Review

Biological Psychiatry

Harnessing Gut Microbes for Mental Health: Getting From Here to There

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ABSTRACT

There has been an explosion of interest in the study of microorganisms inhabiting the gastrointestinal tract (gut microbiota) and their impact on host health and physiology. Accumulating data suggest that altered communication between gut microbiota and host systems could participate in disorders such as obesity, diabetes mellitus, and autoimmune disorders as well as neuropsychiatric disorders, including autism, anxiety, and major depressive disorders. The conceptual development of the microbiome-gut-brain axis has facilitated understanding of the complex and bidirectional networks between gastrointestinal microbiota and their host, highlighting potential mechanisms through which this environment influences central nervous system physiology. Communication pathways between gut microbiota and the central nervous system could include autonomic, neuroendocrine, enteric, and immune systems, with pathology resulting in disruption to neurotransmitter balance, increases in chronic inflammation, or exacerbated hypothalamic-pituitary-adrenal axis activity. However, uncertainty remains regarding the generalizability of controlled animal studies to the more multifaceted pattern of human pathophysiology, especially with regard to the therapeutic potential for neuropsychiatric health. This narrative review summarizes current understanding of gut microbial influence over physiological function, with an emphasis on neurobehavioral and neurological impairment based on growing understanding of the gut-brain axis. Experimental and clinical data regarding means of therapeutic manipulation of gut microbiota as a novel treatment option for mental health are described, and important knowledge gaps are identified and discussed.

Keywords: Depression, Gut dysbiosis, Gut-brain axis, Mental health, Microbiota transplant, Probiotics

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INTRODUCTION AND HISTORICAL CONTEXT

Gut microbiota comprise all microorganisms inhabiting the intestinal tract and their respective genomes. Tens of trillions of microorganisms populate the human intestine; although bacteria predominate, viruses, phages, and fungi are likewise included (1). Accumulating data implicate this dynamic population in physiological functions, including nutrition/digestion, growth, inflammation/immunity, and protection against foreign pathogens (2–4). Experimental and clinical studies suggest that disruption to gut microbiota can impair physical and mental health (3,5–7), suggesting that intestinal microbiota could underlie host susceptibility to illness (8,9). Links between microbiota and pathophysiology have triggered an explosion of interest in this field, with 85% of the more than 10,000 PubMed publications on "intestinal microbiota" arising in the last 5 years, currently averaging about five new publications per day. Indeed, the most recent Rome Foundation guidelines on gastrointestinal (GI) disorders emphasize disruption on the gut-brain axis in functional GI disease (10). Furthermore, the Integrative Human Microbiome Project was deployed in 2014 to drive continuing understanding of microbiome-based influences on health and disease following the 2013 culmination of the National Institutes of Health (NIH) Human Microbiome Project (http://hmpdacc.org/) (11). This substantial investment of intellectual and financial capital reflects the hopeful expectation for new ways to drive beneficial mutualism with these symbiotic microbes to foster optimal health.

Notwithstanding recent investments in discovery-based approaches, microbiome manipulation is actually an ancient concept in human medicine. The first reported application of therapeutic fecal transplantation was from the fourth century by Chinese physician Ge Hong, describing a "yellow soup" prescribed as an oral remedy for a patient with severe diarrhea (12). In the less distant past, Elie Metchnikoff theorized that health could be enhanced and "senility" delayed by manipulating the intestinal microbiome with host-friendly bacteria (13). These progressive theories might have remained adrift among the fringes of biomedical research had it not been for the development of high-throughput sequencing, which revolutionized microbiology with highly efficient and cost-effective strategies to identify and investigate microbial community structure. Historically, microbiology was almost entirely culture dependent, with members of microbial communities identified by structural characteristics, such as affinity for Gram stains. This restriction to cultivable microorganisms hindered researchers' ability to fully assess diversity in physiological niches, especially at lower taxonomic levels. With the advent of inexpensive and culture-independent, next-generation

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high-throughput sequencing (14), analyses of DNA isolated directly from biological sites have enabled characterization of taxonomic diversity and functional metagenomics, driving the explosion of data on human microbiomes. In this nonsystematic narrative review, we summarize current understanding of intestinal microbial influences on physiological function with an emphasis on behavioral and neurological impairment. We also summarize available experimental and clinical data regarding therapeutic manipulation of gut microbiota as a novel GI-based treatment option for mental health. Lastly, we identify important knowledge gaps and discuss potential approaches to filling such gaps.

GUT MICROBIOTA AND MENTAL HEALTH: EXPERIMENTAL EVIDENCE

Mental illness contributes substantially to the global burden of disability, and to uncover new avenues for treatment, the generally tight association of neurobehavioral and metabolic dysfunction has come under intense scrutiny (15–17). The search for underlying mechanisms common to both bowel and mental illness has revealed many humoral and neural pathways of gut-brain communication (18), and gut microbiota have emerged as a key node in this system (19,20). Indeed, bidirectional pathways between gut and brain regulate metabolism and energy balance and represent an ancient biological defense system to guarantee adequate energy (21). The role of gut microbiota in this system is highlighted by the well-established relationship between overnutrition and reduced intestinal microbial diversity and disrupted pathogen/commensal balance (dysbiosis) (22–25). Intestinal dysbiosis is also linked to behavioral impairment (5–7,26,27), stimulating extensive research into the role of gut microbiota in mental and neurological health.

A pivotal early study on gut microbiota and neurobehavioral function revealed that germ-free mice lacking intestinal and other microbiota display maladaptive and exaggerated responses to stress that can be normalized by probiotic-induced intestinal recolonization (28). Indeed, germ-free mice show that gut microbiota are essential for development of neuronal circuits underlying motor control, anxiety behavior, and social responses (7,29). Fecal microbial transfer experiments likewise demonstrate the link between intestinal microbiota and behavior. For example, germ-free BALB/c mice typically display impaired sociality and exaggerated caution (30). However, microbiome transplants from NIH Swiss mice, which lack social and exploratory impairment, normalize behavior in BALB/c recipients (31). The reverse is also true, as NIH Swiss mice transplanted with BALB/c microbiota display exaggerated caution and hesitancy (32). Subsequent studies in conventionally housed mice with microbiome transplants from donor mice fed a high-fat diet revealed that microbiota shaped by a high-fat diet are sufficient to disrupt exploratory, cognitive, and stereotypical/impulsive behaviors (6). Other reports reveal that probiotics improve mood, anxiety, and cognition as well as signaling and neural activity in animal models (33–36). Finally, experimental studies have shown that probiotics prevent stress-induced decreases in hippocampal neurogenesis and enhance expression of hypothalamic genes involved in synaptic plasticity (37).

The intestinal ecosystem is thought to be established at or soon after birth, facilitated by vertical transmission and exposure to and/or ingestion of environmental flora (38–40). Thus, maternal influences on the offspring's microbiome are significant, potentially altering the risk for mental impairment. Indeed, it has been proposed that both the development of the brain and the risks of future illness can be viewed in the context of the developing microbiome (41). For example, data suggest that obesity and diabetes during pregnancy increase risk for neuropsychiatric disorders in offspring (42) and that maternal diet–induced intestinal dysbiosis can impair offspring behavior in a sex-specific manner (43). Maternal stress and immune activation can also program maladaptive offspring behavior via microbiome alterations. For example, maternal immune activation causes behavioral impairment in offspring that is prevented by probiotics (44). Furthermore, prenatal stress-induced changes to the vaginal microbiome alter vertical transmission of microbiota, seemingly shaping an intestinal niche that increases disease risk (45,46). These collective data suggest a significant and essential link between maternal microbiota and offspring programming, raising the possibility that maternal microbiota could link unhealthy modern diets to the increased prevalence of neurodevelopmental and childhood disorders (47–49). While currently under intensive study [reviewed in (50)] (51), the potential pathways whereby maternal microbiota affect neurological function of offspring remain unknown (Figure 1).

POTENTIAL MECHANISMS WHEREBY INTESTINAL MICROBIOTA INFLUENCE HOST HEALTH

Numerous pathways between the gut and the brain have been delineated, and data indicate that gut-brain communication is bidirectional and mediated by neural and humoral mechanisms. Specific descending pathways include autonomic and enteric pathways and the hypothalamic-pituitary-adrenal axis. Ascending pathways include sensory vagal and dorsal root ganglion pathways, cytokines and immune mediators, and secreted microbial and intestinal metabolites. With neural pathways acting in a rapid and somatotopic manner combined with the slower and somatically less specific humoral route, these complementary pathways facilitate the effects of gut microbiota on brain and behavior (Figure 2).

Direct Activation of Neuronal Pathways

Vagal primary afferents provide pervasive sensory innervation of the GI tract, with an estimated 60,000 fibers in humans and 20,000 fibers in mice comprising the only set of fibers that directly connect the GI mucosa to the brain (52). Numerous studies have demonstrated activation of GI tract vagal afferents by gut hormones, cytokines, microbial signals, and mechanical stimuli [reviewed in (53)], and vagal afferents have been implicated in probiotic-induced neurobehavioral changes in mice (34,54). For example, the probiotic *Lactobacillus rhamnosus* can directly increase single-unit and multiunit firing rate of the mesenteric nerve bundle and can decrease stress-induced corticosterone and anxiety and depression in mice (34,55). Moreover, these behavioral effects of *L. rhamnosus* are abolished by vagotomy (34). However, selective vagal deafferentation has not yet been used to conclusively prove a role