



Irritable Bowel Syndrome: The Pathophysiologic Links to More Effective Future Therapy

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Introduction

While the biopsychosocial model in the origin and development (etiopathogenesis) of irritable bowel syndrome (IBS) has been extensively studied over the last 20 years, there is increasing evidence that the pathophysiological (disease) processes in the “big brain” in the skull, the “little brain” in the gastrointestinal tract and their linked functions contribute to the abnormal motility, sensation, and secretion that result in IBS (Figure 1).

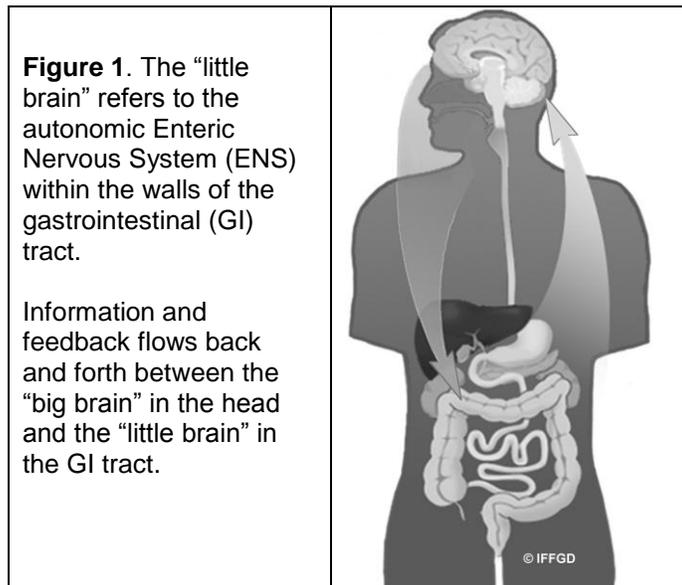


Figure 1. The “little brain” refers to the autonomic Enteric Nervous System (ENS) within the walls of the gastrointestinal (GI) tract.

Information and feedback flows back and forth between the “big brain” in the head and the “little brain” in the GI tract.

These data suggest that investigators and clinicians need to be dissuaded from approaching IBS as though it was a single disorder in all patients, or as though only one mechanism is responsible for development of symptoms. In essence, this is a plea for the importance of integrated rather than reductionist approaches to research, diagnosis, and management of IBS, and to a holistic approach to the management of the patient.

It's Not All in the Head

Researchers agree that stress and psychological traits contribute to some extent to the development of IBS. But it is clearly *not* “all in the head”! Reflexes induced by eating and centered in the lower portion of the brain (brainstem) are sometimes exaggerated in patients and induce symptoms such as postprandial (following a meal) cramping and urgency to have a bowel movement or diarrhea. The psychologic “make-up” of the individual determines how concerned he or she is by symptoms of IBS and, hence, who consults the physician. Novel imaging studies of the brain in IBS patients in response to threat suggest that parts of the brain that interpret the unpleasantness of symptoms, or pay attention to those symptoms are critical to the patient’s experience. Hence there are treatments with medications or behavioral therapy that may help some patients with IBS.

It's Not All Motility

The occurrence of several symptoms such as cramping pain, loose bowel motions, and relief of pain with passage of loose bowel motions suggest that there is a component of abnormal motility causing either painful spasm or rapid transit through the small bowel or colon. Conversely, slow movement of content through the colon may result in constipation. Researchers have identified the same types of contractions occurring with similar frequency in healthy individuals and IBS patients, suggesting that those contractions are not abnormal per se but are sensed more acutely and are perceived as painful by patients with IBS. Equally important, there are many patients with constipation or a sense of incomplete rectal evacuation whose symptoms are attributed to the disordered colonic function;

however, the primary problem in these patients is often in the pelvic floor or anal sphincters and results in abnormal stool evacuation that leads to secondary bloating, constipation and pain. Physicians should exclude evacuation disorders in all these patients since the treatment is totally different and it does not respond to “IBS” medications.

Is It All Due to Enhanced Bowel Sensation?

Recent studies have confirmed an important role for enhanced sensation or, at least, perception of bowel function in some patients with IBS; however, it is now clear from studies in different centers that probably less than 50% having increased rectal sensation. Sensory testing is no more accurate in diagnosis of IBS than a careful history and examination. Much research is exploring the role of the nerve fibers between the bowel and the brain, including those in the spinal cord, to determine whether patients with IBS have different sensory wiring. However, extrapolations from animal studies and models based on inflammation or parasitic infections seem too distant to the reality of IBS in humans to be truly relevant or realistic. There is no proven or effective medication approved for the treatment of pain sensation in IBS.

What is the role of secretion in IBS patients?

There is little evidence that the intestine secretes more fluid in IBS with diarrhea. However, medications have been developed to increase water and salt secretion to liquefy bowel movements and facilitate their passage through the colon.

A Best-Fit Model

Sensation from the bowel reaches the brain through a chain of three nerve fibers. First there are nerve endings located in the wall of the intestine. If the state of background contraction or tone of the intestine is altered, or if strong contractions distort the bowel's wall, the nerve endings located between the two muscle layers of the intestine will be stimulated and send a message to the brain. Hence, the state of contraction or relaxation influences sensations arising in the bowel.

Current research is exploring what hormones and nerve transmitters alter the state of contraction (background tone) of the bowel and how the brain's function might influence these activities. For

example, some centrally acting medications (medicines that act on the brain and central nervous system) that are not specifically approved for IBS may relieve pain (e.g., antidepressants, clonidine). However, the evidence supporting their efficacy is limited.

Researchers at Mayo Clinic have shown that several classes of approved medications normalize the passage of content through the small intestine and colon. These include serotonin type 3 (5-HT₃) receptor antagonists, which relieve diarrhea and rectal urgency, and lubiprostone and linaclotide (latter not yet approved) for constipation. With improved bowel function, these medications also relieve abdominal discomfort.

Mental stress and progressive muscular relaxation respectively increases and decreases sensation of a standard distention stimulus in the human colon. Some of these agents may also have effects on brain centers involved in sensation and perception of gut stimuli. These abnormal responses may be normalized with hypnotherapy, relaxation or cognitive behavioral therapy. The roles of the brain, nerve fibers, and the gut are closely intertwined in the development of IBS and call for integrated and holistic approaches to management of the syndrome.

Summary

Motor, secretory, and sensory functions in the human bowel are intimately connected functions that are linked with higher and lower centers in the brain. Further understanding of the interactions involved in this model of IBS will provide the basis for more effective pharmacology or other therapy in irritable bowel syndrome.

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