Feeding the microbiota-gut-brain axis: diet, microbiome, and neuropsychiatry

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The microbial population residing within the human gut represents one of the most densely populated microbial niche in the human body with growing evidence showing it playing a key role in the regulation of behavior and brain function. The bidirectional communication between the gut microbiota and the brain, the microbiota-gut-brain axis, occurs through various pathways including the vagus nerve, the immune system, neuroendocrine pathways, and bacteria-derived metabolites. This axis has been shown to influence neurotransmission and the behavior that are often associated with neuropsychiatric conditions. Therefore, research targeting the modulation of this gut microbiota as a novel therapy for the treatment of various neuropsychiatric conditions is gaining interest. Numerous factors have been highlighted to influence gut microbiota composition, including genetics, health status, mode of birth, and environment. However, it is diet composition and nutritional status that has repeatedly been shown to be one of the most critical modifiable factors regulating the gut microbiota at different time points across the lifespan and under various health conditions. Thus the microbiota is poised to play a key role in nutritional interventions for maintaining brain health. (Translational Research 2017;179:223–244)

Abbreviations: ASD = Autism spectrum disorder; ADHD = Attention-deficit hyperactive disorder; AMPK = AMP-activated protein kinase; ANS = Autonomic nervous system; BDNF = Brain-derived neurotrophic factor; BMI = Body mass index; BCFA = Branched chain fatty acid; CCK = Cholecystokinin; CNS = Central nervous system; CREB = cAMP response element-binding protein; DA = Dopamine; EECs = Enteroendocrine cells; ENS = Enteric nervous system; FOS = Fructo-oligosaccharides; FXR = Farnesoid X receptor; GOS = Galacto-oligosaccharides; GF = Germ-free; GLP1 = Glycogen-like protein 1; GABA = Gama-aminobutyric acid; GI = Gastrointestinal tract; HPA = Hypothalamus-Pituitary Axis; IBS = Irritable bowel syndrome; IL = Interleukin; LPS = Lipopolysaccharide; LTP = Long-term potentiation; MAMP = Microbes-associated molecular patterns; NOD = Nucleotide-binding-oligomerization domain containing peptide; PYY = Peptide YY; PUFA = Polyunsaturated fatty acid; Reg3γ = Regenerating family member 3 gamma; SCFA = Short chain fatty acid; sp = Species; SPF = Specific-pathogen-free; TMAO = Trimethylamine oxide; TNF = Tumor necrosis factor; T-regs = regulatory T cells; WHO = World Health Organization; ZO = Zonula occludens

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INTRODUCTION

"Let food be thy medicine and medicine be thy food."

—Hippocrates

This oft-quoted adage from Hippocrates from over two thousand years ago may still be as relevant today where there is a growing renaissance in our appreciation of the importance of diet in maintaining health, including brain health.[1] In parallel, the importance of diet in regulating the composition of the human gut microbiota has gained much attention of late.[2] Accumulating evidence continues to highlight the importance of the gut microbiota in maintaining homeostasis and contributing to a variety of different physiological processes including protection from pathogens,[3] food metabolism,[4,5] host fat storage,[6] and even regulation of brain physiology and behavior.[7-9] More recently researchers have started to address the role of the gut microbiota within multiple different neuropsychiatric conditions, including autism,[10] depression,[11,12] stroke,[13] and schizophrenia.[14] The gut microbiota is influenced by various factors such as host genetics, health status, lifestyle, mode of delivery at birth, antibiotic usage, and dietary pattern based on different cultural practices.[15-18]

Given that diet is a key contributor in shaping the composition of the gut microbiota and that changes in dietary patterns show a direct effect on the composition of the gut bacteria.[18-22] It is important to contextualize diet and nutrition effects on the microbiota-gut-brain axis. Therefore, in this review, we discuss recent advances in the understanding of the critical role diet plays in establishing a link between the gut microbiota and host health. Furthermore, the role of the microbiota in the gut-brain axis in relation to its association with various neuropsychiatric disorders will be explored.

BIDIRECTIONAL CROSS-TALK BETWEEN GUT MICROBIOTA AND THE CNS

The gut-brain axis acts as an integrative physiological system amalgamating endocrine, immunologic, nutritional, efferent, and afferent neuronal signals between the gastrointestinal (GI) system and the brain.[23] The microbiota is now seen as a key component of this gut-brain axis, and disturbances in the homeostasis or dysregulation of the gut-microbiota-brain axis have been implicated in various immunologic, neurologic, and psychiatric conditions.[23-25] The complex network of communication between the gut microbiota and central nervous system (CNS) is mediated through the autonomic nervous system (ANS), the enteric nervous system (ENS), the immune system, and the bacterial metabolites.

Neuronal pathways. After ingestion of a meal, the presence of nutrients in the GI tract initiates complex neural and hormonal responses informing the brain of the ongoing change in the nutritional status. The gut is innervated with primary visceral afferent nerve fibers from both sympathetic and parasympathetic branches of the ANS.[26] The afferent fibers project information from the gut to the subcortical and cortical centers of the brain including the cerebral cortex, cingulate, and insular regions, whereas effector fibers project to the smooth muscles of the gut.[27] In addition, the gut also informs the brain about the current nutritional status by secreting a host of gut peptides from intestinal cells including enteroendocrine cells (EECs). Some of these hormones communicate with CNS primarily via effects on nearby afferent nerve fibers supplying the gut, whereas others are secreted from the gut into the circulatory system and whereupon they enter the brain to mediate their central effects.[28]

This bidirectional communication helps in maintaining a proper GI homeostasis and cognitive function.[23] The vagus nerve is the major nerve of the parasympathetic system of the ANS and crucial for mediating the effects of gut microbiota on different neurophysiological function[29] (Fig 1). For example, vagotomized mice failed to show any improvement in anxiety or depressive-like behaviors following treatment with a potential probiotic *Lactobacillus rhamnosus* indicating that behavioral properties of this bacterial strain are dependent upon gut-brain signaling via the vagus nerve.[32] Similarly, a potential probiotic *Bifidobacterium longum* failed to produce an anxiolytic effect in a vagotomized colitis mouse model.[33]

The vagus nerve terminating near the mucosa conveys information from the intestine to the brainstem through nuclei such as the nucleus tractus solitaries and the nodos ganglion, which represent an intermediate relay in brain-gut axis bidirectional communication.[34] (Fig 1). The vagus nerve does not project directly into the lumen, and its activation is partly dependent on the secretion of chemical signals such as peptide hormones (peptide YY [PYY], glucagon-like peptide 1 [GLP-1], cholecystokinin [CCK]) by EECs, specialized endocrine cell in intestinal tract[35] (Fig 1). For instance, $PYY_{3–36}$, the major circulating PYY, binds to the hypothalamic neuropeptide YY_2 receptors and is associated with reduction in food intake in rodents and humans[36] and vagotomy blocks $PYY_{3–36}$-induced hypophagia and associated activation of neurons in the hypothalamic arcuate nucleus.[37]