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Title	Kynurenine pathway metabolism and the microbiota-gut-brain axis
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Publication date	2016-07-05
Original Citation	Kennedy, P. J., Cryan, J. F., Dinan, T. G. and Clarke, G. (2016) 'Kynurenine pathway metabolism and the microbiota-gut-brain axis', Neuropharmacology, 112, pp. 399-412. doi:10.1016/j.neuropharm.2016.07.002
Type of publication	Article (peer-reviewed)
Link to publisher's version	10.1016/j.neuropharm.2016.07.002
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Download date	2026-11-17 04:42:10
Item downloaded from	https://hdl.handle.net/10468/5302

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Kynurenine Pathway Metabolism and the Microbiota-Gut-Brain Axis

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Abbreviations: BBB, blood brain barrier; CNS, central nervous system; DSM, diagnostic and statistical manual; GABA, gamma-aminobutyric acid; GF, germfree; GI, gastrointestinal; GPR35, G-protein coupled receptor 35; HPA, hypothalamic-pituitary-adrenal; IBS, irritable bowel syndrome; IDO1, indoleamine-2,3-dioxygenase; IFN-γ, Interferon-gamma; LNAA, large neutral amino acid; mRNA, messenger Ribonucleic acid; NMDA, N-methyl-D-aspartate; SCFAs, short-chain fatty acids; TDO, tryptophan-2,3-dioxygenase; TLRs, toll-like receptors; 3HAA, 3-hydroxyanthranilic acid oxygenase; 3-HANA, 3-hydroxyanthranilic acid; 16S rRNA, ribosomal Ribonucleic acid.

Abstract

It has become increasingly clear that the gut microbiota influences not only gastrointestinal physiology but also central nervous system (CNS) function by modulating signalling pathways of the microbiota-gut-brain axis. Understanding the neurobiological mechanisms

underpinning the influence exerted by the gut microbiota on brain function and behaviour has become a key research priority. Microbial regulation of tryptophan metabolism has become a focal point in this regard, with dual emphasis on the regulation of serotonin synthesis and the control of kynurenine pathway metabolism. In this review, we focus in detail on the latter pathway and begin by outlining the structural and functional dynamics of the gut microbiota and the signalling pathways of the brain-gut axis. We summarise recent preclinical and clinical investigations demonstrating that the gut microbiota influences CNS physiology, anxiety, depression, social behaviour, cognition and visceral pain. Pertinent studies are drawn from neurogastroenterology demonstrating the importance of tryptophan and its metabolites in CNS and gastrointestinal function. We outline how kynurenine pathway metabolism may be regulated by microbial control of neuroendocrine function and components of the immune system. Finally, preclinical evidence demonstrating direct and indirect mechanisms by which the gut microbiota can regulate tryptophan availability for kynurenine pathway metabolism, with downstream effects on CNS function, is reviewed. Taken together, targeting the gut microbiota represents a tractable target with which to modulate kynurenine pathway metabolism. Efforts to develop this approach will markedly increase our understanding of how the gut microbiota shapes brain and behaviour and provide new insights towards successful translation of microbiota-gut-brain axis research from bench to bedside.

Keywords (max 6): Tryptophan; kynurenine; Stress; Immune system; microbiota-gut-brain-axis; behaviour.

Highlights

- Brain function and behaviour are under substantial microbial control
- Kynurenine pathway metabolism is critical in a range of CNS and GI functions
- Gut microbiota may regulate kynurenine pathway metabolism via numerous mechanisms
- The gut microbiota may be targeted to modulate kynurenine pathway metabolism
- Microbial-modulated kynurenine metabolism may prove beneficial for CNS function

1. Introduction

The importance of the gut microbiota has moved front and centre on the healthcare agenda. One of the most exciting developments in gut microbiota research over recent years has been the discovery that the collection of microorganisms in our gut can regulate aspects of brain function and behaviour (Cryan and Dinan, 2012; Mayer et al., 2014). Understanding the neurobiological mechanisms underpinning the extent of the influence exerted by this microbial organ on host physiology, brain and behaviour is now a key research priority. A number of pathways and potential mechanisms which may regulate microbiota-brain interactions are under investigation. One focal point in this regard is the microbial regulation of circulating tryptophan availability, with a dual emphasis on the regulation of serotonin synthesis and the regulation of kynurenine pathway metabolism. In addition to the ability to modulate the expression of relevant central nervous system (CNS) receptor subtypes, this attribute gives the gut microbiota a broad neuropharmacological repertoire and makes it an appealing and tractable target for the treatment of a range of stress-related disorders.

This review places the kynurenine pathway under the spotlight. We first briefly describe the structural and functional dynamics of the gut microbiota across the lifespan and frame its importance in general to health and wellbeing. We then discuss the broad scope of influence across physiology, brain and behaviour as it recruits the scaffolding and reciprocal communication network of the brain-gut axis to mediate both positive and negative effects. Using well established preclinical and clinical examples from the field of neurogastroenterology, we outline the potential translational significance of a dysregulated microbiota-gut-brain axis in the context of kynurenine pathway metabolism. We also explore possible mechanisms, neurodevelopmental implications and the opportunities for intervention

arising from this research, integrating evidence ranging from prenatal and postnatal studies to the older extreme of life.

2. The gut microbiota: Structural and functional dynamics

The microbes that reside in our gastrointestinal tract are together known as our gut microbiota and their collective genomes constitute our gut microbiome (Turnbaugh et al., 2007). When comparing the gut microbiota composition between healthy humans, substantial taxonomic variability is evident. Such inter-individual diversity may be accounted for by a number of environmental, physiological, genetic and psychological factors (Cryan and Dinan, 2012; Lozupone et al., 2012; Penders et al., 2006). Nevertheless, it is becoming accepted that whilst each individual harbours a unique microbiota, there exists a 'core' gut microbiota composition and common trends in microbial colonisation from birth, through infancy to adulthood and old age have been documented.

Initial microbial colonisation largely occurs during the birthing process, with vaginally delivered infants exposed to maternal faecal and vaginal bacteria, and infants delivered by caesarean (C)-section exposed initially to bacteria in the hospital environment and skin of the mother (Borre et al., 2014). However, it must be noted that despite the long held view that the in-utero environment is entirely sterile, it has recently been shown that prior to breastfeeding, the amniotic fluid, placenta and meconium of newborns, might contain small counts of bacteria (Rodríguez et al., 2015). Studies using culture based techniques to measure the gut microbial composition of newborns have demonstrated the presence of facultative anaerobes such as *Enterobacteriaceae*, followed by strict anaerobes, including *Bifidobacterium* and *Bacteroides* (Adlerberth and Wold, 2009). More advanced 16S rRNA sequencing, which has the capability to identify unculturable bacteria, has further revealed that the healthy, vaginally delivered infant gut is populated initially by *Bifidobacterium*,

Lactobacillus, Enterobacteriaceae and *Staphylococcus*, with later increases in *Veillonella* and *Lachnospiraceae* (Palmer et al., 2007). Up until around 2 years of age, when solid foods are introduced, the infant gut microbiota is highly unstable and dynamic (Borre et al., 2014), after which, around the third year of life, the composition diversifies, stabilises and begins to resembles an adult-like microbial composition (Rodríguez et al., 2015).

During adulthood, a healthy individuals' gut microbiota is dominated by four main phyla; *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Verrucomicrobia* (Human Microbiome Project Consortium, 2012). The healthy young adult and middle aged gut microbiota composition is characterised by diversity of the bacterial species which are present (Lozupone et al., 2012). As an individual moves through to old age, the microbial composition of the gut changes to a greater proportion of *Bacteroides* spp. with distinct abundance patterns of *Clostridium* groups identified in elderly compared to younger adults (Claesson et al., 2011). As such, at the extremes of life- infancy and old age- the gut microbial composition is extremely dynamic and undergoes significant changes, whereas the healthy young adulthood and middle age gut microbiota is characterised by relative stability and high diversity. Even during adulthood, however, the microbial composition of the gut can dramatically change over the course of one year (Knights et al., 2014). This has led to controversy as to how best to characterise, and track, the gut microbiota composition in an individual. The concept of 'enterotypes' (3 core clusters of a bacterial genus: *Bacteroides*, *Prevotella* or *Ruminococcus*) is not universally accepted due to inter-individual variation between clusters and difficulties in defining an individual's gut microbial composition within one enterotype (Knights et al., 2014). An alternative view is that the gut microbial composition reflects a core set of functional profiles in which some bacterial species are more critically involved in the functional profile and may thus influence, to a greater degree, health and disease (Flint et al., 2012).

Across the lifespan, a number of factors have been identified which purportedly disturb the normal microbial composition of the gut. These factors have been reviewed extensively elsewhere (Rodriguez, 2015) and include mode of delivery at birth, antibiotic treatment, diet, stress, infection and host genetics. However, two recent articles question the extent to which some of the aforementioned factors disturb the adult gut microbiota composition (Falony et al., 2016; Zhernakova et al., 2016) highlighting the need for further investigation with larger populations. Nevertheless, the health ramifications of disturbing the gut microbiota composition at each stage of life are potentially wide ranging and the implications for brain function behaviour, as will be outlined in the following sections, may be significant.

3. Microbiota -gut-brain axis signalling

Communication between the brain and gut occurs along a network of pathways collectively termed the brain-gut axis (see **Figure 1**). The brain-gut axis encompass the CNS, enteric nervous system (ENS), sympathetic and parasympathetic branches of the autonomic nervous system, neuroendocrine and neuroimmune pathways, and the gut microbiota (Cryan and Dinan, 2012). A complex reflexive network of efferent and afferent fibers between the gastrointestinal (GI) tract and the CNS facilitate interactions within the axis (Furness, 2012). Bidirectional communication along hormonal, neural, and immune pathways allow the CNS to influence motor, sensory and secretory functions of the GI tract, and conversely, signals arising from the GI tract to influence CNS function (Aziz and Thompson, 1998). Much work has been conducted over the past two decades to delineate the role of brain-gut interactions in the context of functional GI disorders such as irritable bowel syndrome (IBS) (Mayer et al., 2006; Mayer et al., 2009), to a lesser degree organic GI disorders such as inflammatory bowel disease (IBD), and other disorders that may be associated with dysregulated brain-gut communication such as obesity and anorexia nervosa (Hoebel, 1997; Schellekens et al., 2012). However, over recent years the gut microbiota has taken the limelight as a key

mediator of brain-gut axis signalling, with a growing body of evidence indicating that the influence of the microbiota extends beyond the gut and is pivotal in many aspects of brain function and behaviour (Cryan and Dinan, 2012; Mayer et al., 2014; Sampson and Mazmanian, 2015). Gut microbiota to brain signaling may occur through a number of inter-related mechanisms including activating afferent sensory neurons of the vagus nerve, neuro-immune pathways, neuroendocrine pathways, microbial metabolites such as short-chain fatty acids (SCFAs), microbial derived neurotransmitters (Cryan and Dinan, 2012) and as will be the focus here, through modulating circulating tryptophan availability with implications for kynurenine pathway metabolism in the periphery and in the CNS.

**********Insert Figure 1 Here**********

4. General influence of the gut microbiota on brain and behaviour

4.1.Anxiety & Depression

A number of approaches have been utilised in preclinical models to investigate how the gut microbiota influences brain function and behaviour, including the use of germ-free (GF) mice, pre/probiotic treatment, antibiotic treatment, deliberate bacterial infection of the GI tract and faecal microbiota transplant (Cryan and Dinan, 2012) . Such studies have demonstrated, with relative consistency, that the gut microbiota modulates anxiety (Arentsen et al., 2015; Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011; Savignac et al., 2014) and depressive like behaviour (Bravo et al., 2011; Desbonnet et al., 2015; Desbonnet et al., 2008; Messaoudi et al., 2011; Wong et al., 2016). Of particular note is a study showing that an anxiety-like phenotype can be transferred from one mouse strain to another by faecal microbiota transplant (Bercik et al., 2011).

Emerging data in healthy humans support preclinical findings suggesting the gut microbiota influence mood and anxiety (Benton et al., 2007; Messaoudi et al., 2011; Steenbergen et al.,

2015). Few investigations have been conducted with psychiatric populations. Emerging data suggests that patients with major depressive disorder have an altered microbial composition when compared to non-depressed individuals (Jiang et al., 2015; Zheng et al., 2016) although an independent study did not identify such differences. Despite these conflicting findings, the fact that a faecal microbiota transplant from patients with major depressive disorder to GF mice induced a depressive-like phenotype in these animals (Zheng et al., 2016), lends support to a role for the gut microbiota in depressive symptomatology. Nevertheless, conflicting results in psychiatric populations are perhaps not surprising due to a wide variation of symptoms within DSM diagnostic categories, and future large trials with well phenotyped populations are needed to delineate the role of the gut microbiota in depression and anxiety.

4.2. Cognitive function

Preclinical studies utilising various strategies including GF and GI infection models (Gareau, 2014; Gareau et al., 2011), antibiotic treatment (Desbonnet et al., 2015; Fröhlich et al., 2016) dietary manipulation (Li et al., 2009; Ohland et al., 2013) and probiotic treatment (Davari et al., 2013; Ohland et al., 2013), have found that cognitive function is influenced by the composition of the gut microbiota. Preliminary findings in healthy populations have shown that a prebiotic can modulate emotional attention performance (Schmidt et al., 2015), and a probiotic can alter functional brain activity when performing a similar emotional attention task (Tillisch et al., 2013).

Targeting the gut microbiota for pro-cognitive benefits may be particularly suited to application at the extremes of life, when brain function is more vulnerable and in a state of flux; rapid development in function characterised by increasingly complex cognitive abilities during infancy and slow decline in function accompanied by a steady reduction in specific cognitive abilities during old age (Prenderville et al., 2015). One small randomised controlled

trial suggests that microbiota-targeted interventions may be beneficial in age-related cognitive decline (Chung et al., 2014). To date there have been no studies to determine the efficacy of microbiota targeted supplementation in promoting cognitive development during infancy. However, when considering preclinical findings that the gut microbiota can profoundly influence neurodevelopment during critical postnatal periods (Clarke et al., 2013; Desbonnet et al., 2014; Stilling et al., 2015b; Sudo et al., 2004), future trials with infants are clearly warranted.

4.3.Social Behaviour

When considering that microorganisms and humans coevolved over millennia, it is perhaps not surprising that there is increasing evidence that the gut microbiota is critical in the development and expression of social behaviour (Stilling et al., 2014a; Stilling et al., 2014b, 2015a). GF animals exhibit altered social novelty preference- a natural social behaviour expressed by conventional mice- (Arentsen et al., 2015; Desbonnet et al., 2014) which can be normalised if bacterial colonisation occurs post-weaning (Desbonnet et al., 2014). The maternal immune activation mouse model has been utilised to investigate, pre-clinically, neurodevelopmental disorders such as autism spectrum disorders which are characterised by marked social and communication difficulties (Carr, 2006). The maternal immune activation model produces offspring exhibiting deficits in social behaviour, gastrointestinal disturbances, increased intestinal permeability and alterations in the composition of the gut microbiota (Malkova et al., 2012). It is noteworthy then, that treatment with the probiotic *Bacteroides fragilis* was found to improve intestinal barrier function and normalize communicative and stereotypic behaviours in maternal immune activation offspring (Hsiao et al., 2013).

4.4.Visceral Pain

Chronic visceral pain affects up to 25% of the population and represents significant challenge for healthcare providers and society as a whole (Moloney et al., 2015). Chronic pain of the GI tract is a predominant symptom of IBS in which dysregulation of the brain-gut axis has long been considered to underlie the pathophysiology in the disorder (Moloney et al., 2016). A number of lines of evidence suggest that the gut microbiota may drive visceral pain in IBS. For example, recent studies have demonstrated an altered gut microbiota composition in IBS (Jeffery et al., 2012) which is associated with symptom scores (Kennedy et al., 2014). A number of probiotic bacteria show efficacy in reducing symptoms in IBS (Clarke et al., 2012a), and in preclinical models, antibiotic treatment during early life leads to visceral hypersensitivity in adulthood (O'Mahony et al., 2014), whilst probiotic treatment ameliorates visceral hypersensitivity (McKernan et al., 2010). As such, there is increasing interest in how alterations in the gut microbiota may impact the development of visceral pain and hypersensitivity, and the potential for microbiota targeted therapies to treat these problematic symptoms (Moloney et al., 2016).

5. Tryptophan metabolism, serotonin & the kynurenine pathway

As the precursor molecule to serotonin (5-HT), kynurenine and downstream metabolites of the kynurenine pathway (Badawy, 2015a; Palego et al., 2016), changes in the supply and availability of the essential amino acid tryptophan has many implications for ENS and CNS functioning and thus brain-gut axis signalling. Around 95% of the body's 5-HT is located within the GI tract, primarily synthesised by enterochromaffin cells, and 5% in the CNS (Camilleri, 2002; Gershon and Tack, 2007; Mayer et al., 2001). In healthy humans, other mammals and in disease states, 5-HT in the GI tract is involved in a range of largely reflexive functions including motility (Chial et al., 2003; Gorard et al., 1994), secretion and absorption

(Bearcroft et al., 1997), intestinal transit (Wilmer et al., 1993) and colonic tone (Klatt et al., 1999; Talley et al., 1990). In addition, 5-HT mediates feelings of nausea and can induce vomiting by stimulating 5-HT_3 receptors on vagal afferent pathways which signal to the nucleus tractus solitarii (Klatt et al., 1999; Talley et al., 1990). In addition, peripheral 5-HT release in the GI tract can modulate food intake by stimulating vagal afferent pathways (Donovan and Tecott, 2013) and inhibition of peripherial 5-HT synthesis has been shown to reduce obesity and metabolic dysfunction through actions on brown adipose tissue thermogenesis (Crane et al., 2015). In the CNS, 5-HT is involved in a range of mood, behavioural and cognitive functions, and is the purported target of many psychiatric medications (Berger et al., 2009; Cryan and Leonard, 2000). Whilst serotonergic signalling is critical in CNS and ENS function, a full review is not within the scope of this article (See (Gershon and Tack, 2007; Mawe and Hoffman, 2013; O'Mahony et al., 2015; Spiller, 2008) for excellent reviews on this topic).

Around 90% of tryptophan is metabolised along the kynurenine pathway (O'Mahony et al., 2015). The rate of tryptophan metabolism along the kynurenine pathway is dependent on expression of indoleamine-2,3-dioxygenase (IDO1), found in all tissues, and tryptophan-2,3-dioxygenase (TDO) which is localised to the liver (Clarke et al., 2012b). IDO1 expression can be induced by the action of inflammatory cytokines, Interferon (IFN)-γ in particular, and TDO expression by glucocorticoids (O'Mahony et al., 2015). IDO1 is the best characterised of these IDO enzymes in converting tryptophan to kynurenine both in the GI tract and other tissues of the body (Ciorba, 2013) although our knowledge of the more recently discovered IDO2 is steadily increasing (Ball et al., 2007; Fatokun et al., 2013). As IDO1 is induced by proinflammatory cytokines, its expression has been proposed as a biomarker of GI diseases, including IBD where it reflects mucosal inflammation, and in colon cancer (Ciorba, 2013).

Downstream metabolites of the kynurenine pathway (See **Figure 2** and **(Badawy, 2015b)** for more detailed description of kynurenine pathway), quinolinic and kynurenic acid are of particular interest for neurogastroenterology as they are neuroactive metabolites that act on *N*-methyl-D-aspartate (NMDA) and alpha7 (α7) nicotinic acetylcholine receptors in the CNS and ENS (Perkins and Stone, 1982; Stone and Darlington, 2002; Stone and Perkins, 1981). In the ENS and CNS, kynurenic acid is an antagonist of NMDA, and α7 nicotinic receptors, and in the ENS is an agonist of G-protein coupled GPR35 receptor (Turski et al., 2013). In the CNS, kynurenic acid has long been viewed as potentially neuroprotective whilst quinolinic acid is primarily considered an excitotoxic NMDA receptor agonist (Stone and Darlington, 2013). Less is understood regarding the functions of kynurenic acid and quinolinic acid in the GI tract; however, both appear to be involved in immunoregulation (Keszthelyi et al., 2009). Interestingly, kynurenic acid may have anti-inflammatory properties in the GI tract (Kaszaki et al., 2012), and has been shown, *in-vitro*, to inhibit the proliferation of colon cancer cells (Walczak et al., 2014).

****************************Insert Figure 2 Here******************************

6. Stress, the gut microbiota and the implications for kynurenine pathway metabolism

It has become clear that there is an intricate relationship between the gut microbiota and stress. Over a decade ago a seminal study was the first to demonstrate that GF mice subjected to a mild-restraint stress exhibited an exaggerated hypothalamic-pituitary-adrenal (HPA) axis (the core mammalian neuroendocrine system) response when compared to specific pathogen free control animals (Sudo et al., 2004). Of note, bacterial colonization with faecal matter from specific pathogen free mice was able to partially normalize the abnormal stress response in GF animals and could be fully normalized in a time-dependent manner by monoassociation with the probiotic *B. infantis* (Sudo et al., 2004). Subsequent preclinical investigations have

replicated this finding (Clarke et al., 2013), and demonstrated that probiotic treatment can normalise early life stress-induced HPA axis dysfunction (Gareau et al., 2007). Moreover, a recent preliminary investigation in a small sample of healthy control participants reported that treatment with a prebiotic supplement can modulate the cortisol awakening response (Schmidt et al., 2015). Taken together these studies suggest that neuroendocrine function is influenced by the gut microbiota. However, it must also be noted that the microbial-neuroendocrine relationship is bi-directional as stress can change the composition of the gut microbiota. This is true of early-life stress (Bailey and Coe, 1999; O'Mahony et al., 2009) prenatal stress (Golubeva et al., 2015a; Jasarevic et al., 2015; Zijlmans et al., 2015) and psychological stress (Bailey et al., 2011; Bharwani et al., 2016; Galley et al., 2014; Reber et al., 2016)

As outlined above and elsewhere in this issue, glucocorticoids modulate the expression of TDO (O'Farrell and Harkin, 2015; O'Mahony et al., 2015). As such, TDO activity may at least partly be contingent on a microbial-neuroendocrine interplay with significant implications for brain function and behaviour.

7. The immune system, the gut microbiota and implications for kynurenine pathway metabolism

As noted above, kynurenine pathway metabolism is tightly regulated by inflammatory mediators and multiple enzymes in the pathway are immunoresponsive (Campbell et al., 2014). The gut microbiota engages dynamically with the host across the lifespan to educate and regulate the immune system (El Aidy et al., 2015; Round and Mazmanian, 2009). This is clear not just from GF animals but also in the compromised immune response to infection of animals whose gut microbiota is depleted using antibiotics (Holzscheiter et al., 2014). Conversely, the immune system also acts to govern community composition and diversity of the intestinal microbiota (Hooper et al., 2012).

Microbiota-deficient GF animals have an immature immune system which could explain the reduced kynurenine pathway metabolism in these animals (see below) (Clarke et al., 2013). Normalisation of this metabolic abnormality following colonisation post-weaning tallies with the fact that immune system function can also be reinstated by introduction of an intestinal microbiota to GF animals (Clarke et al., 2013; O'Hara and Shanahan, 2006; Tlaskalova-Hogenova et al., 1983; Umesaki et al., 1995). Indeed a feature of the germ-free state is a reduced expression of gastrointestinal toll-like receptors (TLRs) which recognise microbial components in the gastrointestinal tract (Kawai and Akira, 2010; Wang et al., 2010). Activation of TLRs is associated with increased kynurenine pathway metabolism (Clarke et al., 2012b; Mahanonda et al., 2007; Wang et al., 2011), a feature which may be via IFN-γ dependent or IFN-γ independent IDO1 induction (Campbell et al., 2014). The translational relevance of these findings is bolstered by knowledge that in IBS, there is evidence of low-grade immune activation that is associated with gut microbiota alterations (Kennedy et al., 2014b) and increased kynurenine pathway metabolism (Clarke et al., 2009a; Clarke et al., 2012b; Fitzgerald et al., 2008). Interestingly, TLRs are also expressed in the CNS (Kigerl et al., 2014) where they play a role, for example, in visceral pain following chronic stress (Tramullas et al., 2014) and the TLR3 ligand poly(I:C) induces the expression of IDO in human astrocytes (Suh et al., 2007).

The aryl hydrocarbon receptor also serves as a sensor to pick up exogenous and endogenous stimuli and to subsequently modulate the immune response (Julliard et al., 2014). Activation of aryl hydrocarbon receptor facilitates host-microbe homeostasis and indole produced from tryptophan by microbes is an important ligand for this transcription factor (Hubbard et al., 2015). Although kynurenine has been regarded as an inert precursor to downstream neuroactive agents, it also activates the aryl hydrocarbon receptor (Julliard et al., 2014; Kawasaki et al., 2014; Nuti et al., 2014; Opitz et al., 2011). Meanwhile, aryl hydrocarbon

receptor itself plays a role in the regulation of IDO and TDO expression (Bessede et al., 2014; Jaronen and Quintana, 2014). This complex crosstalk is an important example of the interface between the gut microbiota, kynurenine pathway metabolism and the immune response. Interestingly, in the absence of aryl hydrocarbon receptor receptors, studies in mice indicate that endogenous kynurenic acid levels are increased (Garcia-Lara et al., 2015) while kynurenine mediates aryl hydrocarbon receptor activation in the brain after experimental stroke (Cuartero et al., 2014). In addition, it has recently been demonstrated that astrocyte activity and CNS inflammation is modulated by Type I interferons and tryptophan metabolites, via the aryl hydrocarbon receptor (Rothhammer et al., 2016) and administration of a aryl hydrocarbon receptor agonist attenuates intestinal inflammation in a preclinical mouse model of colitis (Lamas et al., 2016)

Alternatively, microbial metabolites such as SCFAs can impact on intestinal barrier integrity and the systemic inflammation arising from increased intestinal permeability could also lead to alterations in kynurenine pathway metabolism (Kelly et al., 2015b; Tilg and Moschen, 2015). Given the compartmentalisation of the different arms of kynurenine pathway metabolism between microglia and astrocytes in the CNS, it is also interesting to note recent observations that the gut microbiota acts to regulate microglia maturation and function (Erny et al., 2015). However, to date, to our knowledge, kynurenine pathway metabolites in the CNS have not been reported in studies of microbiota-deficient animals. Interestingly, mice infected with *Toxoplasma gondii* do have elevated levels of kynurenine, kynurenic acid, 3-hydroxykynurenine and QUIN in the brain (Notarangelo et al., 2014) and reactivation of *Toxoplasma gondii* is associated with activation of brain IDO, likely via IFN-γ dependent mechanisms (Mahmoud et al., 2016).

8. Preclinical evidence supporting a role for the gut microbiota in regulating the availability of tryptophan for kynurenine metabolism

The link between the availability of tryptophan metabolism for kynurenine metabolism and the composition of the gut microbiota is underlined by a number of different preclinical approaches. Firstly, using both targeted and unbiased analysis in GF animals, it has been demonstrated that circulating total tryptophan levels are increased in the absence of a gut microbiota (Clarke et al., 2013; El Aidy et al., 2012a; Mardinoglu et al., 2015; Wikoff et al., 2009). Despite increased circulating tryptophan availability, both kynurenine pathway metabolism and circulating serotonin concentrations are decreased (Clarke et al., 2013; Wikoff et al., 2009). This is consistent with the observation that gastrointestinal serotonin synthesis, which modulates circulating levels, is driven by microbial metabolites such as SCFAs or tryptophan-derived indole metabolites (Reigstad et al., 2015; Yano et al., 2015). Antibiotic-induced microbiota depletion from weaning onwards also increases circulating tryptophan availability and reduces peripheral kynurenine pathway metabolism (Desbonnet et al., 2015). Importantly, colonisation of GF animals post weaning normalises circulating tryptophan availability and kynurenine pathway metabolism (Clarke et al., 2013; El Aidy et al., 2012b). More subtle microbiota manipulations such as deliberate infection with *Trichuris muris*, also increases the kynurenine/tryptophan ratio (Bercik et al., 2010).

The majority of preclinical studies to date have focused on total circulating tryptophan levels with less attention given to the dynamics of tryptophan flux down the kynurenine pathway, including the assessment of free tryptophan levels (Badawy, 2015a). Nevertheless, it is clear that total tryptophan concentrations inform the equilibrium with free tryptophan and many consider total tryptophan to be important for brain tryptophan uptake (Fernstrom and Fernstrom, 2006). Circulating levels of many of the amino acids which compete with tryptophan for transport across the BBB such as tyrosine, phenylalanine, isoleucine and

valine are also increased in GF animals (Mardinoglu et al., 2015; Wikoff et al., 2009). Despite this, it is interesting to note that increased circulating total tryptophan levels do result in increased hippocampal serotonin concentrations in GF animals (Clarke et al., 2013). It remains to be seen if the reduced circulating availability of kynurenine associated with a gross microbiota deficiency is reflected in alterations in CNS kynurenine and downstream metabolites.

These preclinical studies to date have spurred interest in whether targeting the gut microbiota might be a viable strategy to influence circulating tryptophan availability for kynurenine metabolism in the periphery and CNS. In this context, administration of *B. infantis* to rodents increased tryptophan concentrations, reduced onward tryptophan metabolism to kynurenine and increased circulating kynurenic acid concentrations (Desbonnet et al., 2008). Administration of *L. johnsonii* to rats also resulted in a reduction in serum kynurenine concentration, a result associated with the ability of *L. johnsonii* to reduce IDO activity in vitro in HT-29 intestinal epithelial cells, possibly by increasing hydrogen peroxide production (Freewan et al., 2013; Valladares et al., 2013). Achieving functional outcomes by translating current preclinical microbiota findings to a precision approach for microbial regulation of kynurenine production in human subjects is a challenge that now needs to be embraced.

9. Microbial regulation of CNS receptors, Neurogenesis and Myelination

One of the remarkable features of the gut microbiota is the impact on gene expression in the CNS as indicated, for example, by studies in GF animals (Diaz Heijtz et al., 2011; Stilling et al., 2015c). This includes GABA receptor expression in the amygdala following ingestion of *L. rhamnosus* (Bravo et al., 2011) and 5-HT_{1A} receptor expression in the hippocampus under GF conditions (Neufeld et al., 2011). The intersection between the pharmacodynamic interactions of kynurenine pathway metabolites and those CNS receptor subtypes whose

expression is influenced by the gut microbiota is narrow at present but potentially important. For example, studies have indicated that NMDA receptor subunit NR_{2B} mRNA expression is decreased in the central amygdala of germ-free mice (Neufeld et al., 2011). Moreover, NR1 subunit expression in the hippocampus was increased following prebiotic supplementation (Savignac et al., 2013). However, an alternative prebiotic did not alter CNS NDMA receptor expression in the frontal cortex (Savignac et al., 2015) and further studies are required to demonstrate that deliberate effects on relevant receptors can be achieved with other interventions such as probiotics.

Studies demonstrating that the gut microbiota can influence cognitive function, anxiety and depressive-like behaviour in animals should be appreciated in the context that adult hippocampal neurogenesis is under microbial influence (Möhle et al., 2016; Ogbonnaya et al., 2015). However, it is not yet apparent whether this has any consequences for discrete populations of neurons that provide the interface between endogenous kynurenine pathway neuroactives and glutamatergic, and cholinergic neurotransmission. In addition, recent preclinical evidence using different approaches demonstrating that the gut microbiota regulate myelination in the prefrontal cortex (Gacias et al., 2016; Hoban et al., 2016) further expands the repertoire of CNS functions influenced by gut microbial composition.

10. Microbial regulation of features relevant to CNS tryptophan and kynurenine pathway metabolism

Both the regulation of circulating tryptophan availability and distribution and subsequent kynurenine pathway metabolism in the periphery and CNS, is tightly regulated during all stages of life (Badawy, 2015a, b; Ruddick et al., 2006). This is desirable, especially in the context of having checks and balances in place for the control of CNS availability of neuroactive metabolites with such a broad pharmacodynamic impact (Muller and Homberg, 2015; Schwarcz et al., 2012). From a pharmacokinetic perspective, there are recent

indications that the gut microbiota impacts not just the availability of circulating tryptophan and kynurenine but also has the potential to modulate their distribution and subsequent CNS fate. For example, under normal circumstances tryptophan and kynurenine enter the CNS via the LNAA transporter (Ruddick et al., 2006). kynurenic acid and quinolinic acid are not considered to cross the BBB in appreciable quantities (Schwarcz et al., 2012). However, the integrity of the BBB may be contingent on the gut microbiota (Braniste et al., 2014) such that the brain appears more accessible in germ-free animals. Similarly, the metabolic fate of kynurenine reaching the CNS is influenced by microglia (See **Figure 3** (Schwarcz and Pellicciari, 2002)), whose maturation and function is defective in the absence of a gut microbiota (Erny et al., 2015). As indicated above, microbially-derived indole metabolites of tryptophan can also act via astrocytes to influence CNS inflammation (ref). In all instances, it remains to be demonstrated that less-extreme microbiota-based manipulations can be successfully applied to either improve BBB integrity, or influence the neurobiological consequences of microglialactivation states or astrocyte function. Nevertheless, understanding the role of the gut microbiota in regulating the fluctuation of kynurenine metabolite distribution to the CNS as well as their subsequent metabolic fate might yield some interesting insights to expedite the therapeutic opportunities arising from compartmentalisation of kynurenine pathway metabolism in the CNS.

****************************Insert Figure 3 Here********************************

11. Microbial metabolism of tryptophan and the impact of microbial metabolites generated from tryptophan on host physiology

The metabolic transformation of tryptophan by bacteria is an important but neglected feature which might be important in microbial regulation of circulating tryptophan availability to the host for kynurenine pathway metabolism in the periphery and CNS. Most tryptophan

supplied for bacterial metabolism in the colon comes in the form of undigested protein and the major metabolite is indole (Berstad et al., 2015). Indole production by bacteria is catalysed by tryptophanase, an enzyme not present in eukaryotic cells (Scherzer et al., 2009). Indeed, tryptophan itself can be synthesised via the shikimic acid pathway in bacteria and plants (Maeda and Dudareva, 2012; Martinez et al., 2015) with the last two steps of bacterial tryptophan biosynthesis catalysed by tryptophan synthase (Raboni et al., 2009; Yanofsky, 2007). Given that tryptophan synthesis is energetically expensive for cells and that it is usually readily available via dietary proteins (Priya et al., 2014), the evolutionary loss of this feature in mammals is understandable. The exact contribution of bacterial tryptophan synthetic pathways to circulating levels is unclear.

The consequences for the host of tryptophan-derived indoles are varied and include an impact on oxidative stress, intestinal inflammation, and hormone secretion (Lee and Lee, 2010; Lee et al., 2015). Indoles produced by bacteria also have a beneficial impact on intestinal epithelial cells by acting to strengthen the mucosal barrier (Bansal et al., 2010). Recently, it has been demonstrated that these indole metabolites can promote gastrointestinal serotonin synthesis from tryptophan (Yano et al., 2015), a feature shared with other microbial metabolites such as SCFAs (Reigstad et al., 2015). It is likely then that the increase in circulating tryptophan availability arises at least partially as a consequence of the interaction between microbial metabolites and the host. Interestingly, bacteria are responsive to psychotropic drugs acting on the serotonergic system, such as selective serotonin reuptake inhibitors (Munoz-Bellido et al., 2000). The might be related to the ability of drugs like tricyclic antidepressants to bind to LeuT, a bacterial homologue of neurotransmitter transporters (Henry et al., 2007; Singh et al., 2007).

Our gut bacteria synthesise a variety of neuroactive agents recognised by the host and this includes the use of tryptophan to generate serotonin (Clarke et al., 2014b). They can also

produce kynurenic acid which is present in rat small intestine at micromolar concentrations where it could activate the GPR35 receptor (Kuc et al., 2008). This is possibly due to the bacterial enzyme aspartate aminotransferase (AspAT) which is capable of the transamination of kynurenine and 3-HK to kynurenic acid (Han et al., 2001). In bacteria, quinolinic acid can be produced from aspartate (Begley et al., 2001). Although it was thought that the tryptophan to quinolinic acid was unique to eukaryotes, analyses of bacterial genomes have identified TDO, kynurenine-3-monooxygenase, kynureninase, kynurenine formamidase and 3-hydroxyanthranilate-3,4-dioxygenase homologs (Kurnasov et al., 2003a; Kurnasov et al., 2003b). In bacteria, kynureninase acts directly on l-kynurenine to produce anthranilate and l-Ala (Phillips, 2011).

In addition to the examples mentioned above, bacteria can also use tryptophan to produce multiple other bioactive products with diverse properties (Alkhalaf and Ryan, 2015). The major direct microbial influence then on circulating availability of tryptophan, assuming an adequate dietary supply of this essential amino acid, likely arises as a result of bacterial tryptophan utilisation and metabolism and the impact of microbial metabolites on host serotonergic production. This raises the possibility, for example, that the reduced diversity of the gut microbiota in disease states could contribute to fluctuating levels of tryptophan and kynurenine. Moving forward, it will be important to establish which specific members of the bacterial consortium are most important for this function.

12. Behaviours influenced by the gut microbiota and tryptophan metabolites

As outlined above, the gut microbiota has been shown to influence an array of behaviours in preclinical, and to a lesser degree, clinical studies, many of which are also influenced by the 5-HT system (Berger et al., 2009). Over recent years, the influence of kynurenine pathway metabolites on brain function and behaviour has been the focus of increasing investigation

(Schwarcz et al., 2012; Stone and Darlington, 2013). Despite methodological difficulties in definitively linking the gut microbiota, tryptophan metabolism and behaviour, it is clear there is significant overlap in behaviours under microbial influence and those modulated by neuroactives derived from tryptophan (Berger et al., 2009; O'Mahony et al., 2015a). This includes depression and anxiety, as well as cognitive performance, social behaviours and visceral pain perception (McKernan et al., 2010; Moloney et al., 2016; Muller et al., 2015; Nestler et al., 2002; O'Mahony et al., 2014; Schwarcz et al., 2012). Early neurodevelopmental programming by the gut microbiota has become a topic of significant interest. Moreover, the prenatal period represents an important period during which the gut microbiota could be targeted for improved health outcomes (Clarke et al., 2014a). There are now strong indications that variable kynurenine pathway metabolism during the first 1000 days of life could have important neurodevelopmental implications. Prenatal inhibition of the kynurenine pathway in rats produces changes in hippocampal neuron morphology as well as differences in neocortical and cerebellar protein expression which persist into adulthood (Khalil et al., 2014; Pisar et al., 2014). Conversely, increases in brain kynurenic acid in rats following dietary exposure to kynurenine during gestation and postnatal development also results in neurochemical and cognitive deficits in adulthood (Alexander et al., 2013; Pershing et al., 2015; Pocivavsek et al., 2012). This corresponds to a time period during pregnancy in which the maternal microbiota undergoes major remodelling (Clarke et al., 2014b) and during early life when the gut microbiota is seeded and undergoes extensive development (Borre et al., 2014; O'Mahony et al., 2015b). It is plausible that many of the detrimental effects of disturbances in the assembly of the infant microbiota (mode of birth, antibiotic use, maternal transmission of a suboptimal microbiota) could be mediated at least partially via aberrant microbially-regulated patterns of circulating tryptophan availability and kynurenine metabolism in the periphery and CNS. In parallel, this is also a vulnerable period of both

CNS glutamatergic and serotonergic system development (Golubeva et al., 2015b; Haberny et al., 2002; O'Mahony et al., 2015a; O'Mahony et al., 2015b). Marrying these research themes together is an important research objective and could inform the mechanisms through which interventions aimed at counteracting the detrimental impact of early-life microbiota disturbances produce their effects.

13. The importance of tryptophan supply and availability in neurogastroenterology

Tryptophan metabolism along kynurenine pathway has important implications for neurogastroenterology due to the dual effects of kynurenine and downstream metabolites in GI and CNS function, and thus brain-gut axis signalling. IBS is the best characterised microbiota-gut-brain axis disorder and there is evidence for immune related tryptophan metabolism along the kynurenine pathway (Clarke et al., 2012b; Clarke et al., 2009c; Keszthelyi et al., 2013), which has been linked to the severity of GI symptoms (Fitzgerald et al., 2008). IBS is commonly co-morbid with mood and anxiety problems, which may reflect a dual effect of altered tryptophan metabolism on GI and CNS function in the disorder (Clarke et al., 2012b; Clarke et al., 2009b; Fitzgerald et al., 2008). This is supported by the finding that mucosal kynurenic acid and 5-HT levels correlated with self-reported anxiety and depression scores in patients with IBS (Keszthelyi et al., 2013).

Acute tryptophan depletion (ATD) is the most common clinical method to determine the impact of manipulating peripheral levels of tryptophan on CNS and ENS function, and has been utilised to investigate brain-gut axis communication in healthy control participants and individuals with IBS (Kilkens et al., 2005; Kilkens et al., 2004; Labus et al., 2011; Shufflebotham et al., 2006). Systemic free tryptophan competes with all other large neutral amino acids (LNAAs; valine, leucine, isoleucine, methionine, phenylalanine and tyrosines) for transportation across the BBB (Silber and Schmitt, 2010) where once across, it is

subsequently synthesised into a variety of agents including kynurenine via specific metabolic processes. As such, ATD is based on the premise that by reducing the plasma tryptophan to LNAA ratio, the rate of tryptophan subsequently crossing the BBB for further metabolism is also reduced (Hood et al., 2005). As tryptophan is an essential amino acid, ATD is normally achieved by administering an amino acid mix to study participants that contains a large amount of all other LNAAs, but lacks tryptophan. Despite a predominant focus on the effects of ATD on serotonin, this specificity has often come into question over the years and alternative mechanisms mediating the central and peripheral effects of ATD have been speculated upon (van Donkelaar et al., 2011). In support of an alternative/additional mechanism of action, it has been demonstrated in healthy control participants that ATD increases plasma kynurenic acid (Keszthelyi et al., 2012) and decreases plasma kynurenine levels in both healthy controls and female patients with IBS (Kennedy et al., 2015). Of note, ATD concurrently improved visuospatial memory performance in patients with IBS (Kennedy et al., 2015), which has previously been shown to be impaired in this clinical population (Kennedy et al., 2014a). Moreover, an intriguing study further demonstrated that the brain response to visceral pain stimulation in healthy females following ATD reflected the brain response in patients with IBS who underwent the same visceral pain stimulation, but not ATD (Labus et al., 2011). Together these studies lend further support for altered tryptophan metabolism in brain-gut axis dysregulation in IBS.

Finally, although not generally considered a brain-gut axis disorder, mood and anxiety problems are common in IBD (Casellas et al., 2002) which may be linked to inflammatory mediated tryptophan metabolism along the kynurenine pathway (Forrest et al., 2003; Forrest et al., 2002). As such there is increasing interest in how dysregulated brain-gut communication impacts on peripheral and central symptoms in IBD (Bernstein et al., 2010; Bonaz and Bernstein, 2013).

Taken together, targeting the kynurenine pathway in brain-gut axis disorders such as IBS may prove beneficial; however, the basic functions of kynurenine pathway metabolites, particularly in the ENS, have yet to be fully delineated.

14. Perspectives and conclusions

One of the important implications of our discussion to date is that the gut microbiota might be a tractable target to regulate circulating tryptophan availability and kynurenine pathway metabolism in the periphery and CNS across the lifespan, either via direct or indirect mechanisms. For example, restoring intestinal permeability via the gut microbiota might be an important point of control (Kelly et al., 2015b). Similarly, promoting gut microbiota diversity during old age might improve health outcomes by mitigating the detrimental impact of aging on the CNS, which could in part be mediated via the kynurenine pathway (Claesson et al., 2012; Oxenkrug, 2007; Prenderville et al., 2015). Regulation of the stress response via the gut microbiota could also be a viable strategy where the underlying pathophysiology favours TDO activation (Dinan and Cryan, 2012).

There is much interest in the minute regarding the possible wider application of faecal microbiota transplant beyond its use for the treatment of *Clostridium difficile* infection (Kelly et al., 2015a; Shanahan and Quigley, 2014). In the preclinical literature, the adoptive transfer of behavioural phenotypes via the gut microbiota is a fascinating area of research whose translational relevance needs to be established (Collins et al., 2013). This could have implications for broadening the remit of faecal microbiota transplants and it remains to be demonstrated that transfer of a microbiota profile associated with activated kynurenine pathway metabolism can manifest in the host as a similar physiological profile. The flip side of the coin of course is whether this strategy could be exploited to restore normal levels of kynurenine metabolism. In any case, less controversial options for beneficially manipulating

the microbiota are likely to emerge and early studies in rodents suggest that probiotics might be an option (Desbonnet et al., 2008). Developing 'psychobiotics' with precise kynurenine modulating capabilities could be an interesting option in this regard (Dinan et al., 2013). Of course, diet plays a major role in shaping the gut microbiota (Dinan and Cryan, 2015; Goyal et al., 2015) and may provide a means to sculpt aspects of kynurenine pathway metabolism. There are recent indications that a more nuanced approach might need to be considered with this approach as taxa that are missing from a low diversity gut microbiota are unlikely be restored by supplementation with fiber alone (Sonnenburg et al., 2016).

In conclusion, fluctuating levels of kynurenine pathway metabolites are associated with numerous neuropsychiatric and gastrointestinal disorders. New and emerging research implicates the gut microbiota in the regulation of circulating tryptophan availability and downstream kynurenine pathway metabolism in the periphery and CNS. Integrating these observations suggests that novel interventions targeting the gut microbiota might be exploited to restore pathway equilibrium and improve mental health outcomes. This research stream is at an early stage and the best method and time of intervention remains a matter of debate and requires extensive elaboration on the key bacterial players, including their relevant metabolic outputs. This will markedly increase our understanding of how the gut microbiota shapes brain and behaviour and provide new insights towards successful translation of microbiotas-gut-brain axis research from bench to bedside.

Acknowledgements

The APC Microbiome Institute is funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan (SFI grant number SFI/12/ RC/2273). This review is specifically supported by a Health Research Board Health Research Award (Grant number HRA-POR-2014-64) G.C. is also supported by a NARSAD Young Investigator Grant from the Brain and Behavior Research Foundation (Grant Number 20771). P.J.K., T.D. and J.F.C. are also funded by the European Community's Seventh Framework Programme (MyNewGut, FFP7- KBBE/2013–2018, grant agreement no 613979). The APC has conducted studies in collaboration with several companies including GSK, Pfizer, Wyeth, and Mead Johnson.

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Figures

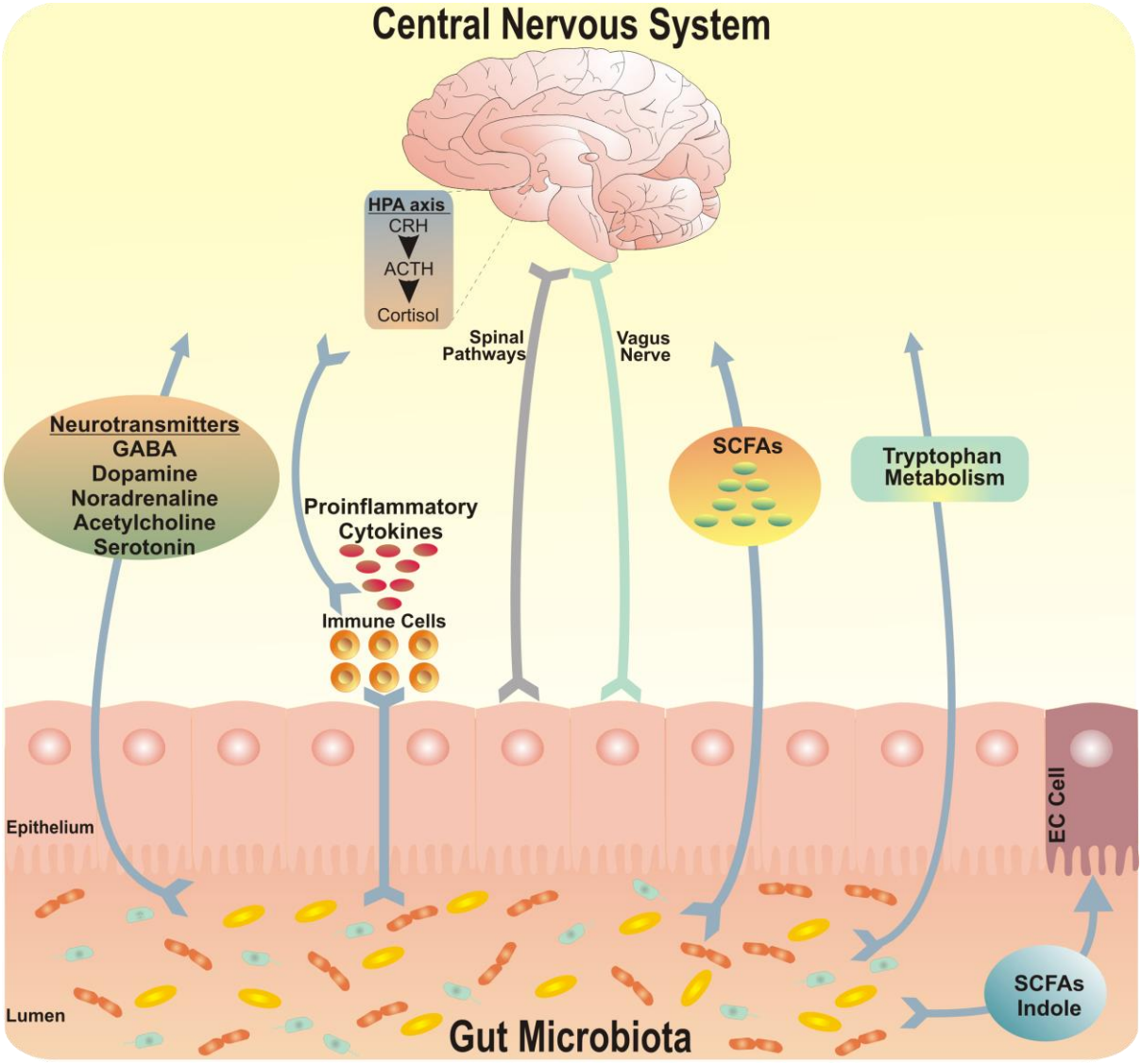

Figure 1. Microbiota -gut-brain axis. The gut microbiota can signal to the brain via a number of pathways which include, regulating immune activity and the production of proinflammatory cytokines that can either stimulate the HPA axis to produce CRH, ACTH and cortisol, or directly impact on CNS immune activity; through the production of SCFAs such as propionate, butyrate, and acetate; the production of neurotransmitters which may enter circulation and cross the blood brain barrier; by modulating tryptophan metabolism and downstream metabolites, serotonin, kynurenic acid and quinolinic acid. Neuronal and spinal pathways, particularly afferent signalling pathways of the vagus nerve, are critical in mediating the effect of the gut microbiota on brain function and behaviour. Microbial produced SCFAs and indole also impact on EC cells of the enteric nervous system. **Abbreviations:** ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; EC, enterochromaffin cells; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; SFCAs, short-chain fatty acids.

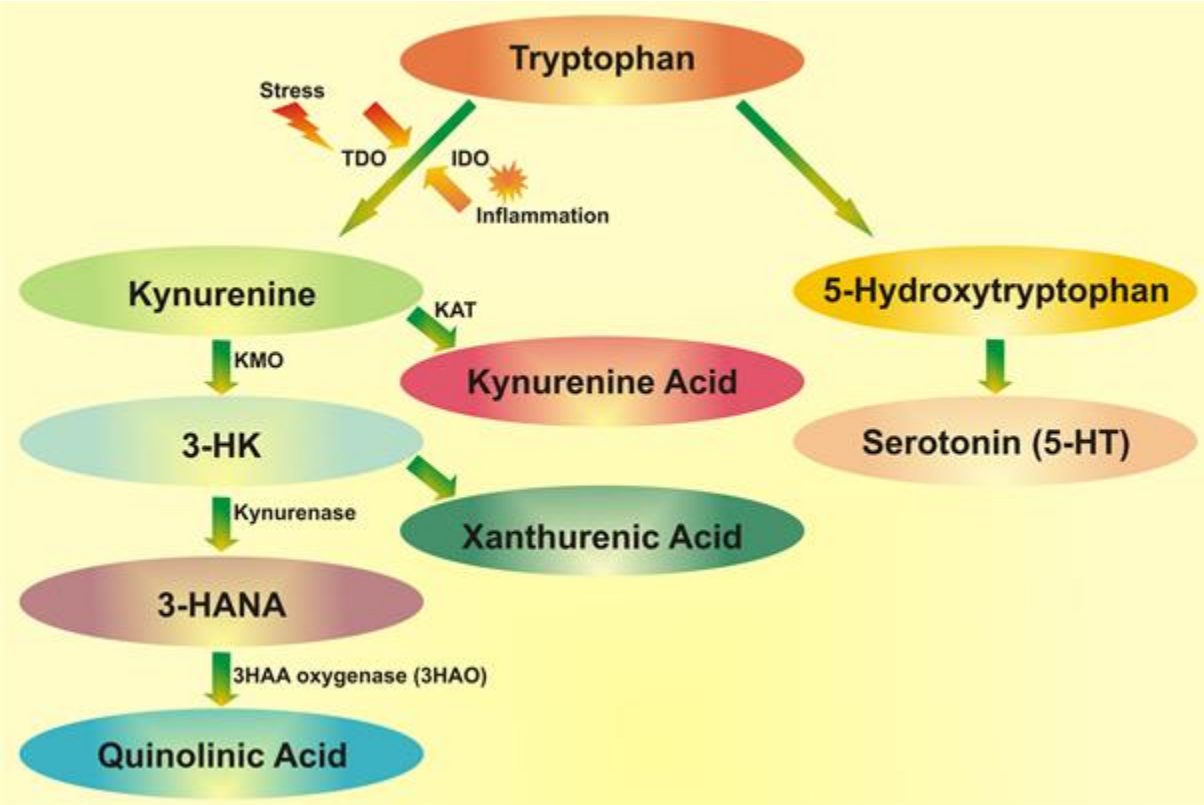

Figure 2. Tryptophan Metabolism. Tryptophan metabolism along the kynurenine pathway is dependent on indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). The expression of IDO and TDO can be induced by stress elevated glucocorticoid levels or inflammatory cytokines, respectively. Once formed, KYN proceeds along two different branches of the pathway, one leading to QUIN production and one to KYNA production. **Abbreviations:** KAT, kynurenine aminotransferase; KMO, Kynurenine 3-monooxygenase; 3HAA, 3-hydroxyanthranilic acid oxygenase; 3-HANA, 3-hydroxyanthranilic acid; QUIN, quinolinic acid; KYNA, kynurenic acid.

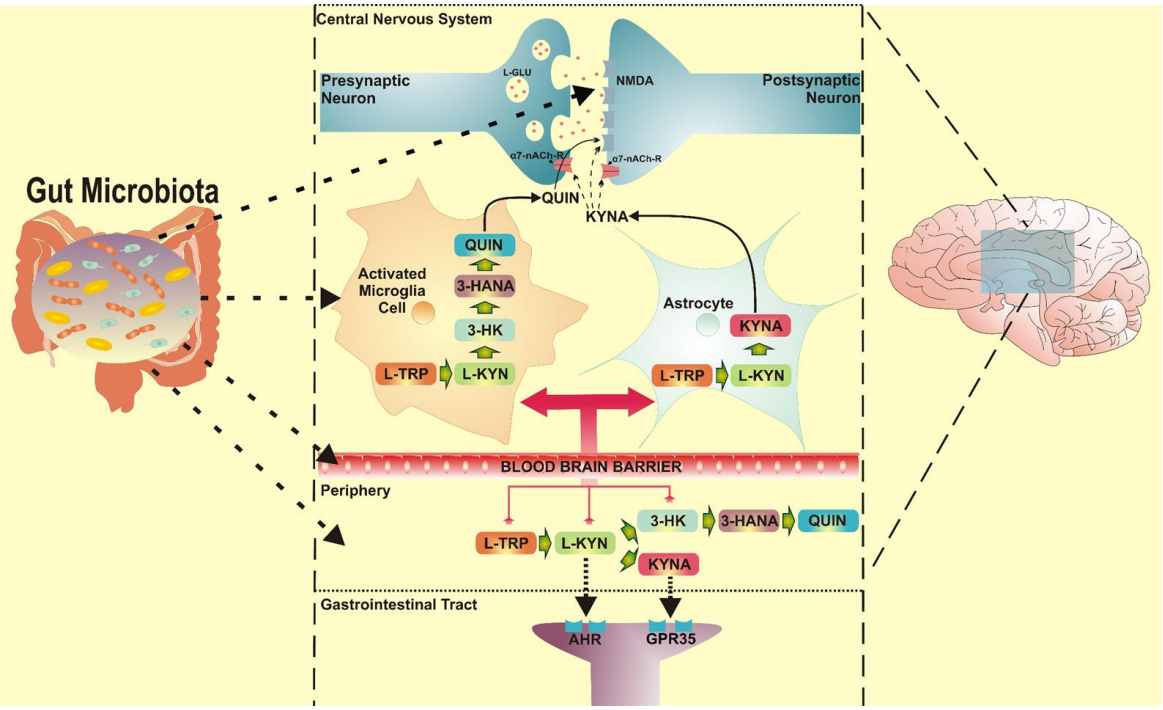

Figure 3. The impact of the gut microbiota on critical points of control in kynurenine pathway metabolism. The gut microiota may regulate the circulating availability of both tryptophan and kynurenine for onward CNS metabolism as well as peripheral KYNA levels. Kyn and KYNA can activate GI AHR and GPR35 receptors respectively. Normally KYNA and QUIN do not cross the BBB in appreciable quantities. However, under germ-free conditions, the BBB is more permeable suggesting a mechanism through which these metabolites might cross more readily following gut microbiota manipulation. In the CNS, the gut microbiota can influence microglia cells to regulate QUIN production. QUIN is an excitotoxic NMDA receptor agonist and KYNA a NMDA receptor antagonist. NMDA receptor expression in the CNS is also regulated by the gut microbiota. Taken together, this suggests that the gut microbiota can potentially influence both the pharmacokinetic and pharmacodynamics of kynurenine pathway metabolism. **Abbreviations**: α-7-nACh-R, alpha-7-nicotinic-acetylcholine receptor; AHR, aryl hydrocarbon receptor; GI, gastrointestinal; BBB, blood brain barrier; CNS, central nervous system; GPR35, G-protein coupled receptor 35; KYNA, kynurenic acid; L-GLU, L-glutamine; L-KYN, kynurenine; L-TRP, L-tryptophan; NMDA, N-methyl-D-aspartate; QUIN, quinolinic acid; 3-HK, 3-hydroxykynurenine.