Neuropharmacology 112 (2017) 399–412

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Kynurenine pathway metabolism and the microbiota-gut-brain axis

P.J. Kennedy [a, b], J.F. Cryan [a, c], T.G. Dinan [a, b], G. Clarke [a, b, *]

[a] Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland
[b] APC Microbiome Institute, University College Cork, Cork, Ireland
[c] Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland

ARTICLE INFO

Article history:
Received 23 February 2016
Received in revised form
30 June 2016
Accepted 4 July 2016
Available online 5 July 2016

Keywords:
Tryptophan
Kynurenine
Stress
Immune system
Microbiota-gut-brain-axis
Behaviour

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. Here, 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 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. Targeting the gut microbiota represents a tractable target 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.

This article is part of the Special Issue entitled 'The Kynurenine Pathway in Health and Disease'.

Contents

Abbreviations: BBB, blood brain barrier; CNS, central nervous system; DSM, diagnostic and statistical manual; ENS, enteric nervous system; 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; mRNA, messenger Ribonucleic acid; NMDA, *N*-methyl-D-aspartate; SCFAs, short-chain fatty acids; TDO, tryptophan-2,3-dioxygenase; TLRs, toll-like receptors; 5-HT, serotonin; 16S rRNA, ribosomal Ribonucleic acid.

* Corresponding author. 1.15, Biosciences Institute, University College Cork, Cork, Ireland.
E-mail address: g.clarke@ucc.ie (G. Clarke).

http://dx.doi.org/10.1016/j.neuropharm.2016.07.002
0028-3908/

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 (GI) 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 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 resemble 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