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Review

Control of Brain Development, Function, and Behavior by the Microbiome

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Animals share an intimate and life-long partnership with a myriad of resident microbial species, collectively referred to as the microbiota. Symbiotic microbes have been shown to regulate nutrition and metabolism and are critical for the development and function of the immune system. More recently, studies have suggested that gut bacteria can impact neurological outcomes—altering behavior and potentially affecting the onset and/or severity of nervous system disorders. In this review, we highlight emerging evidence that the microbiome extends its influence to the brain via various pathways connecting the gut to the central nervous system. While understanding and appreciation of a gut microbial impact on neurological function is nascent, unraveling gut-microbiome-brain connections holds the promise of transforming the neurosciences and revealing potentially novel etiologies for psychiatric and neurodegenerative disorders.

Introduction

Metazoans evolved in a world dominated by microbial life. Despite the long evolutionary history that has forged elaborate host-microbial symbioses over many millennia, it is only recently that science and society have begun to appreciate the inextricable connection between microbes and mammals. We are witnessing a groundswell of research that is describing and defining how gut bacteria (known as the microbiota) influence critical aspects of our physiology. The last decade of research has illuminated numerous complex interactions between the microbiota and the immune and metabolic systems, many of which have significant implications on human health. While the fascinating and profound mechanisms by which gut bacteria control immunity and metabolism has led to a modern renaissance in biomedical research, regulation of the nervous system by the microbiota had remained relatively unexplored until very recently (Mayer et al., 2014, 2015; Stilling et al., 2014b). How could simple gut microbes influence a complex and distant organ such as the brain? This seemingly improbable concept that specific microbes influence the behavior and neurological function of their hosts had, in fact, already been established. One prime example of ''microbial mind control'' is the development of aggression and hydrophobia in mammals infected with the rabies virus (Driver, 2014). Another well-known example of behavior modification occurs by *Toxoplasma gondii*, which alters the host rodents' fear response. Infected rodents lose their defensive behavior in the presence of feline predators and instead actually become sexually attracted to feline odors (House et al., 2011). This results in infected rodents being preyed upon more readily by cats and allows *Toxoplasma* to continue its lifecycle in the feline host (House et al., 2011). Further, a variety of parasitic microbes are capable of altering the locomotive behavior and environmental preferences of their hosts to the benefit of the microbe. For instance, the *Spinochordodes tellinii* parasite causes infected grasshopper hosts to not only jump more frequently but also seek an aquatic environment where the parasite emerges to mate and produce eggs (Biron et al., 2005). Temperature preference of the host can even be altered, such as observed during infection of stickleback fish by *Schistocephalus solidus*, which changes the hosts' preference from cooler waters to warmer waters where the parasite can grow more readily (Macnab and Barber, 2012). Other microbes can even alter host behavior to seek higher elevations, believed to allow the infected host to be noticed more easily by predators or to eventually fall and disperse onto susceptible hosts below (Maitland, 1994). More coercively still, microbes can influence the social behavior of their hosts, causing insects, such as ants, to become more or less social to the benefit of the parasite (Hughes, 2005). In fact, the sexually transmitted virus IIV-6/CrIV causes its cricket host (*Gryllus texensis*) to increase its desire to mate, causing its rate of mating to be significantly elevated and allowing for transmission between individual hosts (Adamo et al., 2014).

While all of the above examples most certainly represent pathogenic and/or parasitic relationships, they nonetheless raise the possibility that the indigenous microbes, which are in constant, life-long interaction with their human and animal hosts, could influence neurological function and behavior during development or within health and disease states. It is becoming increasingly recognized that psychiatric and neurological illnesses are often co-morbid with gastrointestinal (GI) pathology (Vandvik et al., 2004), including schizophrenia, autism, neurodegenerative diseases, and depression. Furthermore, recent observations have indicated that the commensal microbiota of the intestine do indeed alter aspects of their hosts' neurological function, leading to effects on mood and behavior, including depression, anxiety, social behavior, and mate choice (Table 1) (Bravo et al., 2011; Desbonnet et al., 2010; Foster and McVey Neufeld, 2013; Hsiao et al., 2013; Neufeld et al., 2011; Sharon et al., 2010). The intestinal microbiota are, however, well established to have a profound impact in shaping the host immune system, which itself may subsequently influence host behavior (Dantzer et al., 2008) and indirectly have effects on neurodegeneration and repair during the process of aging, neurological trauma, and disease. The precise mechanisms of how the intestinal microbes impact neurological function and behavior remain largely unknown, but are likely vast, varied, and complex.

Table 1. Selected Phenotypic Attributes Influenced by Gut Microbes

Category	Attribute	Effect	Citation(s)
Behavioral	Anxiety	Reduced self-reported anxiety in humans treated with *L. helveticus* R0052 and *B. longum* R0175	Messaoudi et al., 2011
Behavioral	Anxiety-like behavior	Decreased anxiety-like behavior in GF mice (Swiss Webster, NIH Swiss, and NMRI)	Clarke et al, 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011; Selkrig et al., 2014
Behavioral	Anxiety-like behavior	Increased anxiety-like behavior in GF mice (BALB/c, C57Bl6)	Bercik et al., 2011; Selkrig et al., 2014
Behavioral	Anxiety-like behavior	Reduced anxiety-like behavior in rodents treated with *Bifidobacterium breve* 1205, *B. longum* 1714, *B. longum* R0175 *Lactobacillus helveticus* R0052, or *L. rhamnosus*JB-1	Bravo et al., 2011; Messaoudi et al., 2011; Savignac et al., 2014
Behavioral	Depression	Reduced self-reported feelings of depression and aggression in humans treated with probiotics	Steenbergen et al., 2015
Behavioral	Depression-like behavior	Decreased depression-like behavior in mice treated with *B. infantis* or *L. rhamnosus* JB-1	Bravo et al., 2011; Desbonnet et al., 2010; Savignac et al., 2014; Savignac et al., 2015
Behavioral	Emotional processing	Reduced activation following emotional stimulus in humans treated with probiotic milk product	Tillisch et al., 2013
Behavioral	Social recognition	Reduced novel and familiar social recognition in GF mice	Desbonnet et al., 2014
Behavioral	Stereotyped behaviors and vocalizations	Restoration of social behaviors in *Bacteroides fragilis*-treated MIA mice	Hsiao et al., 2012
Behavioral	Stress response	Increased response to restraint stress in GF mice	Sudo et al., 2004
Hormonal	Corticosterone	Increased hypothalmic corticosterone in GF mice	Sudo et al., 2004
Hormonal	Cortisol	Reduced urinary cortisol in humans treated with *L. helveticus* R0052 and *B. longum* R0175	Messaoudi et al., 2011
Neurochemical	BBB	Decreased expression of tight junction proteins, and subsequent increase of BBB permeability	Braniste et al., 2014
Neurochemical	BDNF	Decreased hypothalmic BDNF in GF mice	Sudo et al., 2004
Neurochemical	Dopamine and GABA	Decreased serum levels of dopamine and GABA in GF mice	Matsumoto et al., 2012; Velagapudi et al., 2010
Neurochemical	G-CSF	Reduced serum levels of G-CSF in GF mice	Deshmukh et al., 2014
Neurochemical	Peripheral serotonin	Decreased peripheral and intestinal serotonin in GF mice, restored by colonization with spore forming bacteria	Wikoff et al., 2009; Yano et al., 2015
Neurochemical	Serotonin and Serotonin receptor	Decreased serotonin and receptor ($5HT_{1A}$) in the amygdala and hippocampus of GF mice	Bercik et al., 2011; Clarke et al., 2013; Diaz Heijtz et al., 2011; Neufeld et al., 2011; Yano et al., 2015
Neurochemical	Serotonin, noradrenaline, and dopamine	Increased turnover of serotonin, noradrenaline, and dopamine in the striatum of GF mice	Diaz Heijtz et al., 2011

Interactions between a host and its microbiota are decidedly intricate. Intestinal microbes influence numerous aspects of metabolism, producing metabolic precursors to hormones and neurotransmitters or directly producing the active metabolites themselves (Lyte, 2014; Sharon et al., 2014) (Figure 1). Symbiotic bacteria additionally have the capability to influence the status of the systemic immune system, which may alter how the immune system subsequently interacts with the nervous system (Belkaid and Hand, 2014; Hooper et al., 2012; Round and Mazmanian, 2009) (Figure 1). Furthermore, the enteric nervous system (ENS) is directly connected to the central nervous system (CNS) through the vagus nerve, providing a direct neurochemical pathway for microbial-promoted signaling in the GI tract to be propagated to the brain (Forsythe et al., 2014) (Figure 1). Herein, we review the current understanding of how the intestinal microbiota influence behavior and neurological function during both health and disease. First, we will focus on how indigenous microbes shape mood and cognitive behaviors, as well as social behaviors. We will next discuss the physiological aspects that are modulated by signals derived from the microbiota. In particular, we will