



Targeting Histamine Receptors in Irritable Bowel Syndrome: A Critical Appraisal

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Irritable bowel syndrome is a group of functional gastrointestinal disorders with not yet fully clarified etiology. Recent evidence suggesting that mast cells may play a central role in the pathogenesis of irritable bowel syndrome paves the way for agents targeting histamine receptors as a potential therapeutic option in clinical treatment. In this review, the role of histamine and histamine receptors is debated. Moreover, the clinical evidence of anti-histamine therapeutics in irritable bowel syndrome is discussed.

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Key Words

Ebastine; Irritable bowel syndrome; Mast cells; Receptors, histamine

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder without completely elucidated etiology. The typical symptoms are abdominal pain and change in bowel habits. Additionally, bloating, tenesmus, bowel urgency, and abdominal distension can occur. A recent meta-analysis estimated the international prevalence of IBS at 11.2%¹ based on the Rome III criteria; however, a recent study in China showed that the number of patients diagnosed based on the Rome IV criteria is nearly half the number of patients diagnosed according to the Rome III criteria.² However, only one-third of those who suffer from IBS-like symptoms see a physician, the actual prevalence may be much higher. IBS impairs the quality of life in patients to a similar degree as in patients with inflammatory bowel diseases³ and the impairment is proportional to

the severity of the symptoms experienced by the patient.⁴

IBS is a heterogeneous entity with etiology comprising of multiple factors such as inflammation, neuroimmune interactions,⁵ gut microbiota,⁶ environmental pollution,⁷ and abnormal gut-brain axis.⁸ This heterogeneity has a significant impact on treatment. As the disease profile may vary between the patients, the treatment should be personally tailored with regard to predominant symptoms and disease characteristics. It is particularly crucial due to the plethora of drugs available on the market nowadays.⁹ However, despite the number of drugs available the treatments are not fully satisfactory in all patients. Also, the symptoms eventually relapse.

A large portion of both established and investigated treatment options include drugs based on serotonin (5-hydroxytryptamine, 5-HT). Indeed, 5-HT plays an important role in the gut by affecting motility and secretion.¹⁰ Moreover, it was recently found that alterations in 5-HT metabolism may be implicated in visceral hy-

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persensitivity, which is an important feature of IBS.¹¹ Interestingly, in a study performed by Cremon et al¹² the lamina propria mast cell (MC) count positively correlates with the increase in spontaneous 5-HT release in patients with IBS. While serotonin has already proven to be implicated in the pathogenesis of IBS, histamine is emerging as an important biogenic amine in this disease. Although the pathophysiological role of histamine in IBS is not entirely clear, there is evidence that supports the use of agents targeting the histamine receptors (HRs) as a potential therapeutic option in these patients. In this review, the role of histamine and HRs in IBS is critically appraised. Moreover, the possible use of anti-histamine therapeutics is discussed.

Overview of Histamine and Histamine Receptors in the Gastrointestinal Tract

Histamine (2-[4-imidazolyl]-ethylamine) is a short-acting endogenous amine, which is widely distributed in the human body.¹³ Histamine is synthesized by the enzyme histidine decarboxylase in all human tissues, but is particularly abundant in the skin, lungs, and GI tract.¹⁴

Histamine is produced mainly by MCs and, to a lesser extent, by basophils, gastric enterochromaffin-like cells, and histaminergic neurons.^{15,16} However, platelets, dendritic cells (DCs), T cells, and even microbes can also express histidine decarboxylase following a stimulation by cytokines, including IL-1, IL-3, IL-12, IL-18, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, and TNF- α .^{13,17,18} Only MCs and basophils are capable of storing large quantities of histamine. Other cell types such as DCs and lymphocytes do not store histamine intracellularly but the synthesis is followed by an immediate secretion.

Histamine is involved in several physiological functions, including cell proliferation and differentiation, hematopoiesis, regeneration, and the regulation of innate and adaptive immune systems.¹⁹ Histamine exerts its biological actions by binding to 4 subtypes of HRs, which are named chronologically in order of their discovery: H₁R-H₄R. These 4 binding sites belong to the rhodopsin-like family of G protein-coupled receptors, which are differentially expressed in numerous cell types. Although all 4 HRs are expressed in the human body, the intestines seem to be devoid of H₃Rs.²⁰ The expression pattern of HRs does not change anatomically along the intestine.

In the GI tract, histamine is believed to impact at least 3 major functions: modulation of GI motility, enhancement of gastric acid production, and alteration of mucosal ion secretion.²¹⁻²³ H₁Rs are involved in mediating sensorineural signaling and vascular dilatation.²⁴ Activation of H₁R is known to regulate food and water intake and diurnal feeding rhythm.²⁵ Stimulation of H₂R results in degranulation of MCs, synthesis of antibodies, production of T helper (Th) 1 cytokines, and T-cell proliferation.^{16,26} H₄R plays a significant role in nociception, autoimmune disorders, colon cancer, and allergy.²⁷⁻²⁹ Clear interpretation of histamine involvement in regulation of GI motility is currently lacking. However, the evidence indicates that overproduction of histamine by MCs may be responsible for diarrhea caused by increased neuronal secretomotor function.³⁰ Another hypothesis assumes that in constipated patients histamine induces altered enteric neuron function as a result of an excessive segmental contractile colonic motor activity.³¹ However, the pathological relevance of increased histamine levels in diseases, such as IBS, is not yet fully elucidated.

Table 1 describes the localization and role of specific HRs in the GI tract. Localization of HRs in the intestinal wall is depicted

Table 1. Localization and Role of Specific Histamine Receptors in the Gastrointestinal Tract

Receptors	Localization	Role
H1	Enterocytes, connective tissue cells, immune cells, blood vessels, myocytes, and myenteric plexus	Regulation of diurnal feeding rhythm, mediation of sensorineural signaling, control of vascular dilatation and permeability, impact on gastrointestinal contractility and motility, and modulation of visceral pain
H2	Enterocytes, immune cells, myocytes, and myenteric plexus	Immunomodulatory properties and control of gastrointestinal contractility and motility
H3	Not found in the human gastrointestinal tract	
H4	Lamina propria mononuclear cells and intestinal mast cells, leukocytes in mucosal and submucosal blood vessels, and enterocytes in the apical end of intestinal glands	Immunomodulatory properties, impact on gastrointestinal contractility and motility, and modulation of visceral pain

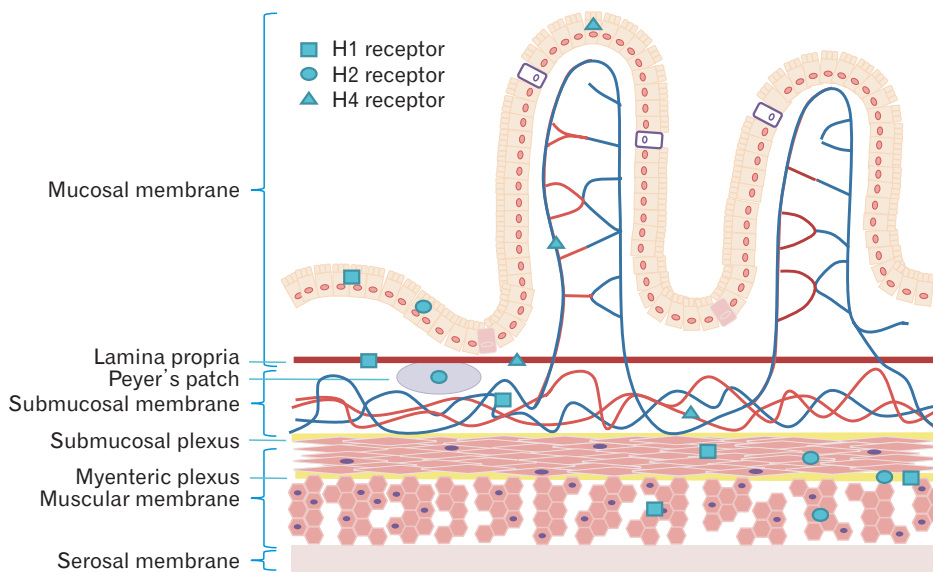


Figure. Localization of histamine receptors in the intestinal wall.

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Irritable Bowel Syndrome and Histamine

The summary on animal and human studies with MCs and HRs as targets is shown in Table 2.³²⁻⁴¹

The etiology and the pathophysiology are only partly understood, with some evidence suggesting that intestinal infections, and dysfunctional mucosal immune responses may play a role in the development of IBS and its symptoms.

Patients with IBS frequently experience post-prandial worsening of their symptoms. Moreover, a vast majority of IBS patients feel that distinct foods play pivotal role in triggering their symptoms. In a recent study,⁴² 58% of patients with IBS experienced GI symptoms from histamine-releasing food items such as milk, wine or beer, and foods rich in biogenic amines (wine, beer, and cheese). Interestingly, the use of spherical carbon adsorbents, known for adsorbing molecules (for instance histamine) from the gut lumen has been proven to be beneficial in some patients.⁴¹

High levels of histamine were found in supernatants from IBS colonic samples.⁴³ Application of this supernatant to rat submucous neurons resulted in increased neuronal activity. Furthermore, positive correlation between histamine levels in the supernatant and the degree of activation was stated.⁴⁴ The neuronal response of submucous neurons to the artificially designed cocktail, which is a combination of mucosal and immune mediators mimicking nerve activating components found in colonic biopsy supernatants and serum of IBS-patients, was lower in mucosal IBS biopsies compared

to healthy controls.⁴⁵ This effect appears in IBS most likely due to the desensitization to mediators, which is caused by the chronic contact of the gut wall with the mediators found in the gut lumen. Additionally, histamine induced murine jejunal afferent firing and excited primary sensory neurons.^{46,47} According to the study of Barbara et al,⁴³ the pronociceptive effect of histamine appears to be mediated, at least partly, by H₁R expressed on sensory afferents. In contrast, Guarino et al⁴⁸ found that supernatants from patients with IBS impair contractility of isolated human colonic smooth muscles and the phenomenon is histamine-independent. The effect was significantly reversible by apocynin, a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor, suggesting the intracellular oxidative stress damage to be the main cause of this contractility impairment.

The expression of H₁R and H₂R in the intestinal tissue samples of IBS patients is upregulated.²⁰ Moreover, it has been reported that H₁R activation results in proinflammatory effects such as IFN production and Th1 cell proliferation, while H₂R activation appears to suppress inflammation.^{19,49,50} Activation of H₂R by histamine suppresses IL-12 production by monocytes,⁵¹ IFN- γ production by macrophages,⁵² TNF- α secretion by MCs,⁵³ and IL-12 release by immature DCs.⁵⁴ In vivo studies showed that histamine suppresses both Th1- and Th2-type responses by H₂R.⁵⁵ It is noteworthy that in colonic biopsies of IBS patients or patients with food allergy, no alterations in H₄R mRNA levels were reported.²⁰ However, involvement of the H₄R in visceral sensory signaling and GI contractility has been documented⁵⁶; yet, more studies are needed to fully elucidate the contribution of H₄R in IBS.

Table 2. Animal and Human Studies Focusing on Histamine Receptors and Mast Cells as a Potential Target in Irritable Bowel Syndrome Treatment

Compound	Mechanism of action	Dose	Species	Effect	References
Animal studies					
Disodium cromoglycate	MCs stabilizer	2.5 and 50 mg/kg, ip	Rat	Inhibition of visceral hypersensitivity during colorectal distension in stress-sensitive rats	Carroll et al, ³² 2013
Doxantrazole	MCs stabilizer	2 mg/kg, ip	Rat	Suppression of stress- and corticotropin releasing factor-induced rectal hyperalgesia to rectal distension	Gué et al, ³³ 1997
Ebastine	H ₁ R antagonist	0.1 and 1 mg/kg administered 3 times, ip in 24 hr	Rat	Reversed post stress visceral hypersensitivity at the dose 1 mg/kg	Stanisor et al, ³⁴ 2013
Fexofenadine	H ₁ R antagonist MCs stabilizer	1.8 and 18 mg/kg administered 3 times, ip in 24 hr	Rat	Reversed post stress visceral hypersensitivity	Stanisor et al, ³⁴ 2013
Ketotifen	H ₁ R antagonist and MCs stabilizer	10 mg/kg/day, po in drinking water	Rat	Prevention of hypermotility and mucosal MC hyperplasia	Serna et al, ³⁵ 2006
Human studies					
Disodium cromoglycate	MCs stabilizer	1500 mg/day for 8 wk	Human	Improvement of symptoms	Stefanini et al, ³⁶ 1992
Disodium cromoglycate	MCs stabilizer	1500 mg/day for 1 mo	Human	Improvement of symptoms	Stefanini et al, ³⁷ 1995
Ketotifen	MCs stabilizer and H ₁ R antagonist	2 mg bid for 2 wk, 4 mg bid for 4 wk and 6 mg bid for another 4 wk	Human	Increased tolerance to discomfort in patients with IBS with visceral hypersensitivity, reduced IBS symptoms and improved health-related quality of life	Klooker et al, ³⁸ 2010
Ebastine	H ₁ R antagonist	20 mg/day for 12 wk	Human	Reduced visceral hypersensitivity and abdominal pain, increased symptom relief in patients with IBS	Wouters et al, ³⁹ 2016
Famotidine	H ₂ R antagonist	20 mg bid	Human	Improvement of symptoms	Dave and Rubin, ⁴⁰ 1999
Ranitidine	H ₂ R antagonist	150 mg/kg bid	Human	Improvement of symptoms	Dave and Rubin, ⁴⁰ 1999
AST-120 (spherical carbon adsorbent)	Adsorption of low molecular substances (including histamine and serotonin among others)	2 g or placebo 3 times/day for 8 wk, placebo for 2 wk, and 2 g of drug for 8 wk	Human	Improvement in bloating and stool consistency	Täck et al, ⁴¹ 2011

MCs, mast cells; ip, intraperitoneally; H₁R, histamine H1 receptor; H₂R, histamine H2 receptor; po, per os; bid, twice daily; IBS, irritable bowel syndrome.

There is a large body of evidence suggesting that MCs are an important factor in the pathophysiology of IBS.³⁹ IBS patients have an increased number of MCs, which contain granules rich in mediators such as histamine, tryptase, and nerve growth factors that can activate and sensitize enteric nerves, and modulate the integrity of the epithelial barrier.^{57,58} An increased number of mucosal MCs has been observed in biopsy samples from the rectum,⁵⁹ rectosigmoid,⁶⁰ descending colon,⁴³ ascending colon,⁵⁹ cecum,⁶¹ terminal ileum,⁵⁹ jejunum,⁶² and duodenum⁶³ of patients with IBS. Also, the level of activation and intensity of MCs degranulation is increased. Activated MCs spontaneously secreting higher amounts of histamine in close proximity to colonic nerves correlated with severity and frequency of abdominal pain in IBS patients.³¹ According to the study of Cremon et al⁶⁴ it is possible that the number of functionally active MCs is more important in IBS, rather than the absolute number of cells. The recent review by Zhang et al⁶⁵ profoundly embraces all aspects of MCs in IBS.

Possible Application of Anti-histamine Drugs in Irritable Bowel Syndrome

Abdominal pain, often described as discomfort, is believed to be linked to visceral hypersensitivity which seems to be multifactorial.^{66,67} MCs and histamine seem to contribute majorly to visceral hypersensitivity. A study on H₁R knockout mice showed that they are more prone to visceral pain, measured by abdominal stretching after intraperitoneal injection of either acetic acid or MgSO₄ than their wild type littermates.⁶⁸ A study in the rat model of IBS induced by acetic acid revealed a higher degranulation rate of MCs in the colon from rats with IBS-like symptoms. Moreover, pretreatment with a MC stabilizer, doxantrazole, decreased visceral sensory response to rectal distention in these rats.⁶⁹ Finally, histamine was shown to activate enteric neurons through H₁ and H₂ receptors.^{70,71}

MCs with their stored enzymes are important players in dysregulated brain-gut axis. Thus, targeting MCs or HRs arises as a potent treatment option for selected patients with IBS. A few clinical studies have addressed this hypothesis. Klooker et al³⁸ attempted to translate the research on the use of MC stabilizers in IBS from animals³³ to humans. The randomized double-blinded controlled trial showed that ketotifen increased tolerance to abdominal discomfort in patients with IBS with visceral hypersensitivity, improved symptoms and the quality of life. However, no effect on the number of MCs, release of tryptase and histamine from rectal biopsies could

be demonstrated. Since ketotifen is a H₁ receptor antagonist, an MC stabilizer, a phosphodiesterase inhibitor and a functional leukotriene inhibitor, it was not completely evident which of its features was responsible for the anti-IBS effects. Therefore, MC stabilization and H₁R blockade could be further explored as potential new treatments for IBS.

A recent study showed that by blocking H₁R with ebastine, a second generation H₁R antagonist, attenuation of visceral hypersensitivity and other IBS symptoms could be achieved.³⁹ Interestingly, the transient receptor potential vanilloid 1 (TRPV1) was found to be implicated in the process; either histamine alone or the supernatant from rectal biopsies from patients with IBS sensitize TRPV1 channels. Upon activation by stimuli such as noxious heat, acidosis or endovanilloids, TRPV1 becomes non-selectively permeable for ions. It is most likely that sensitization lowers the threshold for channel activation possibly leading to activation by the normal body temperature. The involvement of TRPV1 in IBS has been investigated before. Akbar et al⁶⁰ discovered increased sensory fibers which express TRPV1 channel in patients with IBS. Also, the results from animal studies suggested the contribution of TRPV1 in visceral hypersensitivity.^{72,73} However, TRPV1 is distinctive, involved in both physiological and pathophysiological actions in the human body, such as maintaining proper lower urinary tract function.⁷⁴ Thus, prior to the discovery of a crosstalk between MCs and TRPV1, it was unreasonable to talk about the TRPV1 as a stand-alone therapeutic target. Now, as the connection between the two became apparent, it is easier to indicate plausible therapeutic agents.

The aforementioned HR antagonists are without doubt a part of that group with ebastine in the lead. Ebastine is a second-generation H₁R antagonist free of any significant influence on the central nervous system as it does not penetrate the blood-brain barrier.⁷⁵ The occurrence rate of the most common adverse events such as drowsiness, headache and dry mouth is comparable to placebo. Ebastine showed a satisfactory utility in abating the symptoms of allergic rhinitis and chronic idiopathic urticaria.⁷⁵ Smaller studies also indicate its possible use in cold urticaria, atopic asthma, mosquito bites, and the common cold (with pseudoephedrine).⁷⁶⁻⁷⁹ Additional advantages include the once-daily administration, pharmacokinetics independent of food intake, and availability of a novel formulation—fast dissolving tablet—which does not require the aid of a drink. Currently, there is an ongoing multicenter trial assessing the efficacy of ebastine in patients with IBS (ClinicalTrials.gov Identifier: NCT01908465).

Conclusions and Future Perspectives

The following questions remain unanswered: should we focus more on histamine receptors in IBS? The answer cannot come as a simple binary result but requires further elaboration. We already use MCs as a target, though in a rather indirect way. McIntosh et al⁸⁰ recently reported that diets low in fermentable oligosaccharides, disaccharides, mono-saccharides, and polyols (FODMAPs) changes the metabolome, significantly reducing histamine levels in the urine. Consequently, by administering the diet low in FODMAPs we could modulate the histamine levels in patients with IBS thus altering the symptoms. Although histamine is not the only mediator found to be implicated in the pathogenesis of IBS, it is evident that this biogenic amine is pathologically of great importance.

In conclusion, HR antagonists are definitely worth being considered as potential therapeutic agents in treating IBS, especially the second generation agents which lack activity in the central nervous system, but display a considerably safe profile. Larger studies on ebastine will reveal the efficacy of H₁R antagonists in patients with IBS. For other HR compounds like ketotifen, famotidine, ranitidine, and AST-120, there is already evidence from clinical trials in patients with IBS that suggest that their use may be beneficial. However, until the mechanisms of action of these compounds are elucidated the possibility of using HRs-targeting agents remains speculative.

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