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Review article

A gut feeling: Microbiome-brain-immune interactions modulate social and affective behaviors

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ABSTRACT

The expression of a wide range of social and affective behaviors, including aggression and investigation, as well as anxiety- and depressive-like behaviors, involves interactions among many different physiological systems, including the neuroendocrine and immune systems. Recent work suggests that the gut microbiome may also play a critical role in modulating behavior and likely functions as an important integrator across physiological systems. Microbes within the gut may communicate with the brain via both neural and humoral pathways, providing numerous avenues of research in the area of the gut-brain axis. We are now just beginning to understand the intricate relationships among the brain, microbiome, and immune system and how they work in concert to influence behavior. The effects of different forms of experience (e.g., changes in diet, immune challenge, and psychological stress) on the brain, gut microbiome, and the immune system have often been studied independently. Though because these systems do not work in isolation, it is essential to shift our focus to the connections among them as we move forward in our investigations of the gut-brain axis, the shaping of behavioral phenotypes, and the possible clinical implications of these interactions. This review summarizes the recent progress the field has made in understanding the important role the gut microbiome plays in the modulation of social and affective behaviors, as well as some of the intricate mechanisms by which the microbiome may be communicating with the brain and immune system.

1. Introduction

A wide variety of experiences can influence physiology and behavior; in order to produce appropriate behavioral responses, neuroendocrine circuits must integrate sensory stimuli with internal physiology. Research has shown that even modest activation of the immune system early in life may increase susceptibility to a range of nervous system disorders and can influence the physiological and behavioral responses to challenges later in life (Bilbo and Schwarz, 2009; Harvey and Boksa, 2012; Knox et al., 2009). Such studies investigating early-life stress, as well as adult stress, often focus on the neuroendocrine and immune systems alone to explain the behavioral phenotype, including aggression, investigation, exploration, and anxiety- and depressive-like behaviors. More recent work, however, suggests that the gut-brain axis (i.e., the bidirectional communication between the brain and gastrointestinal tract) is capable of interacting with these physiological systems and it too may facilitate behavioral responses (Collins and Bercik, 2014; Cryan and O'Mahony, 2011).

Inside the mammalian body lies a complex ecological community, termed the microbiota, consisting of commensal, symbiotic, and pathogenic bacteria, fungi, and viruses. The microbial genome of these microorganisms is termed the microbiome. This system of living microorganisms is critical for mammalian survival (Lee and Mazmanian, 2010), and interestingly, most of these microbes reside in the large intestine of the gastrointestinal (GI) tract (Wallace et al., 2011). More importantly, the microbiome may play a critical role in modulating behavior by connecting the neuroendocrine and immune systems (Fig. 1) through both direct (e.g., vagus nerve) and indirect (e.g., cytokines) mechanisms. Further, the gut microbiome develops in parallel with the neonatal central nervous system (CNS) via the transmission of signals from the vagus nerve (the major nerve of the parasympathetic nervous system) to the GI tract, therefore perturbations of either system have the potential to affect both (Clarke et al., 2014; Cryan and O'Mahony, 2011; see Table 1).

Later in life, these systems can influence one another as well. For example, adult house mice challenged with the common GI pathogen, *Campylobacter jejuni* (*C. jejuni*), exhibit increased anxiety in a standardized behavioral assay, suggesting that information from the gut may

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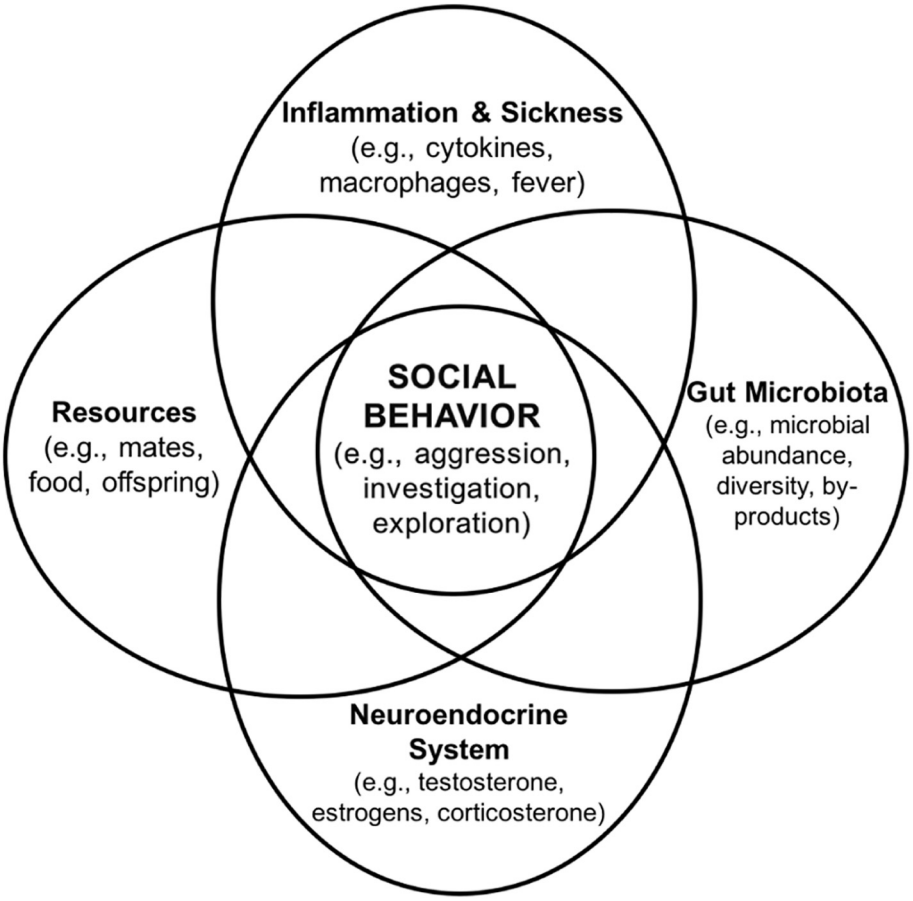

Fig. 1. Previous work has been aimed at determining the role that the central nervous system, the gut microbiome, and the immune systems play in social behavior and adult sensitivity to subsequent stressors, yet some previous studies have overlooked the interactions between these systems and the communication among the systems used to regulate (or dysregulate) social behavior. This theoretical model illustrates some of the brain-gut-immune interactions that play a role in behavioral outcomes, including social and affective behaviors (e.g., investigation, aggression, and anxiety- and depression-like behavior). The interactions among these systems are key to understanding how social behavioral changes occur and the potential mechanisms mediating psychopathologies.

be transferred to the brain to mediate behavior via direct or indirect routes (Goehler et al., 2008). The gut microbiome also plays a direct role in immunity and is therefore likely to explain some of the variation in behavioral responses to infection. The underlying physiological changes that occur during an immune challenge and the potential ways in which crosstalk among the immune system, microbiome, and endocrine system takes place are important factors in explaining how behavior is regulated (Fig. 1). The behavioral effects of both early-life and adult experience on the brain, gut microbiome, and the immune system have often been studied independently, but because these systems do not operate in isolation, it is essential to elucidate the connections and interactions between them. Therefore, this review will focus on the state of current research surrounding the role of the interactions among the gut microbiome, the immune system, and the neuroendocrine system in modulating social and affective behaviors.

2. Overview of the immune system

2.1. Inflammation and the brain

In order for the body to maintain a state of balance in times of immune challenge, it must appropriately integrate information received and convey it to the brain to coordinate proper physiological and behavioral responses. Treatment with lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, is commonly employed to induce a robust immune response in animals, triggering an increase in circulating glucocorticoids (e.g., cortisol) and pro-inflammatory cytokines (e.g., interleukin [IL]-1β, tumor necrosis factor [TNF]-α), which can impair development of many physiological systems (Bilbo and Schwarz, 2012; French et al., 2013). When LPS is injected into the peritoneal cavity, it enters circulation within 15 min and levels stay elevated for at least two hours following injection (Hansen et al., 2000). The release of LPS mimics a bacterial infection, by binding to the toll-like receptor (TLR)-4, which stimulates the activation of transcription factors and subsequent pro-inflammatory mediators in the body, particularly cytokines, IL-1β, IL-2, IL-6, TNF-α, and interferons (IFNs) that act on the brain. These processes initiate the acute-phase response (APR), including fever, lethargy, decreased food intake, and enhanced pain response (Harvey and Boksa, 2012; Perry, 2004; Quan and Banks, 2007). Interestingly, these physiological and behavioral responses to LPS (or other immune challenges) are similar to those described in CNS disorders (e.g., autism spectrum disorder, depression, anxiety) and are of particular interest when thinking about the relationships between the gut-brain axis and the immune system (Cryan and O'Mahony, 2011; Harvey and Boksa, 2012; Perry, 2004; Quan and Banks, 2007).

2.2. Behavioral responses to inflammation

Cytokines play a vital role in the response to immune challenge, as they can mediate changes in behavior, though age can be a particularly important factor in the behavioral response. For example, treatment with LPS can cause an increase in both IL-2 and IL-1α in male and female rats (Costalonga and Zell, 2007), however, the age in which animals are exposed influences their response greatly. In particular, rats treated with IL-2 at three weeks of age exhibit enhanced locomotor activity and greater levels of exploration, whereas rats treated with IL-1α at eight weeks of age show an increase in startle response and an increase in investigative behavior, but no changes in locomotion (Tohmi et al., 2004). This suggests that the release of specific cytokines as a result of immune activation at particular time points in an individual's life can influence the amount and duration of some behaviors, though the precise mechanisms have not yet been determined. Further, work from our lab suggests that in Siberian hamsters (*Phodopus sungorus*), LPS exposure in the early postnatal period affects