Research report
Gut bacteria interaction with vagal afferents
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ABSTRACT

Contemporary techniques including the use of germ-free models and next generation sequencing have deepened our understanding of the gut microbiota dynamics and its influence on host physiology. There is accumulating evidence that the gut microbiota can communicate to the CNS and is involved in the development of metabolic and behavioral disorders.

Vagal afferent terminals are positioned beneath the gut epithelium where they can receive, directly or indirectly, signals produced by the gut microbiota, to affect host behavior, including feeding behavior. Supplementation with L. Rhamnosus in mice notably causes a decrease in anxiety and these effects are abolished by vagotomy. Additionally, chronic treatment with bacterial byproduct lipopolysaccharide (LPS) blunts vagally-mediated post-ingestive feedback and is associated with increased food intake. Inflammation in the nodose ganglion (NG), the location of vagal afferent neurons’ cell bodies, may be a key triggering factor of microbiota-driven vagal alteration. Interestingly, several models show that vagal damage leads to an increase in immune cell (microglia) activation in the NG and remodeling of the vagal pathway. Similarly, diet-driven microbiota dysbiosis is associated with NG microglia activation and decreased vagal outputs to the CNS. Crucially, preventing dysbiosis and microglia activation in high-fat diet fed rodents normalizes vagal innervation and energy intake, highlighting the importance of microbiota/vagal communication in controlling feeding behavior.

As of today, new consideration of potential roles for glial influence on vagal communication and new methods of vagal afferent ablation open opportunities to increase our understanding of how the gut microbiota influence its host’s health and behavior.

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1. Introduction

Early consideration of the gut microbiota looked principally at its role as an internal ecosystem that may have, via competition for resources, an ability to protect our guts from pathogenic invasions (Greenberg, 1969; Mushin and Dubos, 1965). Viewing the gut microbiota as having a larger impact on host health was not far behind (Whitt and Savage, 1980; Williams, 1973) and a role for the gut microbiota in the development of immunity was proposed early on (Klaasen et al., 1993). The use of germ-free animals (Backhed et al., 2004; Falk et al., 1998) combined with improved methods for microbial species identification (Gill et al., 2006) greatly advanced microbiota research and unraveled the crucial influence of microbiota composition on host physiology (Ley et al., 2006; Sen et al., 2017; Turnbaugh et al., 2006; van Tongeren et al., 2005) as well as behavior (Goehler et al., 2008; O’Mahony et al., 2009).

The prominent role of the microbiota in innate and adaptive immunity has been well established (Yamamoto et al., 2012). Pattern recognition receptors (PRRs), including Toll-Like receptors (TLRs) can recognize bacterial products, such as lipopolysaccharide (LPS) or peptidoglycans to induce the appropriate immune response, for example the release of pro-inflammatory cytokines (Aderem and Ulevitch, 2000). Chronic over-activation of PRRs has been implicated in inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis (Cario and Podolsky, 2000). A recent meta-analysis found fecal microbiota transfer to be an effective treatment in 45% of IBD cases overall and in as many as 60% of Crohn's disease patients (Colman and Rubin, 2014) Limited
2. The bug-gut-brain axis

In mice, infection with *Campylobacter jejuni* increases anxiety-like behavior (Goehler et al., 2005, 2008) while supplementation with *Lactobacillus rhamnosus* reduces stress and anxiety behavior (Bravo et al., 2011). Changes in central gamma-aminobutyric acid (GABA) signaling are implicated in the etiology of anxiety disorders and *L. rhamnosus* supplementation is associated with alterations in GABA_A and GABA_B receptors in several cortical regions, including the amygdala and hippocampus. Such evidence of communication between commensal bacteria and the brain have supported the emergence of the “microbiota-gut-brain axis” concept (Berclí, 2011; Bienenstock and Collins, 2010). Interestingly, *C. jejuni* infection leads to vagal activation (Goehler et al., 2005) while *L. rhamnosus*’ positive effects on anxiety are abolished by vagotomy (Fig. 1) (Bravo et al., 2011), identifying the vagus nerve as a potential relay pathway for microbiota-to-brain signals. Vagal afferent neurons (VAN) express GABA_A receptor (Ashworth-Preece et al., 1997) and strains of *Lactobacillus* and *Bifidobacterium*, common members of the gut microbial community, can produce GABA (Barrett et al., 2012) but *L. rhamnosus* was not found to be a GABA producer suggesting that bacteria can influence vagal signaling via both direct and indirect pathways.

The vagus nerve is a bidirectional communication line between visceral organs and the central nervous system (CNS). Vagal efferent neurons send motor information from the brain to peripheral organs but are outnumbered 9:1 by vagal afferents that convey sensory information from the periphery to the CNS (Foley and DuBois, 1937). VAN play a crucial role in regulating host behavior, including feeding behavior (de Lartigue et al., 2012), VAN, located in the nodose ganglion, notably relay information on quantity and quality of ingested nutrients to the nucleus of solitary tract (NTS) to regulate meal termination (Sutton et al., 2004). Vagal afferent terminals are located in the gastrointestinal lamina propria where they can directly or indirectly interact with the microbiota or sense immune or endocrine signals originating from the GI tract (Patterson et al., 2002). In animal models, chronic consumption of energy dense diet leads to microbiota dysbiosis (Turnbaugh et al., 2006) and disrupts vagal afferent signaling resulting in overeating (de La Serre et al., 2010, 2015; Sen et al., 2017; Vaughn et al., 2017).

3. The gut microbiota influences regulation of food intake

Commensal bacteria have been shown to produce neurotransmitters such as serotonin (Hsu et al., 1986), GABA (Barrett et al., 2012), dopamine, and noradrenaline (Oleskin et al., 2016) and microbiota-originating neural signals could potentially directly affect vagal signaling. However, there is accumulating evidence pointing towards indirect interactions between the gut microbiota and the vagal afferent pathway.

Firstly, microbiota composition appears to influence enteroenocrine cell (EEC) signaling. EEC release satiety peptides such as cholecytokinin (CCK) (Gutzwiller et al., 2000) and glucagon-like peptide (GLP)-1 (Novak et al., 1987) in response to feeding. Gut-originating peptides bind to their specific receptors on vagal afferents to reduce food intake. Supplementing a high-fat diet with oligofructose, a known prebiotic, induces an increase in GLP-1 expression in mice (Cani et al., 2005). More recent research suggests that oligofructose can be fermented into short chain fatty acids (SCFA) by members of the gut microbiota, especially *Bifidobacteria* (Meyer and Stasse-Wolthuis, 2009). SCFA can act as endogenous ligands for free fatty acid receptor (FFAR)2 and FFAR3, two G-protein coupled receptors that are involved in controlling the secretion of GLP-1 (Tolhurst et al., 2012). In another study, oligofructose supplementation in ob/ob mice led to significant increases in *Bifidobacteria* and *Lactobacillus*. These increases were associated with increased GLP-2 expression (Cani et al., 2009). GLP-2 acts as a trophic factor in the gut promoting epithelial growth and strengthening the intestinal barrier (Cani et al., 2009). This is critical since high-fat diet fed rats’ propensity towards obesity is associated with increased GI permeability while resistance to weight gain is correlated with an intact intestinal barrier (de La Serre et al., 2010). A leaky gut would allow for bacterial products and/or metabolites to cross the gut epithelia and enter in close contact with vagal terminals providing another means for the microbiota to communicate with the host. In human (Creely et al., 2007) and rodent models (Cani et al., 2007) obesity is a state of metabolic endotoxemia, a chronic elevation in circulating bacterial LPS. VAN express PRRs, including the LPS receptors, TLR-4 (Hosoi 2018)
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