

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***An Allergic Basis for Abdominal Pain**

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Gastrointestinal symptoms are common in children and adults and often include abdominal pain after eating. Millions of people have chronic symptoms that have been labeled as functional gastrointestinal pain or irritable bowel syndrome (IBS) with no identifiable cause. This situation is frustrating for patients and their health care providers, since few effective treatments are available and those that are available do not provide satisfactory relief for many patients. Moreover, clinicians often have the impression that the disease is all in the head.

A prevailing theory of IBS relates to the gut-brain axis. This theory holds that the symptoms may be caused by overly sensitive nerves in the gastrointestinal tract and the way their signals are processed in the brain. Indeed, the intestinal nerves of such patients are hypersensitive to a variety of stimuli, and therefore, daily functions, such as gastrointestinal stretching and food motility, may feel more painful in these patients than in unaffected persons. During periods of emotional or physical stress (e.g., anxiety or infection), symptoms flare owing to the close interaction between the brain and the gut.

It is hypothesized that an interaction between the immune system and the enteric nervous system causes idiopathic gastrointestinal symptoms. Infectious gastroenteritis is a risk factor for IBS; many enteric infections lead to new-onset IBS, and patients with IBS often report that their symptoms started at the time of a gastrointestinal infection. Furthermore, increases in the numbers of mast cells and in the release of mediators, including neurotropic substances, may be involved in visceral hypersensitivity.¹

Mast cells are white cells that reside in various tissues near mucosal interfaces, especially those that are proximal to blood vessels and nerve fibers. They are classically known for their

pivotal role in allergic reactions; they harbor high-affinity receptors for IgE and can rapidly release mediators, such as histamine, after exposure to allergens.² A recent study by Aguilera-Lizarraga and colleagues³ suggests that a peripheral immune mechanism involving local mast cells stimulated by food-induced local IgE may underlie the symptoms associated with IBS and functional abdominal pain; these findings prompt consideration of new therapeutic strategies to target mast cells and allergies.

Aguilera-Lizarraga et al. investigated whether normal tolerance to oral antigens (food) in mice would be broken if the mice were simultaneously infected with an experimental gut bacterium (*Citrobacter rodentium*) and fed antigens from egg whites (ovalbumin). After the gut infection cleared, the mice ingested the ovalbumin again; this time, they had abdominal pain, as assessed by contractions of the stomach muscles, which were measured with the use of an implanted device that quantified visceral hypersensitivity. These mice also had diarrhea and a reduced intestinal transit time. In contrast, mice that did not receive ovalbumin during gut infection did not have similar effects or other abnormalities. Furthermore, in ovalbumin-treated, bacteria-infected mice, ovalbumin-specific IgE antibodies were present in the colon — the site colonized by *C. rodentium* — but were not present in the small intestine or the serum. In these mice, the ingestion of agents that interfered with allergy, including anti-IgE, mast-cell stabilizers, and histamine H₁ receptor antagonists, attenuated the pathologic and symptomatic responses. In addition, mice that were engineered genetically to be deficient in mast cells or in histamine H₁ receptor were protected to an extent similar to that of the control mice. Stimulation of colonic splanchnic nerves, which transmit visceral pain signals

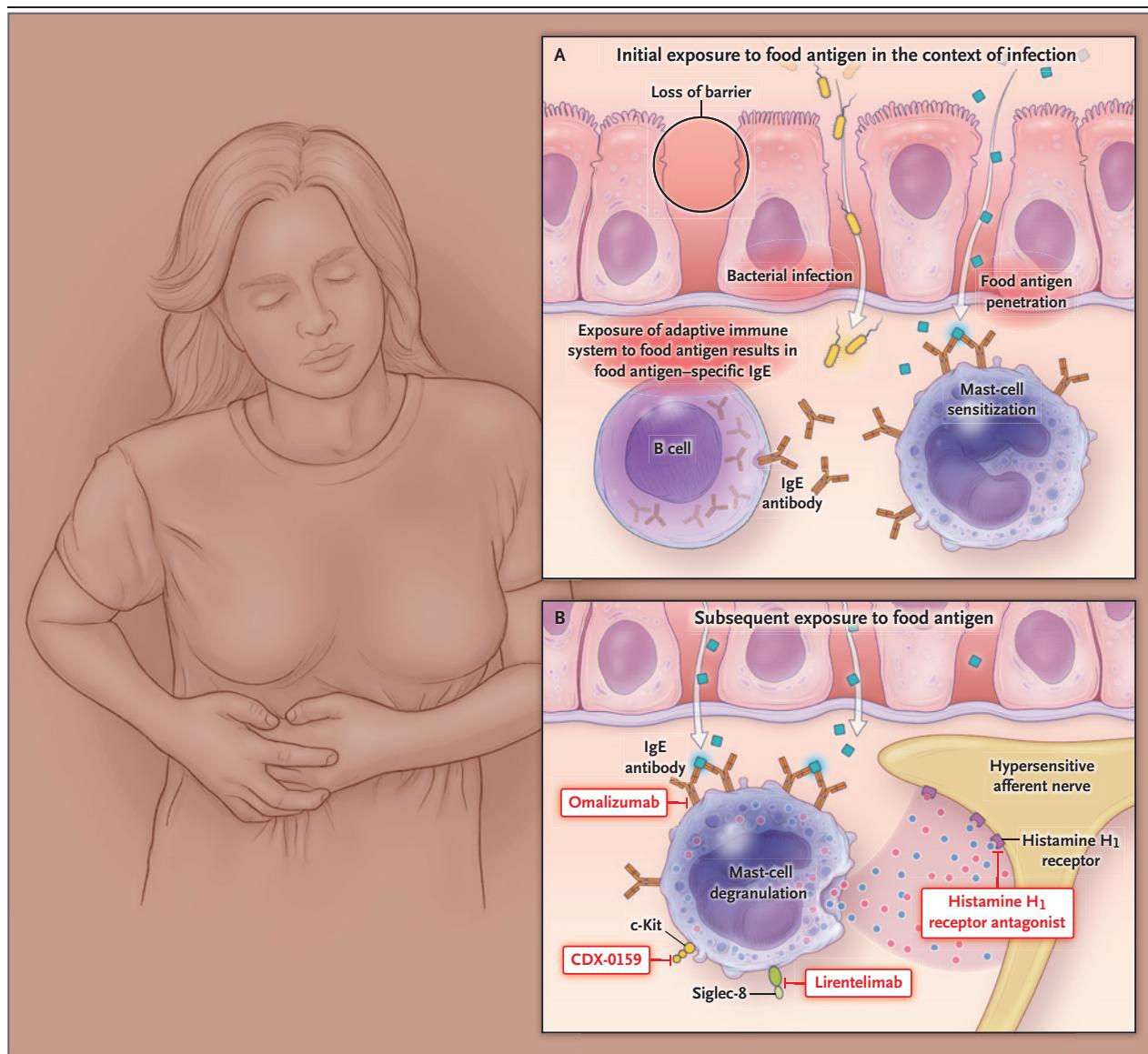


Figure 1. Allergic Immune Response and Food-Induced Gastrointestinal Symptoms.

A study recently reported by Aguilera-Lizarraga et al.³ supports the theory that a peripheral immune mechanism involving mast cells stimulated by food-induced local IgE may underlie the symptoms associated with irritable bowel syndrome (IBS) and functional abdominal pain, prompting consideration of new therapeutic strategies to target mast cells and allergies. In persons with a genetic predisposition to IBS, bacterial infection triggers a loss of barrier function in the colon. Subsequently, food allergens penetrate the mucosa and lead to IgE sensitization and loading of mast cells with surface-bound IgE (Panel A). After reexposure to the allergens, local mast cells bearing allergen-specific IgE degranulate, which results in the release of neurotropic mediators, including histamine. Exposure to these mediators renders afferent nerves hypersensitive, and hypersensitivity may persist even in the absence of the triggering food antigen. Targets of potential therapeutic intervention include IgE (targeted by omalizumab), the inhibition of mast cells (with the use of lirentelimab, which binds Siglec-8, a receptor expressed by mast cells), the depletion of mast cells (through anti-c-Kit antibody), and antihistamine receptors.

to the spinal cord, induced greater neuronal excitability in allergic mice than in control mice, and this effect was blocked by antihistamine treatment. These findings indicate that a gastro-

intestinal bacterial infection can break oral tolerance to a dietary antigen and result in an adaptive immune response toward that antigen, which in turn can lead to increased gut perme-

ability and abnormal pain signaling when re-exposure to the antigen occurs (Fig. 1).

Do these results apply to patients? The investigators explored whether 12 patients with IBS and 8 unaffected persons had evidence of food-triggered mast-cell responses. The results showed no evidence of systemic IgE against common foods, findings that were consistent with those of the studies in mice. However, when the investigators injected common allergens into the rectal mucosa, every patient with IBS had a localized reaction to at least one of the antigens; 2 of the 8 participants in the control group had a reaction to a single allergen.

Should the study by Aguilera-Lizarraga et al. shift our view of functional gastrointestinal symptoms and IBS? Possibly, but there is still more to know, partly because the translation of the findings in mice rests on an unconventional research test (injection of antigens into the rectal mucosa) in a very small number of human participants. In addition, which of the mast-cell mediators, if any, are involved in the human disease remains to be determined. Furthermore, the examination of mast cells in human gastrointestinal biopsy specimens is not routinely performed and may require measurement of the proximity of mast cells to nerve endings — a challenging task. Data from other studies conducted by the same senior author provided preliminary evidence that prolonged and high doses of a histamine H₁ receptor antagonist reduce visceral hypersensitivity, symptoms, and abdominal pain in patients with IBS.⁴ In addition to anti-histamine therapy, there are existing and emerging targeted therapies that block the allergic pathways and may have value in the treatment of the functional symptoms of IBS and other diseases (Fig. 1).

It is increasingly evident that food allergy is not a disease that involves only systemic IgE-mediated reactions.⁵ Rather, there is a spectrum of food-induced allergic responses, with IgE-mediated systemic anaphylaxis at one end and

gastrointestinal tissue-specific allergic responses on the other end. In the middle are diseases in which specific segments of the gastrointestinal tract are the sites of local food-induced allergic responses, such as the colon-specific mast-cell responses described by Aguilera-Lizarraga et al. and the esophagus-specific eosinophilic responses in eosinophilic esophagitis.⁵ A fundamental difference between the allergic responses described by Aguilera-Lizarraga et al. and classic food allergy is that the ovalbumin-specific IgE antibodies identified by Aguilera-Lizarraga et al. were detectable only in colonic tissue, which indicated a local rather than a systemic immune response against dietary antigens. The tissue-specific nature of this response probably involves an interaction of genetic and environmental factors, as has been uncovered for eosinophilic esophagitis, the risk for which is associated with genetic variants in an esophageal mucosal pathway.⁵ In summary, although a great deal remains to be elucidated, recent data support the hypothesis that common gastrointestinal ailments, such as IBS and functional abdominal pain, may instead be food-induced allergic disorders.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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