-HT2A Cerebellum, lateral septum, hypothalamus, amygdala; Sleep, hallucinations, neurochemical and behavioural effects of psychostimulants

5-HT2B Nucleus Accumbens, ventral tegmental area, amygdala, spinal cord; Modulation of 5-HT release, may be required for MDMA-induced behavioural effects, hyperphagia, grooming behaviours

5-HT2 C Cerebral cortex, hippocampus, amygdala, Choroid plexus; Mood, food intake, cerebrospinal ﬂuid secretion

5-HT3 Hippocampus, dorsal motor nucleus of the solitary tract area postrema, spinal cord; Emesis, pain, modulates release of other neurotransmitters

Contraction of gut smooth muscle

Fundus, myenteric nerves, colonic smooth muscle cells; Smooth muscle contraction Visceral sensitivity

N/A

Enteric neurons, smooth muscle cells, vagal and spinal primary afferent neurons; Pain, secretory and motor responses, regulate the pacemaker activity of the interstitial cells of Cajal

5-HT4 Limbic system; Mood, cognition Enteric neurons, smooth muscle cells; Contraction of smooth colonic muscle, prokinetic effect, neurotransmitter release

5-HT5A Cortex, hippocampus, hypothalamus, amygdala and cerebellum; Mood, sensory perception, neuroendocrine functions

N/A

5-HT6 Striatum, amygdala, nucleus accumbens, olfactory tubercle, cortex; Mood N/A

5-HT7 Limbic system and thalamocortical regions; Mood, sleep Smooth muscle cells of intestine; Muscle relaxation, accommodation

factors may also determine serotonin synthesis with implications for both ENS and CNS neurotransmission.

# Brain-gut axis development and the serotonergic system across the lifespan

The synthesis of 5-HT and expression of its receptors (see [Table 2)](#_bookmark13) in embryonic development, as well as its maternal and placental sources in the foetus has led to the hypothesis that this neurotransmitter could act as a growth regulator in selective developmental events [[87].](#_bookmark85) The serotonergic system is capable of inducing effects on target cells and organs during both the prenatal and postnatal periods [[88].](#_bookmark86) The brain-gut axis describes a complex bi-directional system that exists between the CNS and the gas- trointestinal tract (see [Fig. 1)](#_bookmark6) [[9].](#_bookmark30) Elements of this axis, including hormonal, immune and neuronal pathways, develop and mature both in utero and postnatally with some components only becom- ing fully established in late teenage life [[89].](#_bookmark87) As mentioned, the serotonergic system functions at both terminals of this axis and is also not fully mature at birth hence there is a developmental over- lap with potential for this axis to impact on the serotonergic system and vice versa (see [Fig. 3](#_bookmark10) for inﬂuence of 5-HT across the lifespan).

* 1. *CNS development and inﬂuence of serotonin*

While a large proportion of the CNS framework is established before mid-gestation in the foetus, growth and modiﬁcations extends into puberty [[90].](#_bookmark89) Due to the rapidly changing nature of the brain during early life, vulnerability exists that allows both genetic and environmental perturbations to inﬂuence adaptive changes in neuronal circuits. Before the formation of synaptic interneuronal connections and the development of the BBB, neurons function as secretory cells so the developing brain has been considered as an early endocrine organ [[91].](#_bookmark92) The physiologically active substances produced at this time and released from the brain into systemic

circulation are proposed to participate in regulation of the devel- opment, not only of the brain but also of visceral target organs and potentially the gastrointestinal tract [[91].](#_bookmark92) 5-HT is considered as an integral signalling molecule that regulates the development of many targets throughout the body [[88].](#_bookmark86) The lack of 5-HT in the CNS, as shown with Tph2 knockout mice, leads to a reduction in body growth and affects the proper wiring of the brain that may pre- dispose to the emergence of neurodevelopmental disorders [[92].](#_bookmark94) The sequence in which the major CNS developmental events occur appears similar across species although the timescale is consider- ably different [[93],](#_bookmark95) hence presenting different vulnerability time windows. Brain growth peaks in humans around birth while in rodents this is postnatal day seven [[94].](#_bookmark98) Although the BBB is func- tional at birth, the fragility of the developing cerebral vasculature indicates that the neonatal brain is more vulnerable to circulating toxins than during adulthood [[95].](#_bookmark99) This is particularly important in the context of the variety of new molecules which the infant may be exposed to postnatally and at various nutritional milestones, many of which can be either directly or indirectly attributed to the metabolic capability of the microbial complement in the gut [[96,97].](#_bookmark101)

* 1. *The developing central serotonergic system*

The central serotonergic system originates in the raphe nuclei in the brainstem which project to virtually every part of the central nervous system and is implicated in modulating physiological pro- cesses such as mood, sleep, aggression and sexual behaviour [[98].](#_bookmark105) Serotonin regulation shows age-dependent adaptations [[99].](#_bookmark107) Sero- tonin neurons are one of the most early born in the CNS [[100]](#_bookmark109) and 5-HT uptake as seen in animal studies is higher in the developing brain when compared with adult values [[101].](#_bookmark110) In rats, mRNA for SERT is evident from embryonic day 13, and the uptake of 5-HT reaches adult levels in brain synaptosomes by birth, at ﬁve weeks of age uptake is doubled and then decreases to adult levels again

[[102].](#_bookmark111) SERT binding in humans from 3 to 18 years of age shows an increase [[103],](#_bookmark113) followed by a decrease at the approximate rate of 10% per decade [[104].](#_bookmark114) Numerous studies on the development of 5-HT neurons indicate that from very early stages 5-HT raphe cells appear to be subdivided into speciﬁc subsets, projecting to different brain areas and may require speciﬁc transcriptional and environmental factors for their development [[105].](#_bookmark117)

Given the inﬂuence the developing gut microbiota (see Section

[4)](#_bookmark8) is proposed to have over behaviour [[10]](#_bookmark27) and other central-related functions such as pain [[106],](#_bookmark119) it is possible that it also plays a role in the developing central 5-HT system. Studies in germ-free mice from our laboratory [[55]](#_bookmark77) have shown that the early bacteria that colonise the gut are necessary for appropriate development of central serotonergic systems (see Section [6).](#_bookmark11) Germ-free mice also display region-speciﬁc changes in the 5-HT1A receptor [[107].](#_bookmark121) Another study employing germ-free mice has shown that normal pain responses in adulthood require the gastrointestinal tract to be colonised [[106].](#_bookmark119) In the human brain the levels of 5-HT remain fairly stable during normal aging yet overall 5-HT receptors appear to reduce by about 30–50% over the lifespan [[108].](#_bookmark123)

* 1. *The developing peripheral serotonergic system*

Serotonin released from the EC cells mediates many gastroin- testinal functions, including secretion, peristalsis, vasodilation, perception of pain and nausea through the activation of the 5-HT receptors (see [Table 2)](#_bookmark13) which are found on intrinsic and extrinsic afferent nerve ﬁbres. The presence of these EC cells is ﬁrst noted in the rat at E15 in the duodenum [[88]](#_bookmark86) which is when they start to produce 5-HT [[109]](#_bookmark125) and already by E21 the concentration of 5- HT in the gut is similar to the adult rat [[88].](#_bookmark86) The concentration of 5-HT in the gut continues to rise as birth approaches and stays on this trajectory into postnatal life [[88].](#_bookmark86) Once the BBB is formed in the rat (postnatal day 4–16) there is a sharp rise in 5-HT in the gut indicating a potential compensatory mechanism to limit the impact of cessation of a 5-HT supply from the brain [[88].](#_bookmark86) The num- ber of EC cells increases signiﬁcantly until about postnatal day 14 [[88].](#_bookmark86) The distribution of these cells also changes with appearance in the crypts ﬁrst and then moving to the villi [[110].](#_bookmark126) An immature clearance mechanism is also evident in the guinea pig gastroin- testinal tract in neonatal life with low expression of SERT and 5-HT turnover [[110].](#_bookmark126) Once SERT expression increases, 5-HT levels drop in the gastrointestinal tract perhaps indicating that the serotonergic modulatory inﬂuence on the developing tract is reducing. Changes in the gut immune and microbiota systems are known to occur with aging [[111]](#_bookmark127) hence it is also plausible that changes occur over time to the 5-HT system within the gastrointestinal system given the interplay between these systems.

* 1. *Serotonin and the development of the enteric nervous system*

The ENS provides the intrinsic innervation of the bowel and is the most neurochemically diverse component of the peripheral nervous system [[112].](#_bookmark128) Essential to life, the ENS is composed of 2 concentric layers of ganglia and ﬁbres encircling the gastroin- testinal tract and regulates motility and secretion within the gut [[113].](#_bookmark80) The ENS is derived vagal and sacral neural crest cells which invade, proliferate and migrates within the wall of the gastroin- testinal tract [[112].](#_bookmark128) These cells respond to a variety of guidance factors and morphogens differentiating into glia and neuronal sub- types that transform into a functional nervous system [[112].](#_bookmark128) Gut colonisation by neural crest cells is complete by embryonic day 15 in the mouse and after 7 weeks gestation in humans [[114].](#_bookmark81) While the ENS of the newborn is sufﬁciently mature to permit oral feeding, the postnatal period is one of developmental turmoil [[115]](#_bookmark82) allowing the events of early life such as longitudinal growth, dietary

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changes as well as bacterial colonisation (see Section [4)](#_bookmark8) to inﬂuence it. This idea provides a basis for research into functional bowel dis- orders that are associated with both adverse early life events and altered ENS function. Thus it is plausible that epigenetic alterations in the enteric microenvironment during neurogenesis can induce lasting changes in the ENS [[115].](#_bookmark82)

* 1. *Serotonin and neurogenesis in the ENS*

Despite the ENS being referred to as the “little brain” or the “sec- ond brain” because of its autonomy, it is still well connected to the CNS via motor and sensory ﬁbres of the sympathetic and parasym- pathetic nervous systems [[114].](#_bookmark81) Studies now indicate, that like the CNS, the ENS is capable of neurogenesis in postnatal and even adult life [[114]](#_bookmark81) and that early-developing enteric neurons or their neu- rotransmitters might inﬂuence the fate of later ones due to the sequential developmental order [[116].](#_bookmark83) Tph2-deﬁcient mice exhibit reduced density of myenteric neurons, particularly GABAergic and dopaminergic nerve cells [[117].](#_bookmark84) Liu et al., [[118]](#_bookmark85) indicated that post- natal neurogenesis occurred *in vivo* between week 16 and 24 in the mouse and this was strongly dependent on the activation on 5-HT4 receptors [[118].](#_bookmark85) The abundance of ENS neurons increased during the ﬁrst 4 months after birth in wild-type but not 5-HT4 knockout mice [[118].](#_bookmark85) Also enteric neurons decreased in both groups over time but at 12 months of age they were signiﬁcantly more numerous in the wild type animals [[118].](#_bookmark85) Moreover, *in vitro* studies indicated that 5-HT4 agonists increased enteric neuronal devel- opment/survival, decreased apoptosis, and activated CREB [[118],](#_bookmark85) suggesting that 5-HT4 receptors are required postnatally for ENS growth and maintenance. The 5-HT2B receptor, expressed by crest derived neural precursors, was found to promote the differentiation of enteric neurons [[119].](#_bookmark86) Both 5-HT and a 5-HT2 receptor agonist promoted *in vitro* differentiation of enteric neurons, the effect of which is blocked by the 5-HT2B/2C antagonist SB206553 [[119].](#_bookmark86) The 5-HT2C receptor was not found in the foetal bowel and hence it is more likely that the 5-HT2B receptors are the drivers with regard to neuronal differentiation here [[119].](#_bookmark86)

The ENS develops in close correspondence with the enteric

microenvironment and hence by affecting the activity of enteric serotonergic neurons and/or mucosal EC cells, the luminal content can be involved in determining the number and potentially the phe- notypic composition [[120]](#_bookmark88) of the neurons of the ENS. Cells of the adult ENS exhibit plasticity and undergo changes later in life as well as postnatally [[121].](#_bookmark90) This is due to the highly dynamic nature of the gastrointestinal tract such as the variation in diet, microbial changes, disease, inﬂammation and medication [[121].](#_bookmark90) Also con- tributing is the normal cellular process of ageing that occurs where there appears to be increased vulnerability to neuronal degenera- tion and cell death [[121].](#_bookmark90) Gastrointestinal dysfunction is common in the elderly and may be attributed to enteric degeneration and age- related neuronal loss [[122].](#_bookmark91) Stimulation of 5-HT4 receptors protects enteric neurons against apoptotic death and inhibits inﬂammation induced axon terminal degeneration and autophagy [[118].](#_bookmark85) 5-HT4 receptors are also involved in the mobilisation of extraganglionic adult stem cells to form new neurons that may replace damaged or killed ones [[123].](#_bookmark93) The development of microvilli, which increase the surface area for efﬁcient absorption of nutrients, is induced by 5-HTP, the 5-HT precursor, but not 5-HT [[124].](#_bookmark96) 5-HTP speciﬁ- cally induced actin remodelling and decreased phosphorylation of extracellular signal-regulated kinase (ERK) in the gut [[124].](#_bookmark96)

* 1. *Development of the immune system*

The immune system forms an integral component of the signalling pathway in the brain-gut axis [[7].](#_bookmark18) In the newborn,

immunity is passively acquired by transplacental transport of maternal immunoglobulin G *in utero* and from breast milk secre- tory antibody IgA postnatally [[125].](#_bookmark97) In humans, the immune system is somewhat functional at birth such that thymectomies are well tolerated in the ﬁrst few postnatal days [[126]](#_bookmark98) while in contrast few B and T cells are present at birth in the rodent with thymectomy causing T cell development failure and wasting syndrome [[126].](#_bookmark98) The initial exposures to bacteria as the microbiota develops is criti- cal for appropriate systemic immunological development [[127]](#_bookmark100) and provides a state of physiological inﬂammation, fosters immunolog- ical tolerance and inﬂuences the future immune phenotype [[128].](#_bookmark102) The elaboration of the mucosal immune system is also contingent on the host microbiota with the colonising and residential bacteria imprinting and instructing the mucosal immune system through- out the life of the host [[125].](#_bookmark97) Gut associated lymphoid tissue, which modulates tolerance versus luminal antigens and prevents the tran- sit of potentially harmful antigens across the intestinal barrier, is dependent on the microbiota for development [[129].](#_bookmark103) The imma- ture immune system of the newborn has a Th2 bias which shifts to a Th1 response with bacterial colonisation [[125].](#_bookmark97) Different lactic acid producing bacteria such as *Biﬁdobacterium* and *Lactobaccillus* have been shown to promote a Th1 shift [[130]](#_bookmark106) indicating that qualitative differences in composition may affect immunological homeostasis. Administration of broad-spectrum antibiotics, frequently used in paediatric practices, has been shown to reduce the biodiversity of faecal microbiota and delay the colonisation by certain *Biﬁdobac- terium* and *Lactobaccillus* strains [[131]](#_bookmark108) (see also Section [4).](#_bookmark8) Also, early-life antibiotic exposure is associated with allergic disease [[132,133]](#_bookmark109) and inﬂammatory bowel disease [[134].](#_bookmark112)

* 1. *Serotonin and immune function*

Serotonin can modulate the immune response and hence poten- tially inﬂuence intestinal inﬂammation [[135].](#_bookmark113) Several of the 5-HT receptors have been associated with immune cells such as lympho- cytes, monocytes, macrophages and dendritic cells which indicates that 5-HT plays an immune-modulatory role [[136].](#_bookmark115) EC cells have been shown to be in close proximity or even in contact with CD3+ and CD20+ lymphocytes, again pointing towards an interaction [[137].](#_bookmark116) In inﬂammatory gastrointestinal disorders, it is becomingly increasingly evident that interactions between gut hormones such as 5-HT and the immune system play a role in the pathogenesis [[138].](#_bookmark118) Changes to the gastrointestinal content of 5-HT and EC cell population are associated with Crohns disease and ulcerative coli- tis [[139–141].](#_bookmark120) Altered 5-HT signalling in both the central nervous system and the gastrointestinal tract have been implicated in IBS which may give rise to some of the intestinal and extra-intestinal symptoms seen in this disorder [[142].](#_bookmark124) This is also suggested by the therapeutic effects of tricyclic antidepressants and SSRIs [[143]](#_bookmark126) as well as 5-HT4 receptor agonists and 5-HT3 receptor antagonists in the treatment of IBS symptoms [[16].](#_bookmark31)

Animal models of experimentally induced colitis show an increase in 5-HT content with reduction in EC cell number asso- ciated with amelioration of inﬂammation [[144].](#_bookmark127) Inﬂammation induced by infection in animal models is mirrored by a downregu- lation in SERT with increased 5-HT and EC cell number [[145,146].](#_bookmark129) Also TPH1−/− mice show delayed onset and decreased severity

of colitis in two models (dinitrobenzenesulphonic acid and dex- tran sodium sulphate) [[147].](#_bookmark131) Serotonin has also been shown to stimulate actin remodelling and increase ERK phosphorylation of macrophages [[124].](#_bookmark96) Taken together, these studies highlight a crit- ical role for 5-HT in gastrointestinal inﬂammation. Whether 5-HT in postnatal life helps shape the immune system is not known but may be possible given its well established immunomodulatory role and the parallel postnatal development of both systems.

* 1. *Development of vagal innervation and the serotonergic system*

Vagal innervation is the major two way neural connection between the brain and the gut providing both motor and sensory innervation for numerous functions (e.g. satiety, nausea, sensation of visceral pain, sphincter operation and peristalsis). While axons from cell bodies in the nodose ganglia and the dorsal motor nucleus ﬁnd their way to their enteric targets in utero, putative efferent terminals increase in number and density dramatically in the early postnatal life [[148].](#_bookmark132) Sensory axons mature slightly later in post- natal life [[148].](#_bookmark132) Given the importance of normal vagal function it is conceivable that disorders of the brain-gut axis (see [Fig. 1)](#_bookmark6) may be rooted in developmental abnormalities of enteric vagal innerva- tion [[148].](#_bookmark132) Importantly, the microbiota inﬂuences the maturation of many aspects of the gastrointestinal tract [[149]](#_bookmark134) which are inner- vated by the vagal nerve and may provide migratory signals for the developing axons [[150].](#_bookmark136) Also, given the role of 5-HT in the development of the CNS and ENS, it is conceivable that it is also involved in the development of the vagal system. The 5-HTIP and 5-HT3 receptors are both capable of mediating excitatory actions on vagal afferent ﬁbres [[6,142]](#_bookmark23) allowing the 5-HT system to signal the brain and impact on the gastrointestinal tract on functions such as motility and pain (see also [Table 2).](#_bookmark13)

* 1. *Stress axis development*

The main stress axis, the hypothalamic pituitary adrenal (HPA) axis, provides hormonal communication within the brain-gut axis. The appropriate development of this axis determines the ability of an individual to cope and adapt to stressors, be they physical or psychological, in life. Glucocorticoids, the endpoint of HPA axis activation, are required for normal brain development as they ini- tiate terminal maturation, remodelling of axons and dendrites and impact on cell survival [[52].](#_bookmark72) Both supressed and elevated glucocor- ticoid levels impair brain development and functioning [[52].](#_bookmark72) The stress hypo-responsive period (SHRP) occurs during the ﬁrst two weeks of life in the rodent with the majority of stressors evoking a subnormal response from the axis [[52].](#_bookmark72) It is thought that this SHRP may have evolved to protect the rapidly developing CNS from the inﬂuence of elevated glucocorticoids. There is also evidence that this SHRP also exists in human children [[151]](#_bookmark137) and is thought to extend throughout childhood [[152].](#_bookmark138) If this SHRP is maintained, it is evident that the stress system develops normally and the individual responds suitably to stressors as an adolescent and adult. In con- trast, if this period is interrupted through low-quality of parental care or abuse the axis can develop to over-activate in stressful sit- uations [[151].](#_bookmark137)

It is important to note that stress during this period can

also modulate the sympathetic nervous system with associated functional interactions between the adrenal medulla and cortex [[153–155]](#_bookmark139) and potential implications for the CNS serotonergic sys- tem [[156].](#_bookmark144) Indeed, bidirectional sympathetic pathways are also an important communication route of the brain-gut axis [[157,158].](#_bookmark145) Although the sympathetic nervous system represents a major inte- grative and regulatory pathway in the brain-gut-microbiota axis [[5],](#_bookmark26) studying the effects of early-life environmental factors mod- ulating sympathetic nervous system development is notoriously complex and poorly understood due to the multiplicity of function- speciﬁc subunits [[155].](#_bookmark141) The reciprocal interactions with the gut microbiota are even less well studied although there are clearly substantial developmental overlaps and a common susceptibility to factors such as stress and nutrition [[155].](#_bookmark141)

Early-life stressors are associated with increased anxiety and depressive-like behaviours as well as GI disorders that have a stress component [[52,159].](#_bookmark72) Given the inﬂuence of stress on the gut-brain

axis [[10],](#_bookmark27) appropriate development of the HPA axis is essential to the balanced functioning gut-brain axis. Stress has long been known to inﬂuence the composition of the gut microbiota [[160]](#_bookmark147) and we have shown that stress in early life alters the gastrointesti- nal bacterial content of the adult rat [[161].](#_bookmark148) Hence, early life stress capable of activating the HPA axis can impact on the developing microbiota and vice versa, ultimately leading to an imbalance in the gut microbiota and an inappropriate stress response [[97].](#_bookmark104) Ani- mals studies investigating the stability of the indigenous microﬂora in maternally separated rhesus monkeys [[162]](#_bookmark149) have shown a sig- niﬁcant decrease in fecal bacteria, in particular *Lactobacilli*, 3 days after separation, which correlated with stress-related behaviours. These results suggest that stress during this vulnerable period leads to dysfunction within several of the intertwined components of the gut-brain axis and increases susceptability to disease. Moreover, a pioneering study carried out by Sudo et al., [[163]](#_bookmark151) has shown that normal development of the HPA axis is contingent on the pres- ence of bacteria during a speciﬁc postnatal period. Germ-free mice exposed to restraint stress exhibited a signiﬁcantly higher level of adrenocorticotropic hormone (ACTH) and corticosterone than con- ventionally colonised mice [[163].](#_bookmark151) Colonisation of these mice with *B. infantis* during early life (neonatal period) prevented the exagger- ated response to the stressor [[163].](#_bookmark151) Taken together, these studies indicate that the stress system and the gut microbiota are capable of inﬂuencing each other during early life.

* 1. *Interaction of HPA axis and serotonin*

Activation of the HPA axis during early life has been associated with an altered serotonergic system [[164].](#_bookmark152) Maternal separation resulted in changes to 5-HT metabolism and attenuated expression of 5-HT1A and 5-HT2A receptors in various brain regions [[164].](#_bookmark152) This early life stress paradigm has been shown to alter 5-HT through- out the brain-gut axis [[165]](#_bookmark153) with separated rats showing increased 5-HT following colorectal distension in both the colon and spinal cord and increased EC cells number following this stress in the colon. Also, the stressed rats showed an increase in activated 5-HT positive neurons on the dorsal raphe nucleus, an area associated with the descending modulation of pain [[165].](#_bookmark153) Ultimately, early life events are capable of inﬂuencing the development of the 5-HT system within the brain-gut axis. The modulatory role 5-HT has on elements of this axis confers great importance on events that occur early in the postnatal period as essentially the appropriate development of both the brain-gut-microbiome axis and the 5-HT system depend on a balanced and stress-free environment.

# Behaviour, the brain-gut-microbiome axis and the serotonergic system

As indicated at the outset, the serotonergic system regulates an extensive array of behaviours [[1,6].](#_bookmark14) We are just beginning to understand the wide inﬂuence exerted by the gut microbiota on brain and behaviour [[8,9].](#_bookmark28) However, it is already apparent that there is substantial overlap between the physiological relevance and behavioural impact of the gut microbiota, tryptophan metabolism and the serotonergic system.

* 1. *Anxiety and the gut microbiota*

Germ-free mice robustly and reproducibly display less anxiety- like behaviours than their conventionally colonised counterparts [[55,56,107]](#_bookmark77) while a normoanxious state can be reinstated with the introduction of a microbiota prior to critical time windows, particularly immediately post-weaning [[55].](#_bookmark77) To date, it has not been deﬁnitively established that the CNS serotonergic alterations in these animals is directly related to the behavioural phenotype

which can be reversed following colonisation despite the persis- tence of the serotonergic abnormality [[55].](#_bookmark77) Interestingly, germ-free rats display increased anxiety-like behaviours, offering conﬁrma- tion in a different species that this is a behaviour under the inﬂuence of the microbiota, albeit with a discrepancy in the precise nature of the phenotype [[60].](#_bookmark42)

Destruction of the microbiota community in mice with an antimicrobial cocktail also reduces anxiety-like behaviours while it has also been established that anxiety-like traits are trans- missible following transfer of the microbiota between different mouse strains [[166].](#_bookmark154) Infection of the gastrointestinal tract in mice promotes an anxious phenotype [[167–169]](#_bookmark156) while the anxiolytic potential of certain probiotic strains offers further support to the concept [[170].](#_bookmark159) It is now clear that the developmental origins of anx- iety is closely associated with the developing serotonergic system [[171].](#_bookmark160) Whether this also overlaps with changes in the composition and function of the gut microbiota remain to be investigated [[33].](#_bookmark47) However, it is clear that anxiety-related disorders are amenable to treatment in adulthood with SSRI’s being the ﬁrst line option for the treatment of certain anxiety disorders. This suggests the poten- tial utility of microbiota-mediated serotonergic modulation in the treatment of pathological anxiety states during adulthood.

* 1. *Depression and the gut microbiota*

In some animal models of depression, the microbiota is also altered [[161,172,173].](#_bookmark148) A link between the microbiota and depressive-like behaviours is also apparent preclinically follow the administration of probiotic strains such as L. rhamnosus, B. infantis and a formulation of L. helveticus and B. longum [[175].](#_bookmark129) Interestingly, in healthy volunteers, the latter combination of pro- biotic strains alleviated psychological distress including an index of depression. Further clinical evidence comes indirectly from the util- ity of antibacterial agents in the modulation of depression including minocycline (a broad-spectrum tetracycline antibiotic) [[177,178].](#_bookmark130) Another member of this class of antibiotic, doxycycline, also seems to have similar beneﬁcial effects in preclinical studies [[178].](#_bookmark133) The mechanism of antidepressant action of minocycline could be related to neuroprotection, suppression of microglial activa- tion or anti-inﬂammatory actions [[179].](#_bookmark135) Interestingly, minocycline can also indirectly inhibit IDO activity, albeit without impact- ing on CNS 5-HT turnover [[180].](#_bookmark136) The effects of minocycline on the composition of the gut microbiota has not received much attention as a putative mechanism of action but this possibility is increasingly coming into focus [[173].](#_bookmark161) Clinically, the micro- biota composition of depressed subjects has, to date, only been reported in one preliminary study which reported no clear com- positional differences from their control subjects [[181].](#_bookmark138) Unusually, the healthy controls were recruited from an outpatient neurologi- cal clinic and the study may have beneﬁtted from a more detailed bioinformatic analysis of the results. Further studies are urgently required to adequately address this important question and to unravel the complex interactions that might exist at the species level.

* 1. *Cognition and the gut microbiota*

The inﬂuence of the gut microbiota on behaviour also extends to cognitive function and in the novel object recognition test and the T-maze germ-free mice exhibit non-spatial, hippocampal medi- ated, and working memory deﬁcits, [[182].](#_bookmark140) These animals also exhibit pronounced social-cognitive deﬁcits relevant to neurode- velopmental disorders which can be partially rescued by bacterial colonisation of the gut [[183].](#_bookmark142) Infection with *Citrobacter rodentium* in combination with acute stress culminates in memory dysfunc- tion which was prevented by daily administration of a probiotic

before infection [[182],](#_bookmark140) indicating a complex interaction between stress and the gut microbiota on cognitive performance. Indirectly, diet-induced alterations in the composition of the gut microbiota also affected cognition in conventional mice [[185,186].](#_bookmark143) Given the relationship between serotonin, cognition and social responses [[186,187]](#_bookmark146) and the impact of kynurenine pathway metabolites on cognitive performance [[2,20],](#_bookmark16) the ability of the microbiota to inﬂu- ence these behavioural domains should perhaps not surprise us.

Clinically, the cognitive impairment arising due to hepatic encephalopathy, which in some cases may be present as dementia, is mediated by microbial disturbances and can be reversed with oral antibiotic treatment [[189,190].](#_bookmark147) Although the links between gut microbiota alterations and cognitive performance in IBS are unclear, cognitive alterations may be present in IBS and other disor- ders of the brain-gut axis [[190,4].](#_bookmark150) Thus, IBS patients exhibit a greater attention to GI symptoms and pain related stimuli which can main- tain a cycle of symptom exacerbation [[192,193].](#_bookmark151) Further evidence of cognitive alterations in IBS relates to hippocampal mediated vis- uospatial memory deﬁcits which appear to be related to indices of HPA axis function [[193].](#_bookmark153) IBS patients also show impairments on a test of cognitive ﬂexibility and have abnormal brain activ- ity in frontal brain regions during this task [[194].](#_bookmark155) However, not all studies have noted such deﬁcits, possibly reﬂecting the well- known heterogeneity of IBS. Nevertheless, gut microbiota mediated alterations in brain function and cognition in preclinical studies is convincing [[174,182,195].](#_bookmark163) Moreover, a recent study in a healthy human population provided preliminary evidence that intake of a fermented milk product with a probiotic can alter brain activity in regions of relevance to cognitive performance and which are innervated by serotonergic projections [[196].](#_bookmark157) Future studies are needed to investigate directly what the exact role of tryptophan metabolism and the serotonergic system play in modulating the cognitive effects of probiotics, for example. The use of tryptophan depletion studies is one such strategy that can be applied to parse the nuances of this inﬂuence [[28,197].](#_bookmark41)

* 1. *Visceral hypersensitivity, serotonin and the gut microbiota*

Visceral hypersensitivity is currently thought to be a key patho- physiological mechanism involved in pain perception in functional gastrointestinal disorders such as IBS [[198]](#_bookmark158) and is proposed to involve both peripheral and central mechanisms [[199].](#_bookmark159) Imaging of the central nervous system using functional magnetic resonance imaging or positron emission tomography [[200,201]](#_bookmark160) has indicated abnormal central processing of visceral stimuli. There is also a sig- niﬁcant contribution of psychological factors that inﬂuence the perception of pain [[202].](#_bookmark162) Altered signalling from the gut is also proposed as being responsible for visceral hypersensitivity with immune activation, for example, causing sensitisation of neuronal afferents [[203]](#_bookmark164) and neuroplastic changes in the ENS [[199].](#_bookmark159)

* 1. *Altered serotonin in visceral hypersensitivity*

EC cells serve as bidirectional sensory transducers modulating the relationship between the gastrointestinal lumen and the ner- vous system [[6].](#_bookmark23) These cells are innervated by vagal sensory ﬁbres and can be inﬂuenced by the microbiota suggesting a role in the regulation of visceral pain [[6].](#_bookmark23) Amongst its many functions, 5-HT plays a large role in pain modulation in descending pain pathways

[[199]](#_bookmark159) and through the activation of extrinsic afferent nerves, both vagal and spinal [[6].](#_bookmark23) A reduced engagement of the descending pain inhibitory system is thought to be involved in the aetiology of vis- ceral hypersensitivity in IBS [[204]](#_bookmark165) indicating the involvement of central 5-HT and its receptors. Both IBS patients and animal mod- els of IBS do show altered CNS 5-HT responses [[205,206].](#_bookmark166) Functional imaging studies have shown correlations between the severity of

clinical symptoms, with altered activation of central areas associ- ated with pain control and stress response [[207,208].](#_bookmark169) These brain areas are under feedback control through the projections from the brainstem nuclei, in particular from serotonergic nuclei such as the raphe nucleus [[209].](#_bookmark171) 5-HT receptors are expressed in corti- cal and limbic areas of the brain involved in emotional conditions and perception of visceral pain, both clearly involved in IBS [[142].](#_bookmark124) Activation of 5-HT3 receptors on the central terminals of spinal afferents increases the spinal transmission in the entire dorsal horn, which results in increased pain and reﬂex responses [[210].](#_bookmark173)

It is proposed that the 5-HT1, 5-HT2 and 5-HT3 receptors medi- ate noxious visceral stimulus [[211].](#_bookmark174) A main function of 5-HT3 receptors is the activation of extrinsic primary afferent neurons (EPANs), which mediate the pain and swelling of bowel wall asso- ciated with IBS [[142].](#_bookmark124) The 5-HT3 receptor antagonist, alosetron, inhibits c-fos expression in the spinal cord following colorectal dis- tension [[212],](#_bookmark175) indicating that this receptor is involved in visceral pain signalling. The ability of tegaserod to alleviate abdominal pain and discomfort in patients with IBS is likely due not only to its effects on peripheral 5-HT4 receptors, but may also be associated with its actions on 5-HT2A, 5-HT2B and 5-HT2C receptors located in CNS [[142].](#_bookmark124) There is evidence for altered 5-HT metabolism in IBS with an increased number of EC cells in the colonic mucosa along with increased mucosal levels of 5-HT [[213].](#_bookmark177) A decrease in the SERT has been seen in some studies [[140]](#_bookmark122) but this has been controver- sial [[214].](#_bookmark178) Correlations between 5-HT release in gastrointestinal tract and pain and discomfort in IBS patients have been shown [[215].](#_bookmark180) Moreover, the increased mesenteric afferent ﬁring that was observed following application of IBS patient mucosal supernatants was blunted by blocking the 5-HT3 receptor [[215].](#_bookmark180) While taken together these studies indicate that alterations in both central and peripheral 5-HT systems contribute to visceral hypersensitivity in IBS, further studies are needed in order to elaborate on the exact contribution.

* 1. *Brain-gut-microbiome axis signalling in visceral hypersensitivity*

The gut microbiota are involved in pain signalling from the gastrointestinal tract [[216].](#_bookmark183) It has also been shown that the involve- ment of the microbiota in pain signalling extends beyond the gut with a full and balanced microbial community necessary for the appropriate development of pain signalling from the body [[106].](#_bookmark119) Moreover, consumption of *L. casei* Shirota leads to a signiﬁcant improvement in gastrointestinal symptoms, including abdominal pain, in Parkinson’s disease patients [[217].](#_bookmark184) Microbial colonisation in early-life is associated with essential gastrointestinal functions

[[218]](#_bookmark185) and it is possible that factors interfering with the normal microbial ecology during this period may have deleterious effects in adulthood including those affecting appropriate development of pain pathways.

We and others have demonstrated that microbiota disruption following antibiotic administration in the neonatal period was associated with the development of abdominal visceral pain in adult rats [[220,221].](#_bookmark186) Verdu and colleagues also showed that the vis- ceral hypersensitivity induced could be attenuated with probiotic administration, clearly indicating the role of the microbiota in vis- ceral sensation [[220].](#_bookmark188) Microbiota disruption with Gram-negative bacterium *C. jejuni* leads to activation of brain regions that process gastrointestinal sensory information [[221].](#_bookmark189) *L. acidophilus* has been noted to modulate intestinal pain through opioid and cannabinoid receptors [[222].](#_bookmark190) A study carried out in our laboratory has also indicated that a probiotic strain of bacteria is capable of reducing visceral pain in rodents [[223].](#_bookmark191) An improvement in IBS symptoms in patients is also seen following the consumption of a variety of probiotic treatments [[224].](#_bookmark192) It is tempting to speculate that

normalisation of aberrant 5-HT signalling may contribute to such beneﬁts. However, further studies are needed to test this hypothesis. Taken together, these studies indicate that visceral pain can be modulated both through the serotonergic system and the gastrointesintal microbial system but whether there is overlap or linkage between these two systems is yet to be elucidated.

# Therapeutic targeting of the serotonergic system in brain-gut-microbiome axis disorders

The involvement of the stress system has repeatedly shown to be one of the main factors that can modulate motility and visceral perception through brain–gut axis interactions [[10,89,225].](#_bookmark27) Several inﬂuences, such as the high prevalence of anxiety and psycholog- ical disorders, have been shown to increase intestinal response to psychological stress [[173].](#_bookmark161) Clinical response to serotonergic drugs acting at the central level [[226]](#_bookmark166) suggests an involvement of the limbic system in the pathophysiology of IBS ([Table 2](#_bookmark13) highlights the 5-HT receptors and their function in the brain-gut axis). Agents acting at 5-HT receptors are known to modify the main functions altered in IBS i.e. motility and visceral sensation [[226].](#_bookmark166) Action at the SERT, 5-HT1A, 5-HT2A/2C as well as 5-HT6 and 5-HT7 receptors is proposed to be of beneﬁt to the treatment of IBS symptoms [[227].](#_bookmark167) An endocrine mechanism has been proposed for the efﬁcacy of blockade of the 5-HT7 receptor in its fast acting anti-depressant- like action [[227].](#_bookmark167) It shortens the length of time various classes of antidepressants require to take effect [[227].](#_bookmark167)

* 1. *Centrally acting serotonergic therapies*

Centrally acting treatments have been used to treat IBS symp- toms due to their ability to target the prominent features of this disease, namely altered bowel habits and psychological distur- bances [[226].](#_bookmark166) The most commonly prescribed centrally acting agent for IBS and other functional bowel disorders are tricyclic antide- pressants (TCA’s) [[226,228].](#_bookmark166) While TCA’s act on more than the serotonergic system, it is accepted that action at these recep- tors is at least partially accountable for the efﬁcacy in IBS and other functional bowel disorders. Compounds such as desipramine, amitriptyline and imipramine (at doses which are sub-therapeutic for the treatment of depression) have improved quality of life, bowel movements and pain scores in IBS [[226].](#_bookmark166) Selective serotonin reuptake inhibitors (SSRI’s) inhibit the uptake of 5-HT, increasing the synaptic level of 5-HT and have been associated with gastroin- testinal side effects when used to treat depression. While these drugs have been effective in reducing pain in animal models [[229],](#_bookmark170) they are thought to be of most beneﬁt in functional bowel disorders when administered with TCA’s [[226].](#_bookmark166) Another proposed mecha- nism of action is activation of descending opioid spinal pathway. The combined effect of blocking both the serotonergic and nora- drenergic reuptake has been investigated with one compound in IBS, duloxetine [[230].](#_bookmark172) Duloxetine was effective in reducing pain, loose stool, in improving quality of life and anxiety [[230].](#_bookmark172) Although nearly half of the patients withdrew due to side effects, most notably constipation, which is also seen with the TCA’s.

* 1. *Gastrointestinal serotonin receptors as targets*

Extensive reviews on 5-HT receptors, such as the 5-HT3 and 5-HT4 receptors, in the gastrointestinal tract have been written out- lining the pivotal role of 5-HT in both altered motility and sensation of pain frequently seen in disorders of the microbiome-gut- brain axis [[15,231,232].](#_bookmark29) The 5-HT3 receptors are predominantly expressed in the submucosal neurons and alosetron, the 5-HT3 receptor antagonist, affects transit times and inhibits visceral pain in both animal and human studies [[233,234].](#_bookmark174) Thus, this compound

has been used to treat diarrhoea predominant IBS [[234].](#_bookmark176) This recep- tor is also responsible for intestinal secretion and modulation of release of excitatory neurotransmitters as it is also present on the myenteric neurons [[234].](#_bookmark176) The 5-HT4 receptors are also present on both plexi where they also modulate a number of key func- tions. Agonists of this receptor such as tegaserod reduce transit time, reduce constipation and visceral sensitivity [[234,235].](#_bookmark176) Both of these compounds appear to work through spinal mechanisms to reduce visceral pain [[236].](#_bookmark179) Tegaserod and another 5-HT4 receptor agonist, RS67506 have been shown to have neuroprotective and neurotrophic effects on the ENS and could be of beneﬁt in age- related gastrointestinal dysfunction [[237].](#_bookmark181) However, despite the therapeutic beneﬁt, both of these drugs were withdrawn from the US market in 2007 due to side effects [[238].](#_bookmark182) Romosetron is a novel 5-HT3 receptor antagonist that has shown efﬁcacy in improving global symptoms in both women and men with IBS without any serious side effects [[238].](#_bookmark182) This compound is now approved for use in Japan [[239].](#_bookmark183) Prucalopride, AT-7505 and velusetrag are three new 5-HT4 receptor agonists have evaluated for treatment for chronic constipation with prucalopride showing efﬁcacy in three multi- centre studies [[238].](#_bookmark182)

* 1. *Novel serotonin receptors for the treatment of disorders of the brain-gut axis*

There is increasing evidence, however, that the 5-HT3 and 5-HT4 receptors are not the only 5-HT receptors responsible for all of the effects of 5-HT in the gastrointestinal tract [[234].](#_bookmark176) Both alosetron and tegaserod have substantial afﬁnity for the 5-HT2B receptor which may explain their common efﬁcacy in treating of visceral pain. We and others have shown that 5-HT2B receptors are involved in vis- ceral hypersensitivity in animals model of IBS [[206,240],](#_bookmark168) indicating that targeting this receptor presents a novel approach to the treat- ment of IBS. The 5-HT1p and 5-HT7 receptors as well as SERT have also been considered as potential targets in the gastrointestinal tract for the treatment of IBS [[234].](#_bookmark176)

LX-1031 inhibits the rate limiting enzyme, tryptophan hydrox- ylase 1, reduces 5-HT synthesis peripherally and has potential for illnesses characterized by excess 5-HT, such as diarrhea- predominant IBS carcinoid diarrhoea [[241].](#_bookmark185) This compound does not affect central 5-HT while dose-dependently reducing 5-HT, particularly in the small bowel in rodents [[241].](#_bookmark185) In humans, LX- 1031 was associated with improved weekly global scores and improved stool consistency with lower urinary 5-HIAA excretion [[241].](#_bookmark185) There are no dose-limiting toxicities in healthy subjects or remarkable adverse effects in clinical trials to date. This data indicates that 5-HT receptors dispersed throughout the brain- gut axis are capable of the maintenance of symptoms of IBS and, once targeted, symptoms and general quality of life can be improved.

# Therapeutic targeting of the gut microbiome: relevance to the serotonergic system

Probiotic bacteria are capable of producing neuroactive sub- stances such as gamma-aminobutyric acid (GABA) and 5-HT which inﬂuence functioning in the brain-gut-microbiome axis [[242].](#_bookmark187) These bacteria also possess anxiolytic and antidepressant-like activity that can also affect this axis as well as the seroto- nergic system [[61].](#_bookmark44) *B. infantis*, administered to rats, showed anti-inﬂammatory properties as well as increases in plasma con- centrations of tryptophan and kynurenic acid and reduced 5-HIAA in the frontal cortex. The reduction of pro-inﬂammatory immune responses, and effect on both peripheral and central serotoner- gic systems could be of use in the treatment of IBS which is

associated with a low-grade inﬂammation as well as altered 5-HT responses throughout the brain-gut-microbiome axis. As well as indirectly targeting the 5-HT system, certain bacteria are known to produce 5-HT and could potentially be used to deliver this neurotransmitter to the gastrointestinal system where it can inﬂu- ence brain-gut-microbiome axis signalling. Candida, Streptococcus, Escherichia and Enterococcus are producers of 5-HT ([Table 1)](#_bookmark12) [[84].](#_bookmark82) The cognitive impairments and emotional disorder associated with hepatic encephalopathy is thought to be due to hyperammonemia [[243].](#_bookmark188) *L. helveticus* led to an improvement in both cognitive and anxiety-like behaviour as well as reducing central 5-HT in an ani- mal model of hyperammonemia [[243].](#_bookmark188) This probiotic also displayed anti-inﬂammatory properties as well as affecting metabolites of the kynurenine pathway. As indicated above, IBS patients do shown signs of cognitive impairment [[193]](#_bookmark153) and this probiotic could potentially alleviate these symptoms through either the 5-HT or kynurenine pathway.

# Concluding remarks

As outlined in the above review, tryptophan and the 5-HT sys- tem are involved at every level of the brain-gut-microbiome axis, with a range of roles which are both delicate and essential to  life. Our current understanding has seen most attention focused on treatment strategies which are aimed mainly at direct manip- ulation of the 5-HT system. However, these are only partially effective in varying subsets of patients suffering from stress-related disorders of the brain-gut axis. This is mainly due to the hetero- geneity of these disorders in conjunction with the diversity of roles which 5-HT plays. However, a better understanding of the devel- opment and interaction of the brain-gut-microbiome axis and the tryptophan/5-HT system could aid in the design and development of novel therapeutic strategies with more nuanced effects. This approach is not without its challenges and there is nothing simple about the enduring relationship between the bacteria in our gut and brain-gut axis signalling. We note, for example, that a causal role for a gut microbiota mediated defect in tryptophan metabolism or serotonergic signalling remains to be established in relevant clinical populations. The preclinical literature argues strongly in favour of such a fundamental linkage and the limited clinical data to date is promising. However, this is a frontier area of research which is in its infancy and we should proceed with cautious opti- mism. The involvement of other neurotransmitter systems such as GABA, which is known to be altered following administration of a speciﬁc probiotic strain for example [[174],](#_bookmark163) should also not be discounted.

The correct functioning of the brain-gut-microbiome axis, which

confers quality of life on an individual, depends on appropriate 5-HT signalling through the entire life span to nurture develop- ment, function and maintenance of this axis. In tandem, a variety of preclinical experimental strategies have underlined that both tryptophan availability and 5-HT signalling are profoundly inﬂu- enced by the composition of the gut microbiota. Moreover, the gut microbiome is plastic and can be rapidly altered following dietary alterations and other approaches. We are just beginning to understand the potential arising from these complex interac- tions across health and disease. This gives rise to the intriguing possibility that therapeutic targeting of the gut microbiota might be a viable treatment strategy for serotonin-related brain-gut axis disorders.

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