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Review

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

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HIGHLIGHTS

- 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.

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ABSTRACT

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 serotonergic 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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1. 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 system and disease [1–3]. 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 implicates 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), 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]. Recently, it has become clear that the gut microbiome is a critical component of this axis and one which exerts control at multiple levels, not just locally in the gastrointestinal tract [7–10]. Using a variety of preclinical strategies, it has been established that manipulating the composition of the gut microbiota 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 microbiota in serotonergic signalling at the level of the CNS. There is also a substantial overlap between many of the behaviours underpinned by serotonergic signalling and those which are influenced by alterations in the composition, diversity or stability of the microbiota. 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 serotonin 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 neurodevelopmental time windows discussed. The potential consequences across a number of relevant behavioural domains, including pain, depression, anxiety and cognition, are emphasised and we also consider 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.

2. Serotonin synthesis and tryptophan metabolism

A detailed description of serotonin synthesis from tryptophan and the myriad other synthetic pathways beholden to the availability of tryptophan as a precursor are beyond the scope of this review and readers are referred to more detailed descriptions for further information [11]. Tryptophan is an essential amino acid which must be supplied in the diet [3]. This is normally as a constituent of protein [12] 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]. Once absorbed from the gut and made available in the circulation, where it exists in both a free and albumin-bound fraction [14], it can cross the blood-brain-barrier (BBB) via the large amino acid transporter to participate in serotonin synthesis in the CNS [11]. However, the vast majority of serotonin is located in the gut where it is synthesised from tryptophan in the enterochromaffin cells (ECs) of the gastrointestinal tract and is also present in enteric nerves [6,15,16].

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