ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

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The Emerging Role of Mast Cells in Irritable Bowel Syndrome

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G&H What factors contribute to the pathogenesis of irritable bowel syndrome?

GB The diagnosis of irritable bowel syndrome (IBS) is based on symptom criteria, and because the vocabulary of the intestine that is used to express discomfort is rather limited, it is not surprising that IBS is a rather heterogeneous disorder. IBS is actually a collection of diseases that present themselves with a similar clinical phenotype, which implies that there may be various subpopulations of IBS that have different factors contributing to or triggering the disease. However, there are a few well-established factors that contribute to the pathogenesis of IBS, such as stress or an episode of a gastrointestinal infection. Another factor that contributes to the development of IBS is food intake, a topic that has recently seen an increase in interest due to the introduction of the low–fermentable oligo-, di-, and monosaccharide and polyol (FODMAP) diet.

> ... both preclinical and human data show that mast cells seem to be more activated in patients with IBS ...

G&H What are the primary roles of mast cells in the gastrointestinal tract?

GB The roles of mast cells in general are very diverse. Mast cells are mostly viewed as effectors of allergy and anaphylaxis, and are best known for their role in asthma and allergic rhinitis. Within the gastrointestinal tract, mast cells regulate vascular and epithelial permeability, ion secretion, angiogenesis, peristalsis, fibrosis and tissue repair, innate and adaptive immunity, bacterial defense, chemotaxis, and nociception. In particular, mast cells are important for defending against and expelling parasites, and play a key role in food allergy. For more than a decade, and with particular respect to IBS, compelling evidence has shown that mast cells may be involved in the generation of IBS symptoms, particularly visceral hypersensitivity.

G&H Do mast cell counts differ between diarrhea- and constipation-predominant IBS?

GB This is a slightly controversial issue. Researchers in Southern Europe (eg, Italy, Spain) have found increases in the number of mast cells in biopsies of patients with IBS, whereas studies from Northern Europe (eg, the

Netherlands, Belgium, Sweden) have not replicated this finding. A recent meta-analysis of the available data on the number of mast cells also found no difference with respect to diarrhea- or constipation-predominant IBS. However, a more relevant and consistent finding is that patients with IBS have evidence of increased activation of mast cells in mucosal biopsies as compared to healthy controls, which is significant for the induction of symptoms.

G&H What is the role of mast cells in mucosal immunity and low-grade inflammation?

GB This topic is currently being studied in great detail; the ongoing hypothesis is that patients with IBS have an increased mucosal permeability that leads to a higher influx of antigens from the intestinal lumen. These antigens activate the immune system, including mast cells and other immune cells. The literature refers to this as low-grade inflammation. Some clinicians, including myself, are not convinced that this is the correct mechanism of events and doubt that there is significant activation of the intestinal immune system in IBS. However, it is clear that both preclinical and human data show that mast cells seem to be more activated in patients with IBS, releasing mediators known to interact with nerve endings and to trigger pain. A key question that is currently being studied is why mast cells are being activated in patients with IBS.

G&H How does nerve–mast cell interaction influence the pathogenesis of IBS?

GB In general, mast cell activation conduces visceral hypersensitivity by raising the response of nerves when they are activated. More specifically, there are 3 mechanisms of action. The first is a direct activation of nerve endings through the release of mast cell mediators, the most well-studied of which are histamine, serotonin, and proteases. When any of these mediators activate nerve endings, pain signals are transmitted up the spinal cord to the brain, which perceives pain.

The second pathway is the release of nerve growth factors from mast cells that upregulate the expression of pain-sensing molecules on these nerve endings. Some pain-sensing molecules that have been studied extensively in IBS and in somatic pain in general are transient receptor potential (TRP) channels, including the TRP vanilloid receptor-1 (TRPV1), TRP vanilloid receptor-4 (TRPV4), and TRP ankyrin 1 (TRPA1) channels. Expression of these receptors can be upregulated by mast cell–released nerve growth factors, and thereby enhance the response of pain-sensing nerves to a painful stimulus.

The third mechanism, which my colleagues and I are researching in particular, is the sensitization of TRP channels (ie, TRPV1, TRPV4, TRPA1) through the release of mast cell mediators. Increasingly, evidence demonstrates that when mast cell mediators such as histamine are placed on neurons, the neurons will react more intensely to pain-inducing stimuli (eg, capsaicin or red pepper) than under normal conditions. This effect can be compared to sunburned skin, which is much more sensitive to heat (eg, taking a hot shower). A similar mechanism in the gut takes place when pain-sensing nerve endings are exposed to mast cell mediators such as histamine. These nerve endings will react more intensely, which contributes to increased pain. Importantly, my colleagues and I found that this phenomenon indeed occurs in neurons that are present in biopsies of IBS patients, and, thus, represents an important target for treatment.

> ... a low-FODMAP diet does not alter the underlying mechanism of visceral hypersensitivity, meaning that the increased pain response persists.

G&H What is the relationship between psychological stress and mast cell activation?

GB The results of rodent studies have shown that psychological stress can trigger the activation of mast cells, which increases the permeability of the mucosa. Of note, the mediators released by mast cells in response to stress will activate and sensitize pain-sensing neurons, as discussed earlier, and contribute to increased pain perception. It is also important to consider the impact of stress within the brain, as stress significantly contributes to how incoming pain signals from the gut are perceived and integrated.

G&H What therapies are currently available to target mast cells?

GB As far as I am aware, no compound known to target mast cells is registered for the treatment of IBS. Cromoglycin is an old compound that is used for asthma or

allergic rhinitis and is meant to act as a mast cell stabilizer. Thus far, only 1 or 2 very small studies have evaluated this compound in IBS, but not in great detail or with the required study design. Several years ago, my colleagues and I conducted a small trial with ketotifen, a drug with histamine-1 receptor agonist properties that is also used for allergic conditions and has been proposed to have mast cell–stabilizing properties. We were able to show improvement in patients with IBS with this compound; however, biopsies taken before and after treatment did not show a reduction in mast cell mediators. Therefore, we hypothesized that the effect of the drug was actually due to its histamine-1 receptor–blocking properties. To test this, we subsequently performed a small pilot study in which we tested the effect of a compound known to effectively block histamine-1 receptors. We showed that this treatment was very effective and could even reverse or prevent the sensitization of neurons. In a larger randomized, multicenter trial, my colleagues and I are currently trying to confirm these results. Hopefully, the results of this study will demonstrate that patients have improved abdominal pain and general symptom relief on these histamine-1 receptor blockers.

G&H Is an altered diet a useful treatment strategy?

GB Food is one of the main triggers of IBS symptoms. As mentioned earlier, FODMAPs have gained a lot of attention lately and seem to play an important role in IBS symptom generation. These fermentable small sugars cannot be properly digested by humans, leading to an osmotic effect in the small intestine by attracting water, or are fermented with gas production and distension in the colon. Distention is an important trigger for visceral pain; therefore, it is not surprising that reducing the intake of these sugars through a low-FODMAP diet may reduce symptoms in IBS patients. It is important to note that a low-FODMAP diet does not alter the underlying mechanism of visceral hypersensitivity, meaning that the increased pain response persists. Research is ongoing in preclinical models and in patients to investigate the association between certain foods, including FODMAPS, and mast cell activation.

G&H What are the priorities of research?

GB A tool or biomarker that could help clinicians to identify IBS subpopulations with a particular underlying mechanism of disease would aid tremendously in choosing an appropriate treatment. It would also allow clinicians to better select the proper patient population for drug trials and choose a more homogeneous study population. Regarding mast cell research, the main priority is to identify the pathways that lead to mast cell activation so that more efficient treatments can be developed to treat IBS patients, at least those in whom mast cell activation is the main mechanism of disease.

Dr Boeckxstaens has no relevant conflicts of interest to disclose.

Suggested Reading

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