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Review

# Role of enteric neurotransmission in host defense and protection of the gastrointestinal tract

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ABSTRACT

Host defense is a vital role played by the gastrointestinal tract. As host to an enormous and diverse microbiome, the gut has evolved an elaborate array of chemical and physicals barriers that allow the digestion and absorption of nutrients without compromising the mammalian host. The control of such barrier functions requires the integration of neural, humoral, paracrine and immune signaling, involving redundant and overlapping mechanisms to ensure, under most circumstances, the integrity of the gastrointestinal epithelial barrier. Here we focus on selected recent developments in the autonomic neural control of host defense functions used in the protection of the gut from luminal agents, and discuss how the microbiota may potentially play a role in enteric neurotransmission. Key recent findings include: the important role played by subepithelial enteric glia in modulating intestinal barrier function, identification of stress-induced mechanisms evoking barrier breakdown, neural regulation of epithelial cell proliferation, the role of afferent and efferent vagal pathways in regulating barrier function, direct evidence for bacterial communication to the enteric nervous system, and microbial sources of enteric neurotransmitters. We discuss these new and interesting developments in our understanding of the role of the autonomic nervous system in gastrointestinal host defense.

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## 1. Introduction

The mammalian gastrointestinal (GI) tract is a complex organ that has evolved in a cooperative manner with a variety of prokaryotic and

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eukaryotic species, namely the bacteria, fungi, protozoa and archaea (previously known as archaebacteria) that comprise the microbiome of the gut (Backhed et al., 2005; Sommer and Backhed, 2013). The GI tract is in fact a host within a host. In the mammalian host, the primary function of the gut is to provide the nutrients and energy required for survival and reproduction. A secondary function of the GI tract is to defend the host from potentially harmful ingested food antigens, bacteria, parasites or toxins. This defensive function of the gut extends to protect the organ itself, as well as the host, from the processes of digestion: extremes of pH, digestive enzymes, bile and other chemicals that can damage cells (Fasano and Shea-Donohue, 2005; McCole and Barrett, 2007; Turner, 2009). Digestion frequently produces unwanted antigenic peptides, which if not carefully regulated can lead to powerful immune responses that may also be deleterious to the host (Fasano and Shea-Donohue, 2005; Fasano, 2012). As a host itself, the GI tract is home to trillions of bacteria that reside throughout its length and provide the vertebrate host with specific nutritional, defensive and other symbiotic functions in return for a share of the host's nutrients and a unique environment in which to live and reproduce (Backhed et al., 2005; Sommer and Backhed, 2013). The burden of this large number of prokaryotic species is considerable, as these commensals can quickly become pathogenic if the intestinal epithelial barrier—the single layer of cells that separate the inside of the body from the gut luminal contents—is breached or defective. It is perhaps not surprising given this introduction that the gut has evolved to be the largest immune organ of the body; where a rich network of nerves and humoral mediators regulate and control digestion, at the same time as orchestrating elaborate cellular systems of defense that work in concert with the immune system to protect the host.

In recent years, we have learned a considerable amount about how the microbiome contributes to nutritional states in mammalian hosts. Gut bacteria seem to be responsible for conditions of both under- and over-nutrition, with extreme examples ranging from kwashiorkor on one hand to obesity on the other (Turnbaugh et al., 2006, 2008; Ridaura et al., 2013; Smith et al., 2013). But the microbiome is also a critical factor in the development of GI inflammation (Rubino et al., 2012; Knights et al., 2013; Natividad and Verdu, 2013). This can be manifested as an idiopathic condition like inflammatory bowel disease (IBD), where in genetically susceptible individuals, an environmental trigger initiates a breakdown of innate host defenses that leads to an uncontrolled local immune response to antigens and resident commensals in the wall of the gut (Knights et al., 2013). Inflammation may also occur as a result of bacterial dysbiosis when an opportunistic pathogen like *Clostridium difficile* stimulates a massive local immune response and destruction of the epithelium (Peniche et al., 2013). Local control of inflammation in the gut is covered in the accompanying article by Lomax (Cervi et al., in press). Here we will focus on selected recent developments in the autonomic neural control of host defense functions used in the protection of the gut from luminal agents, and how the microbiota may potentially contribute to enteric neurotransmission.

## 2. Enteric innervation

The innervation of the gut consists of both extrinsic and intrinsic components, comprising all three divisions of the autonomic nervous system (Furness, 2006, 2012). In addition, the gut receives a rich primary afferent innervation of both vagal and spinal origin (Blackshaw et al., 2007; Furness et al., 2013). Both vagal and spinal afferent terminals must extensively branch within the wall of the gut; because of the relatively low number of vagal and spinal neurons providing this innervation. For example, it has been estimated that only 1–2% of the total spinal primary afferent neurons innervate the viscera (Janig and Morrison, 1986).

For the most part, the terminals of extrinsic primary afferent, parasympathetic and sympathetic nerves extensively innervate the enteric nervous system (ENS)—the third division of the autonomic nervous system, rather than other targets in the wall of the gut. However, there are specialized sensory endings and direct innervation of the vasculature by sympathetic and primary afferent terminals (Furness, 2012; Furness et al., 2013). The ENS consists of the intrinsic primary afferent, interneurons and motor neurons that control all functions of the GI tract. These neurons are arranged in two ganglionated plexuses: the myenteric plexus that lies between the longitudinal and circular muscle layers of the muscularis externa, and the submucosal plexus the lies in the submucosa (Furness, 2006, 2012). These two neuronal plexuses are interconnected. A small population of myenteric neurons, called viscerofugal neurons, make direct connections to postganglionic sympathetic neurons in the abdominal prevertebral ganglia (Sharkey et al., 1998; Szurszewski et al., 2002). These enteric neurons form the afferent limb of local sympathetic reflexes that control motility (Lomax et al., 2010).

Enteric neurons extensively innervate all the structural and functional elements of the gut: smooth muscle, epithelium, immune elements, and vasculature. However, what is remarkable about the gut innervation is that it frequently seems to act through intermediary cell types that are interposed between nerves and target tissues. Specifically, motor activity is regulated by Interstitial cells of Cajal (Sanders et al., 2010), which may also transduce sensory information (Powley and Phillips, 2011), and platelet-derived growth factor receptor alpha-positive cells (Sanders et al., 2010; Kurahashi et al., 2011; Baker et al., 2013). Secretion is regulated in part by enteric mast and glial cells, as well as subepithelial myofibroblasts (Powell et al., 1999; Bischoff, 2009; Gulbransen and Sharkey, 2012). The immune elements of the gut are also innervated; that is to say, nerves directly innervate lymphoid organs, such as Peyer's patches where adapted lymphocyte responses occur, as well as diffusely distributed immune cells, such as mast cells, dendritic cells and macrophages (Chiocchetti et al., 2008; Nijhuis et al., 2010; de Jonge, 2011; Matteoli et al., in press).

### 2.1. Enteric glia

Like neurons in the brain, enteric neurons are surrounded and outnumbered by glial cells. In the GI tract there is a unique type of peripheral glial cell called enteric glia (Gulbransen and Sharkey, 2012; Neunlist et al., 2013). These cells resemble astrocytes of the brain and are found in both the myenteric and submucosal plexuses and also intramuscularly (Gulbransen and Sharkey, 2012). Perhaps surprisingly, there is also a population of cells which have the phenotypic characteristics of enteric glia that lie just beneath the epithelium (Gulbransen and Sharkey, 2012; Neunlist et al., 2013). These subepithelial enteric glia have an intimate relationship with epithelial cells, and play a role in the maintenance of barrier function. Emerging work from several groups, including our own, has recently demonstrated that protective gut functions may be orchestrated by enteric glial cell mediators or via enteric glial modulation of neurotransmission and secretion in the GI tract (Neunlist et al., 2007; Savidge et al., 2007; Bach-Ngohou et al., 2010; MacEachern et al., 2011; Van Landeghem et al., 2011). It is not easy to reconcile such physiological events *in vivo*, but functional parallels can been drawn to astrocytes which are known to perform protective roles in the brain (Abbott et al., 2006). Enteric glia provide trophic and cytoprotective functions towards enteric neurons (Abdo et al., 2010, 2012). Recently it has become clear that they also possess receptors for many enteric neurotransmitters and are activated by synaptic transmission, e.g. by ATP release from intrinsic and extrinsic neurons following chemical or electrical stimulation (Gomes et al., 2009; Gulbransen and Sharkey, 2009; Gulbransen et al., 2010, 2012; Boesmans et al., 2013). This positions them to “listen” to the signaling in the ENS and respond appropriately. As ATP release is common in damaged tissues, it seems feasible that glial cells are also activated by environmental cues that may emanate from tissue trauma or infection. Not only do enteric glia respond to purines like ATP, they also respond to and make cytokines, possessing, for example, interleukin (IL)-1

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