# The Microbiome-Gut-Brain Axis in Health and Disease

Timothy G. Dinan, MD, PhD[a,b,*], John F. Cryan, PhD[a,c]

**KEYWORDS**

• Microbiota • Psychobiotics • Short-chain fatty acids • Vagus nerve • GABA • Serotonin

**KEY POINTS**

- Gut microbes can communicate with the brain through a variety of routes, including the vagus nerve, short-chain fatty acids (SCFAs), cytokines, and tryptophan.
- Psychobiotics are bacteria that when ingested in adequate amounts produce a positive mental health benefit.
- The brain-gut-microbiota axis represents a paradigm shift in neuroscience and provides a novel target for treating not only irritable bowel syndrome (IBS) but also conditions, such as depression, autism, and Parkinson disease.

## INTRODUCTION

The human adult gut contains more than 1 kg of bacteria, essentially the same weight as the human brain.[1] It is generally estimated that the gut is inhabited by $10^{13}$ to $10^{14}$ microorganisms, which is significantly more than the number of human cells in the body, and contains more than 100 times as many genes as in the genome.[2] Amazingly, the genomic and biochemical complexity of the microbiota exceeds that of the brain. Studies of the brain-gut-microbiota axis have been described as a paradigm shift in neuroscience.[3] Increasing evidence points to appropriate diversity in the gut microbiota that is essential not only for gut health but also for normal physiologic functioning in other organs, especially the brain. An altered gut microbiota in the form of dysbiosis at the extremes of life, both in the neonate and in the elderly, can have a profound impact on brain function. Such a dysbiosis might emerge for a variety of reasons, including the mode of birth delivery, diet, and antibiotic and other drug exposure. Given that the brain is dependent on gut microbes for essential metabolic products,

[a] APC Microbiome Institute, University College Cork, Cork, Ireland; [b] Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork, Ireland; [c] Department of Anatomy and Neuroscience, University College Cork, Cork, Ireland
* Corresponding author. Department of Psychiatry and Neurobehavioural Science, University College Cork, Cork.
*E-mail address:* t.dinan@ucc.ie

Gastroenterol Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.gtc.2016.09.007
0889-8553/16/

it is not surprising that a dysbiosis can have serious negative consequences for brain function both from neurologic and mental health perspectives. Although much of the early data emerged from animal studies, mainly rodent based, there are now an increasing number of human studies translating the animal findings.

This review focuses on the routes of communication between the gut and brain, examines a prototypic disorder of the brain gut axis, explores the ways in which gut dysbiosis may evolve, and provides an up-to-date account of behavioral and neurologic pathologies associated with dysbiosis.

## BRAIN-GUT-MICROBIOTA COMMUNICATION

The brain-gut-microbiota axis is a bidirectional communication system enabling gut microbes to communicate with the brain and the brain with the gut.[4] Although brain-gut communication has been a subject of investigation for decades, an exploration of gut microbes within this context has only featured in recent years. The mechanisms of signal transmission are complex and not fully elucidated but include neural, endocrine, immune, and metabolic pathways.[5,6] Preclinical studies have implicated the vagus nerve as a key route of neural communication between microbes of the gut and centrally mediated behavioral effects, as demonstrated by the elimination of central *Lactobacillus rhamnosus* effects after vagotomy[7] and that humans who have underwent vagotomy at an early age have a decreased risk of certain neurologic disorders.[8] The gut microbiota also regulates key central neurotransmitters, such as serotonin, by altering levels of precursors; for example, *Bifidobacterium infantis* has been shown to elevate plasma tryptophan levels and thus influence central serotonin (5HT) transmission.[9] Intriguingly, synthesis and release of neurotransmitters from bacteria has been reported: *Lactobacillus* and *Bifidobacterium* spp can produce γ-aminobutyric acid (GABA); *Escherichia*, *Bacillus*, and *Saccharomyces* spp can produce noradrenaline; *Candida, Streptococcus, Escherichia*, and *Enterococcus* spp can produce serotonin; *Bacillus* can produce dopamine; and *Lactobacillus* can produce acetylcholine.[10,11] These microbially synthesized neurotransmitters can cross the mucosal layer of the intestines, although it is highly unlikely that they directly influence brain function. Even if they enter the blood stream, which is by no means certain, they are incapable of crossing the blood-brain barrier (BBB). Their impact on brain function is likely to be indirect, acting on the enteric nervous system. SCFAs, which include butyrate, propionate, and acetate, are essential metabolic products of gut microbial activity and may exert central effects either through G-protein–coupled receptors, although such receptors are sparsely concentrated in the brain. It is more likely that they act as epigenetic modulators through histone deacetylases.[2] SCFAs are also involved in energy balance and metabolism and can modulate adipose tissue, liver tissue, and skeletal muscle and function.[12] Immune signaling from gut to brain mediated by cytokine molecules is another documented route of communication.[13] Cytokines produced at the level of the gut can travel via the bloodstream to the brain. Under normal physiologic circumstances, it is unlikely that they cross the BBB, but increasing evidence indicates a capacity to signal across the BBB and to influence brain areas, such as the hypothalamus, where the BBB is deficient. It is through the latter mechanism the cytokines interleukin (IL)-1 and IL-6 activate the hypothalamic-pituitary-adrenal (HPA) axis, bringing about the release of cortisol. This is the most potent activator of the stress system.

The HPA axis, which provides the core regulation of the stress response, can have a significant impact on the brain-gut-microbiota axis.[14–20] It is increasingly clear and probably of relevance in several pathologic conditions that psychological or physical