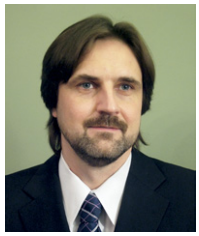
The Relationship Between Intestinal Microbiota and the Central Nervous System in Normal Gastrointestinal Function and Disease



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Although many people are aware of the communication that occurs between the gastrointestinal (GI) tract and the central nervous system, fewer know about the ability of the central nervous system to influence the microbiota or of the microbiota's influence on the brain and behavior. Within the GI tract, the microbiota have a mutually beneficial relationship with their host that maintains normal mucosal immune function, epithelial barrier integrity, motility, and nutrient absorption. Disruption of this relationship alters GI function and disease susceptibility. Animal studies suggest that perturbations of behavior, such as stress, can change the composition of the microbiota; these changes are associated with increased vulnerability to inflammatory stimuli in the GI tract. The mechanisms that underlie these alterations are likely to involve stress-induced changes in GI physiology that alter the habitat of enteric bacteria. Furthermore, experimental perturbation of the microbiota can alter behavior, and the behavior of germ-free mice differs from that of colonized mice. Gaining a better understanding of the relationship between behavior and the microbiota could provide insight into the pathogenesis of functional and inflammatory bowel disorders.

The gut–brain axis (GBA) is a bidirectional neurohumoral communication system that integrates brain and gastrointestinal (GI) functions. The GBA has been implicated in the pathophysiology of functional GI disorders, and evidence is emerging for its role in the pathogenesis of inflammatory disorders of the gut such as inflammatory bowel disease (IBD). It would be a relatively straightforward matter to integrate information about the intestinal microbiota with that of the GBA by simply reviewing literature on interactions between flora and the GI tract. However, the brain is the most influential organ within the axis, and communication is bidirectional. Thus, it is important to consider the influence of the brain on the microbial content of the gut and, conversely, to examine the evidence showing that the intestinal microbiota influences the brain and behavior. Investigation of the integration of the intestinal microbiota into the GBA could improve the understanding of the pathophysiology of both functional[1] and inflammatory[2] bowel conditions.

The GBA contributes to homeostasis of several systems, including GI function, appetite, and weight control. Because GI motility and epithelial function are critical determinants of the habitat for the microbiota, changes induced by the central nervous system or the GI tract alter the habitat and perturb the intestinal microbiota.[3] The longstanding observation that oral antibiotics and laxatives ameliorate hepatic encephalopathy provides a potent reminder that the intestinal microbiota is capable of influencing behavior, albeit under pathologic conditions.[4] Taken together, these observations provide a framework for considering the integration of the intestinal microbiota into the bidirectional GBA.

The Intestinal Microbiota

The gut contains a vast and complex microbial ecosystem, comprising mainly bacteria, of which most are strict anaerobes; it also includes fungi and viruses,[5–7] but only bacteria are considered in this review. Commensal bacteria instruct the immune and physiologic systems throughout life and are responsible for the presence of inflammatory and immune cells in the healthy gut: so-called "physiologic" or "controlled" inflammation. The term physiologic inflammation refers to the presence of

Abbreviations used in this paper: ACTH, adrenocorticotrophic hormone; GBA, gut–brain axis; GI, gastrointestinal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; SPF, specific pathogen-free.

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inflammatory cells in the mucosa and submucosa of the healthy GI tract and reflects the presence and immunologic accommodation (rather than immune tolerance) of the intestinal microbiota. The microbiota serves the host by protecting against pathogens, participating in the intake nutrients from the diet, metabolizing certain drugs and carcinogens, and influencing the absorption and distribution of fat.[8,9] The influence of the intestinal microbiota extends beyond the GI tract, contributing to, for example, pain perception in the skin[10] and fat deposition in the liver.[11,12] Disruption of the symbiotic relationship between the microbiota and the GI tract, referred to as dysbiosis,[13] perturbs host functions and, in some cases, causes the expression of overt and serious diseases such as IBD and *Clostridium difficile* colitis.[14–16]

Influence of the Microbiota on the GI Tract

A strategy that is commonly used to investigate interactions between the microbiota and the host is to compare germ-free animals with those colonized with a single strain or multiple strains of bacteria.[17] The microbiota influences expression of a broad array of host genes. A comparison of germ-free mice and mice colonized with *Bacteroides thetaiotaomicron*, a prominent member of the adult mouse and human gut microflora, showed that the microbiota modulate the expression of genes that regulate nutrient absorption, mucosal barrier enhancement, xenobiotic metabolism, and angiogenesis.[18] Colonization with *B. thetaiotaomicron* also induced a 2- to 5-fold increase in mRNA encoding the synaptic vesicle-associated protein-33,[18] which is involved in synaptic neurotransmission.[19] This finding indicates that commensal bacteria can influence the expression of genes whose products influence function in the nervous system.

Comparisons of germ-free and colonized animals indicate that, although crypt villous formation does not require the presence of bacteria, epithelial cell differentiation, including Paneth cell development, depends on the microbiota in a way that serves both the host and resident bacteria (for review, see Falk et al[17]). Similarly, the production and composition of mucin[20] and the development of 5-hydoxy-tryptamine–secreting enteroendocrine cells is influenced by the microbiota.[21] Germ-free rodents have an enlarged cecum, reflecting a gross disturbance in GI motility[22,23]; its prompt reversal to normal size on bacterial colonization identifies the microbiota as a determinant of GI motility.[24–26] The abnormal motility of germ-free animals probably reflects a combination of the lack of a mature enteroendocrine system,[21] changes in neurotransmission,[18] and immaturity of the mucosal immune system. The intestinal microbiota also has an important influence on the imprinting, maturation, and maintenance of the mucosal immune system (for reviews, see Falk et al[17] and Macpherson et al[27]). Inflammatory cells are sparse in the germ-free intestine, and secondary lymphoid structures are not developed. The significant number of inflammatory cells in the lamina propria of the colonized intestine of healthy hosts and the preservation of normal epithelial structure and function are reflections of the delicate and mutually beneficial relationship between the intestinal microbiota and the host. Disruption of this balance, as a result of perturbation of the microbiota by infection or antibiotics, results in dysbiosis. The effect of dysbiosis on the host is determined by the nature and magnitude of change in the bacteria composition of the GI tract, as well as by host susceptibilities.

Another strategy for assessing the effect of the intestinal microbiota on host function is to perturb the commensal bacteria with the use of oral antibiotics.[28] A combination of neomycin and bacitracin altered the microbiota in mice, substantially reducing the *Lactobacillus* population.[29] As shown in Figure 1, this resulted in a small increment in myeloperoxidase (MPO) activity (a measure of granulocytic inflammatory cell activity) without causing tissue damage. This increment in physiologic inflammation was accompanied by an increase in immunoreactive substance P, a sensory neurotransmitter, in the intestinal wall. The functional consequence was an increase in the visceromotor or pseudoaffective response (abdominal wall contraction after colorectal balloon distension), a widely used measure of visceral pain.[30] Thus, perturbation of the microbiota produced a response profile reminiscent of changes seen in some patients with irritable bowel syndrome (IBS): subclinical inflammation or immune activation and visceral hyperalgesia. Interestingly, when the mice were gavaged with *Lactobacillus paracasei*, the antibiotic-induced changes in inflammation, neurotransmitter content, and the visceromotor response improved.[29] Because the antibiotic-induced changes in the visceromotor response, immunoreactive substance P, and myeloperoxidase activity could also be attenuated by the administration of dexamethasone, it was concluded that the changes in visceral perception were secondary to the increase in the inflammatory or immune cell presence induced by the dysbiosis.[29] These results show that commensal bacteria can influence primary afferent nerves in the gut and serve as an example of a functional relationship between the sensory component of nervous system and the intestinal microbiota.

Influence of GI Physiology on the Microbiota

Although the microbiota exert a broad influence on host physiology, the converse is also true. Under normal conditions, the GI tract provides a stable habitat for commensal bacteria that supports its structural and functional integrity (Figure 2*A*). Disturbance of normal GI physiology destabilizes the habitat, resulting in changes in its microbial composition. An example of this is the change in the bacterial composition of the GI tract