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Microbiome in brain function and mental health

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ABSTRACT

Background: Over recent years it has become evident that the physiological influence of the gut microbiota extends beyond the periphery to the central nervous system (CNS). Current data derived from preclinical studies indicate that the gut microbiota can influence CNS function. Despite limited attempts to translate these findings to clinical populations, emerging evidence suggests that alterations in the composition of the gut microbiota, across the lifespan, may have a fundamental role in the pathophysiology of a number of mental health disorders. Moreover, accumulating evidence demonstrates the central role of food consumed in programming gut microbiota composition, diversity and functionality throughout life.

Scope and approach: In this review, we outline what is considered a healthy infant and adult gut microbiota composition followed by describing how the gut microbiota can influence the CNS via signalling pathways of the microbiota-gut-brain axis. Current findings from preclinical investigations, observation and intervention studies in humans, indicating the gut microbiota in brain function and mental health are reviewed. Finally, we consider microbiota-targeted functional food interventions with potential application in promoting normal brain function.

Key findings and conclusions: Much work is yet to be performed in determining the role of the gut microbiota in brain function and behaviour in human populations. Nevertheless, the potential for microbiota-targeted functional food interventions is evident. As new findings emerge in this rapidly developing field, it is envisaged that a greater understanding of microbe-brain interactions will herald a new era of psychotropic therapies to promote normal brain function and mental health.

1. Introduction

Although a key role for gut bacteria (the gut microbiota) in specific aspects of health and disease, such as regulating immune function and metabolic activity, has been recognised for some time (Sampson & Mazmanian, 2015), only recently has it become apparent that the physiological influence of the microbiota extends beyond the periphery to the central nervous system (CNS). Clinically, the phenomenon of hepatic encephalopathy which, in the extreme, is characterised by dementia like symptoms that can be ameliorated by treatment with antibiotics (Strauss & da Costa, 1998), is often cited as a unique example of how perturbing the microbiota can influence brain function. It has also long been recognised that the acute phase reaction to microbial infection is accompanied by a number of neuro-immune mediated behavioural symptoms such as depressed mood and cognitive impairment (Dantzer, 2009). However, the realisation that not only pathogenic microorganisms, but the commensal/symbiotic gut bacteria can influence CNS activity, has have led to a '*Paradigm Shift*' in brain and behavioural research (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). Moreover, recent discoveries in microbe-brain interactions have revolutionised our approach to investigating psychopathology, and spurred the development of microbiota-targeted interventions (psychobiotics) which hold great potential as a new therapeutic approach in mental health disorders (Dinan, Stanton, &

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Cryan, 2013).

In this review, we first provide an outline of what is, conceptually, considered a healthy infant and adult gut microbiota composition, followed by a description of the key pathways by which the gut microbiota signal to the brain to influence brain function and behaviour. Next, we review current evidence demonstrating a role for the gut microbiota in brain function and mental health, incorporating both preclinical and clinical studies. Finally, we discuss potential food-based microbiota-targeted approaches which have shown promise or have potential in the management of mental health.

2. Healthy gut microbiota composition

Despite large variation in composition between healthy individuals due to a variety of environmental, physiological, genetic and psychological factors, a 'core' or 'normal' gut microbiota composition is emerging, and despite large taxonomic diversity between individuals, colonization trends can be observed in both infants and adults.

Until recently, it was assumed that the infant gut was colonised during delivery, either from contact with the vaginal and faecal bacteria from the mother during standard vaginal delivery (SVD) or, in the case of caesarean section (CS) delivery, from the hospital environment and maternal skin microbes (Borre et al., 2014). However, it has become apparent that this is not the case, as it has been reported that low counts of bacteria can be isolated from the amniotic fluid, placenta and meconium of healthy new-borns before breast-feeding (Rodríguez et al., 2015). Culture based studies have shown that at birth the healthy infant gut is initially colonised by facultative anaerobes such as Enterobacteriaceae, and once oxygen has been depleted and an anaerobic environment is present, strict anaerobes such as *Bifidobacterium* and *Bacteroides* appear (Adlerberth & Wold, 2009). Recently, improvements in 16S rRNA sequencing have led to a more accurate description of the gut microbiota composition, inclusive of the substantial number of unculturable bacteria found in the gut. In healthy, vaginally delivered infants, the most prevalent initial bacterial groups include *Staphylococcus*, *Lactobacillus*, Enterobacteriaceae and *Bifidobacterium,* followed by later increases in the abundance of *Veillonella* and *Lachnospiraceae* and a decline in *Staphylococcus* (Palmer, Bik, DiGiulio, Relman, & Brown, 2007). During infancy, the composition of the gut microbial community is unstable and dynamic and undergoes a variety of changes before resembling an adult gut microbiota at approximately two years of age, after the introduction of solid foods (Borre et al., 2014).

What constitutes a 'healthy gut microbiota' in adults is not entirely clear and indeed may be person specific. Nevertheless, many advances have been made in defining a healthy phylogenetic core, which have led to a consensus that the healthy adult gut is dominated by Firmicutes, Bacteroidetes, Actinobacteria, and Verrucomicrobia (Human Microbiome Project Consortium, 2012). Within these phyla, there is still large inter-individual diversity, with each person harbouring a unique microbiota profile.

It has been proposed that the gut microbiota can be categorised into three core clusters or enterotypes (Arumugam et al., 2011). These are broad clusters which are defined by the presence of a particular bacterial genus - *Bacteroides*, *Prevotella* or *Ruminococcus.* However, this approach to defining the gut microbiota composition is the subject of ongoing debate, and is questionable when considering that over the course of year, a healthy individual's microbiota can vary between clusters and is not strictly defined within one enterotype (Knights et al., 2014). Alternatively, rather than a taxonomic core, the composition may be viewed as a core set of functional profiles, in which some key bacterial species may contribute significantly to the functional profile, and play an important role in health and disease (Flint, Scott, Louis, & Duncan, 2012).

A range of factors are known to disrupt the infant and adult gut microbiota composition, which have been extensively reviewed elsewhere (Rodríguez et al., 2015), and include mode of delivery at birth, antibiotic treatment, diet, stress, infection and host genetics. The extent to which each of these factors influences brain function and mental health via disrupting the gut microbiota composition is not entirely clear and is currently an area of intensive investigation. Nevertheless, the following sections integrate current findings in which these factors are implicated in brain function and behaviour, via interactions with the gut microbiota.

3. The microbiota-gut-brain axis

The microbiota-gut-brain axis is a bi-directional communication network encompassing the central nervous system (CNS), sympathetic and parasympathetic branches of the autonomic nervous system (ANS), the enteric nervous system (ENS), neuroendocrine and neuroimmune pathways, and the gut microbiota (See Fig. 1; (Cryan & Dinan, 2012). A complex reflexive network of efferent fibers projecting to the gastrointestinal (GI) tract and afferent fibers that project to a number of interconnected regions of the CNS facilitate communication within the axis (Dinan, Stilling, Stanton, & Cryan, 2015). Bidirectional communication along neural, hormonal and immune pathways thus enable the brain to influence secretory, sensory, and motor functions of the GI tract, and conversely, signals arising from the viscera to influence CNS activity (Aziz & Thompson, 1998). Although interactions between the brain and enteric nervous system have been the focus of intense study over the past two decades, particularly in the context of functional GI disorders such as irritable bowel syndrome, over recent years there has been growing recognition that the gut microbiota has a dominant influence on signalling along this axis (Cryan & Dinan, 2012; Mayer et al., 2014; Sampson & Mazmanian, 2015).

4. Microbe to brain signalling pathways

4.1. The vagus nerve

The vagus is the major nerve mediating parasympathetic activity of the autonomic nervous system. Vagal afferent sensory neurons relay information from the GI tract to the nucleus of the solitary tract, which projects to the thalamus, hypothalamus, locus coeruleus, amygdala and periaqueductal grey (Aziz & Thompson, 1998). A number of preclinical studies have demonstrated afferent pathways of the vagus nerve are fundamental in mediating the effects of the gut microbiota on brain function and behaviour. For example, in a landmark preclinical study with conventional mice, treatment with the probiotic *Lactobacillus rhamnosus (JB-1)* reduced anxiety and depressive-like behaviour and stress-induced corticosterone levels, however, these behavioural effects were not evident in vagotimized mice (Bravo et al., 2011). Despite the importance of vagal pathways, it must be noted that vagotomy does not mediate all effects of the microbiota on brain function and behaviour (Bercik et al., 2011), and the mechanisms underlying vagal mediated microbiota-brain interactions have not yet been determined (Cryan & Dinan, 2012).

4.2. Microbial regulation of neuro-immune signalling

Bacterial colonization of the gut during early life influences normal development and maturation of the immune system, and across the lifespan, the gut microbiota regulate innate and adaptive immune responses (Shanahan & Quigley, 2014). A recent ground-