The Brain-Gut Axis and Stress in Inflammatory Bowel Disease

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KEYWORDS

• Stress • Depression • Anxiety • Brain-gut axis • Vagus nerve • Gut microbiota

KEY POINTS

- The brain gut axis serves as a circuit that incorporates the human experience, the state of mind, the gut microbiome, and the immune response that ultimately drives the phenotypic expression of inflammatory bowel disease (IBD).
- There are several biological pathways through which stress can play a deleterious role in IBD, including through increasing intestinal permeability and thereby facilitating intestinal translocation of bacteria, which in turn can stimulate innate and adaptive immune responses.
- Increased perceived stress is associated with increased symptoms in persons with IBD; the relationship though between stress and symptoms is bidirectional.
- Although attention to stress and psychiatric comorbidity is important in the management of IBD, there are few clinical trials to direct management based on strong evidence.

THE BIOLOGY OF THE BRAIN-GUT AXIS AND STRESS IN INFLAMMATORY BOWEL DISEASE

A biopsychosocial understanding of illness describes clinical outcome and disease exacerbation as influencing and strongly influenced by both biological and psychosocial factors.[1] The brain and the gut communicate through the autonomic nervous system and the circumventricular organs both in physiologic and pathologic conditions.[1] This brain-gut axis serves as a circuit that incorporates the human experience, the state of mind, the gut microbiome, and the immune response that ultimately drives

Disclosure: Dr C.N. Bernstein is supported in part by the Bingham Chair in Gastroenterology. He has served on advisory boards for Abbvie Canada, Ferring Canada, Janssen Canada, Shire Canada, Takeda Canada, Pfizer Canada, and Cubist Pharmaceuticals and has consulted for Mylan Pharmaceuticals. He has received educational grants from Abbvie Canada, Shire Canada, Takeda Canada, and Janssen Canada. He has been on the speaker's panel for Abbvie Canada, Ferring Canada, and Shire Canada.

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Gastroenterol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.gtc.2017.08.006 **gastro.theclinics.com**
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the phenotypic expression of inflammatory bowel disease (IBD).[1] It is through this circuit that stress impacts gastrointestinal symptoms in health and IBD. Stress is conceptualized as the feeling of being challenged by a threatening event or an evolving situation.[2] Persistent stress may precipitate the development of major depression or chronic anxiety. Depression may affect more than 25% and anxiety more than 30% of persons with IBD, 2 to 3 times higher than in the general population.[3]

Stress may play a deleterious role in IBD through 8 main pathways (as reviewed in Ref.[1]). These pathways include the following: (a) activation of mast cells and the sympathetic nervous system, (b) vagus nerve inhibition on inflammatory pathways, (c) the prefrontal cortex and amygdala control over the hypothalamic pituitary axis (HPA), (d) the hypothalamic-corticotropin releasing factor (CRF)-ergic system, (e) the peripheral CRF-ergic system, (f) the effect of early life events on colitis (the HPA axis is programmed by early life events, and neonatal inflammatory stimuli exert long-term changes in HPA activity), (g) the impact of depression on exacerbating colitis possibly through shared proinflammatory cytokines, and (h) the intestinal microbiota-brain axis.

The vagus nerve is thought to have anti-inflammatory effects, and stress decreases vagus nerve efferent outflow[4] and increases sympathetic outflow and adrenomedullary activity, leading to increased norepinephrine and epinephrine levels.[4] Decreased vagus nerve outflow and increased sympathetic tone can lead to inhibition of immune cell functions and ultimately intestinal inflammation.[1] Furthermore, chronic stress can lead to an adaptation of the hypothalamic CRFergic system.[5] In rats, stress and CRF increase colonic permeability.[6] Stress-increased intestinal permeability allows bacteria to cross the epithelial barrier to activate the mucosal immune response[7] and to translocate to secondary lymphoid organs[8] to stimulate the innate immune system.

The neurohormonal control of intestinal immune response has been studied over decades. However, it has only been in the past 10 to 15 years that the gut microbiome has emerged as a likely critical compartment in the evolution of IBD. Stress-mediated changes may shift the microbial colonization patterns on the mucosal surface and alter the susceptibility of the host to infection. In turn, these changes in host-microbe interactions may also influence neural activity in stress-responsive brain areas.[9] Commensal microbiota can affect the postnatal development of brain systems involved in the endocrine response to stress.[10] Rat models of maternal separation, an important neonatal stress model, are associated with important changes in the HPA axis as well as in intestinal immunologic and microbial responses.[1] Altering the microbiota can also impact behavior and brain structures. Germ-free mice have been shown to reduce anxiety-like behavior in comparison to specific pathogen-free mice. This reduced anxiety-like behavior is accompanied by changes in plasticity-related genes in the hippocampus and amygdala.[11] Altering the gut microbiota in mice with a combination of antibiotics was associated with a change in gut bacteria, also an altered brain-derived neurotropic factor in the hippocampus and amygdala, and an increase in mouse exploratory behavior.[12] Behavioral traits of the donor mice were transferred to adult germ-free mice of a different strain by transplanting gut microbiota.[12]

The mechanisms by which the gut microbiota impact the gut-brain axis are being investigated. Candidates include the gamma-aminobutyric acid (GABA) and serotonin signaling pathways, which are implicated in the neurobiology of depression and anxiety.[13] GABA, a major inhibitory neurotransmitter, is a metabolite of certain gut microbes,[14,15] and increased serotonin turnover is observed in germ-free mice.[16] Neurotransmitters with well-known immune effects, including catecholamines, acetylcholine, and serotonin, are metabolites of gut microbiota.[17–19]

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