

Gut Feelings About Irritable Bowel Syndrome

Stephen M. Stahl, M.D., Ph.D.

Issue: *The brain and the gut have parallel pharmacologic regulatory systems that are also interlinked. Since irritable bowel syndrome may result from malfunctioning of these pharmacologic systems and their regulatory mechanisms, future treatments could be directed simultaneously at both the brain and the gut.*

P sychiatrist to gastroenterologist: "Isn't it surprising how many brain neurotransmitters are also in the gut?" Gastroenterologist to psychiatrist: "Not at all, but it sure is interesting how many gut neurotransmitters are in the brain."

The brain and gut are not only parallel pharmacologic systems, they are also interlinked pharmacologic systems. This link is not surprising given that the enteric nervous system, which innervates the gut, is embryologically derived from the same part of the neural crest that evolves into the brain.¹⁻⁴ Thus, the brain and gut go in separate directions during early development but preserve links that exert mutual and reciprocal regulatory influences on one another.

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

Hence, the enteric nervous system is sometimes called the "little brain."³

Pharmacology Below the Diaphragm

Several neurotransmitters act in both the brain and gut, such as serotonin (5-HT), cholecystokinin, neuropeptide Y, leptin, norepinephrine, opiates, acetylcholine, and dopamine.⁴ Neurotransmitters and drugs can increase or decrease bowel motility by playing on this pharmacology (Table 1). Indeed, about 90% of the 5-HT in the body is in the gut, specifically in enterochromaffin cells and myenteric interneurons.⁴ Serotonin receptors are located throughout the GI tract, including on afferent neurons and enteric and autonomic neurons, where they play a role in mediating sensory and reflex responses to stimuli in the gut as well as regulating and mediating such actions as emesis, diarrhea, abdominal pain, GI reflexes, and eating behavior. The specific 5-HT receptor subtypes in the gut are 5-HT₃ receptors, located on vagal afferent neurons that mediate visceral sensations and GI reflexes, and 5-HT₄ receptors, probably located on presynaptic cholinergic and motor neurons to influence bowel motility. Given the prominence of 5-HT and its receptors

in the gut, it is not surprising that drugs acting on 5-HT or its receptors can alter GI functions (Table 1).

Psychopharmacologic Links With the Gut

Having a "gut feeling" is probably much more than a figure of speech. Gut feelings are literally relayed to the brain; the brain then responds with feedback to the gut. For example, arousal and fear get processed by the brain and sent to the gut via the locus ceruleus. Vice versa, the feeling of a distended gut gets sent to the locus ceruleus in the brain for interpretation and processing.¹⁻³ This setup can lead at times to a vicious cycle in which either the brain or the gut starts a positive feedback system, causing significant GI distress from central sources as well as significant central distress from GI sources.

This interplay between brain and gut may account for the significant association of anxiety and affective disorders with irritable bowel syndrome (IBS). What is IBS? (See reference 5 for diagnostic criteria.) IBS was once classified as a psychosomatic illness, but currently it is conceptualized as a "hard-wired" malfunctioning of brain-gut interactions and gut pharmacologic regula-

tory mechanisms. Although the cause of IBS is unknown, it is known to be associated with increased sensitivity and activity of the GI tract, which lead to abnormal sensations of pain and motor activity, i.e., IBS patients feel more pain and discomfort with rectal distention than do normal volunteers.

The pathophysiologic relationship between IBS and panic disorder is highlighted by the fact that up to 40% of panic disorder patients have IBS and up to 30% of IBS patients have panic disorder.¹⁻³ Furthermore, GI symptoms are the third most common presentation of panic disorder (after cardiovascular-respiratory and neurologic presentations). Observations that panic disorder and IBS tend to remit simultaneously have led to suggestions that treatments for panic disorder may be effective in IBS, even in the absence of panic disorder. Generalized anxiety disorder and social anxiety disorder are also very common in IBS patients, and nearly 30% of IBS patients may have major depressive disorder and 60%, dysthymia.^{6,7} Thus, a profound relationship exists between affective and anxiety disorders and IBS, making it difficult to determine which came first.

Treating Gut Disorders With Psychotropics: Where Is the Target?

Treatment of IBS is largely unsatisfactory and involves the symptomatic use of smooth-muscle relaxants, bulking agents, and drugs for diarrhea. The potential effectiveness of antidepressants in the management of IBS has been observed for over 20 years, starting with the tricyclic antidepressants, and more

Take-Home Points

- ◆ The gut is controlled peripherally by a “little brain,” namely the enteric nervous system, derived from the same neural crest as the central nervous system.
- ◆ Gut motility is regulated by neurotransmitters of enteric neurons that innervate the bowel and also by neurotransmitters in brain regions such as the locus ceruleus and vagal nerve centers.
- ◆ Irritable bowel syndrome may share a common pathophysiology with anxiety and affective disorders, which may also explain why it is so commonly comorbid with them.
- ◆ Effective treatments for anxiety and affective disorders may relieve irritable bowel syndrome, by both a central and a peripheral pharmacologic action directly in the gut.

Table 1. Gut Pharmacology: Parallel and Analogous to the Brain^a

| Speed Up (Prokinetic/Faster Emptying) | Examples | Slow Down (Constipating/Retention) | Examples |
|---------------------------------------|--|------------------------------------|------------------------|
| D ₂ blockade | Metoclopramide | D ₂ stimulation | Levodopa |
| Acetylcholine muscarinic stimulation | Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) | Muscarinic blockade | TCA's |
| 5-HT ₃ stimulation | SSRIs | 5-HT ₃ blockade | Alosetron ^b |
| 5-HT ₄ stimulation | SSRIs | 5-HT ₄ blockade | ? |
| μ-Opiate blockade | ? | μ-Opiate stimulation | Morphine |
| α ₁ Blockade | Tamsulosin | α ₁ Stimulation | Reboxetine |

^aAbbreviations: D₂ = dopamine-2, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressant.
^bWithdrawn from marketing.

recently, the SSRIs and mirtazapine.⁸⁻¹³ Although a preexisting anxiety disorder apparently does not predict response to an SSRI in IBS,¹³ it is still unclear how much of the potential therapeutic actions of antidepressants are due to relief of comorbid anxiety and depression, how much to a direct antinociceptive action in the CNS, and how much to a change in functional serotonergic neurotransmission directly in the gut. Research exploring the potential efficacy of traditional and novel antidepressants for IBS may yet make sense out of gut feelings.

REFERENCES

- Lydiard RB, Falsetti SA. *Am J Med* 1999;107:65S-73S
- Lydiard RB, et al. *Am J Psychiatry* 1994;151:64
- Lydiard RB. *Psychiatr Ann* 1992;22:612
- Hardman JG, Limbird LE, eds. *Goodman & Gilman's Pharmacological Basis of Therapeutics*. 9th ed. NY, NY: McGraw Hill; 1996
- Thompson WG, et al. *Functional Gastrointestinal Disorders Diagnosis: Pathophysiology and Treatment*. McLean, VA: Degnon Assoc; 1994:115-173
- Tollefson GD, et al. *Ann Clin Psychiatry* 1991;3:215-222
- Masand PS, et al. *J Clin Psychiatry* 1995;56:363-367
- Jackson JL, et al. *Am J Med* 2000;108:65-72
- Thomas SG. *Am J Psychiatry* 2000;157:1341-1342
- Emmanuel NP, et al. *Am J Psychiatry* 1997;154:711-712
- Kirsch MA, Louie AK. *Am J Psychiatry* 2000;157:1523-1524
- Masand PS, et al. Presented at the 41st Annual Meeting of the NCDEU; May 28-31, 2001; Phoenix, Ariz. Session 1:95
- Gupta S, et al. Does a preexisting anxiety disorder predict response to paroxetine in IBS? Presented at the 154th Annual Meeting of the American Psychiatric Association; May 5-10, 2001; New Orleans, La