Volume 11, Issue 3
March, 2025

Histamine Reactions and Microscopic Colitis

by Wayne Persky

Histamine intolerance appears to be an increasing problem among members of our discussion and support forum. It's not prevalent enough to be considered common, but certainly, more than a few of us have to deal with it, and it usually proves to be a persistent and frustrating issue for those of us who have to live with it. And once histamine intolerance develops, like microscopic colitis (MC), it tends to become a permanent problem, unless we take precautions to minimize our intake of high histamine foods at all times. Some of us have to minimize our intake of foods with even moderate histamine levels.

And a particularly insidious side effect of this syndrome appears to be the fact that many of us who have successfully put our MC into remission, and have been able to keep it in remission for years, by meticulously following a safe diet, can suddenly find our remission slipping away, for no obvious reason. Naturally, we tend to assume that our diet is being cross contaminated, or we've become sensitive to yet another food. But despite our increasingly desperate efforts to track down the problem, our symptoms continue as we fail to locate the problem.

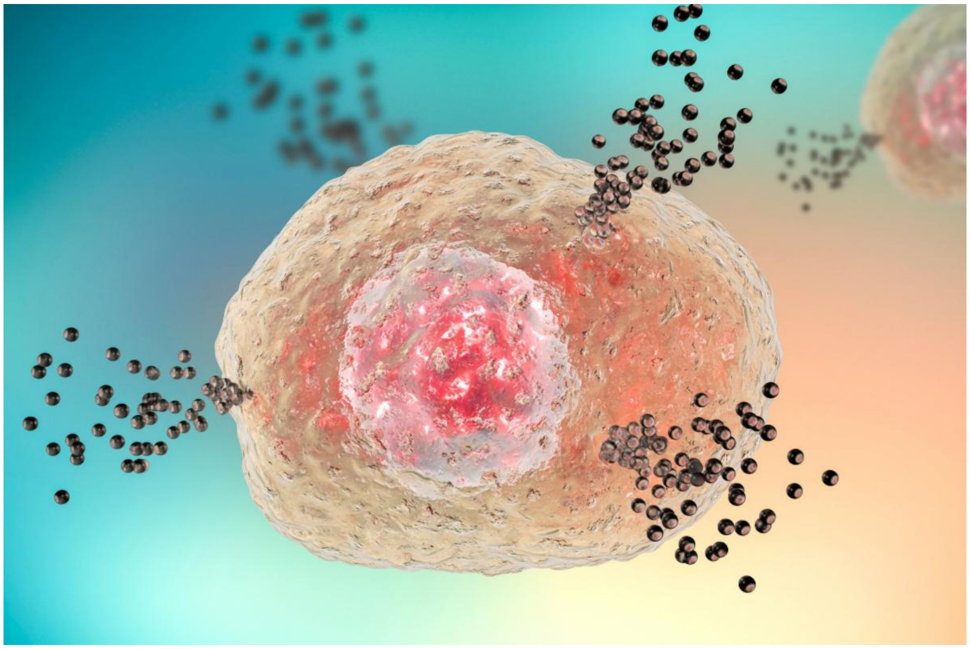
Histamine intolerance can be hard to

Once it develops, we need to minimize our

recognize.

intake of high histamine foods.

Histamine symptoms that result from a bee sting or a pollen allergy are so different from the histamine symptoms typically associated with food sensitivities, that most of us don't immediately see the connection. In the case of food allergies, yes, the connection is obvious, because we react with similar symptoms (watery eyes and nose, itching, throat tightness, breathing difficulty, etc.) almost immediately. But with food intolerances, when the reaction takes several hours before it begins, and it's only marked by a rash or hives, and itching, or bloating, diarrhea, or constipation and/or abdominal pain, the connection is not as obvious.



Our body uses histamine for various important purposes.

Histamine is a biogenic amine that our body uses to initiate inflammation and allergic reactions. It's used as a neurotransmitter for regulating sleep and cognition, and it's associated with wound healing and angiogenesis (growing new blood vessels). In the GI tract, histamine is vital for digestion, as it enhances gastric acid production and modulates gastrointestinal motility. So obviously, we can't simply do without histamine. That's not an option.

Histamine is synthesized from L-histidine by histidine decarboxylase (HDC), and it's primarily stored and released by mast cells and basophils.

Leftover (excess) histamine is degraded by two enzymes:

- Histamine N-methyltransferase (HNMT) – by way of intracellular degradation (mainly in the liver, kidneys, colon).
- Diamine oxidase (DAO) – by way of extracellular degradation (mainly in the small intestine and colon).

Histamine sources include:

- Immune cells such as mast cells, basophils, dendritic cells, T cells
- Some gut bacteria (for example, *Morganella morganii*, *Enterobacter aerogenes*, *Proteus* spp. *Clostridium perfringens*)
- Fermented foods (cheese, alcohol, pickles), certain fish, vegetables (spinach, tomatoes, eggplant)

- Certain medications tend to increase histamine levels in the body, including some types of pain medications (opioids/narcotics) and contrast agents used in medical imaging

It appears that we can become histamine intolerant because of MC.

Our histamine intolerance appears to be associated with a side effect of MC that causes our DAO enzyme production to be significantly compromised. Researchers demonstrated long ago that IBDs compromise DAO production. The DAO enzyme normally purges excess histamine in circulation in our blood, to ensure that our histamine level does not become elevated to the point where it might begin to cause adverse symptoms. Unfortunately, as many of us have found, as our DAO enzyme production continues to decrease, our histamine level continues to build, until it exceeds our reaction threshold, and we begin to react.

“

Histamine is important in the body.

“

Regulation of histamine levels can be impaired with MC.

Histamine intolerance normally causes IgE mediated reactions.

IgE reactions are allergic reactions that result in symptoms such as a rash, hives, itching, swollen airways, watery eyes, and in some cases, an anaphylactic reaction that can be life-threatening due to throat constriction, tachycardia, and dangerously low blood pressure, for example.

The skin contains the greatest number of IgE receptors, specifically, on mast cells. But the intestines also contain a significant number of IgE receptors, specifically the high-affinity IgE receptors known as FcεRI. These receptors are primarily found on mast cells and basophils, which are important components of the immune system. In the intestines, mast cells play a critical role in immune responses, particularly in allergic reactions to food, and responses to parasitic infections.

And for those of us who experience the classic allergy symptoms of a rash, hives, and itching, for example, it's relatively easy to recognize that these symptoms are almost surely caused by an IgE reaction triggered by histamine, within the gut, because of a food, or foods in our diet.

But histamine reactions are not always that simple.

Because they can lead to different symptoms, it's relatively clear that two different types of reactions are possible. They can be either IgE or IgA reactions, because the intestines contain both types of receptors. Those of us who experience bloating and abdominal pain because of a histamine reaction (a reaction not associated with a food sensitivity) are clearly not experiencing symptoms associated with a classic IgE reaction. Instead, the symptoms appear to be due to an IgA reaction.

Where's the research?

There's a huge area of study involving issues such as food sensitivities, histamine reactions, and various other gastrointestinal events, for which no medical research data exist. And specifically, while histamine is known to influence gut inflammation and immune responses, the connection between histamine intolerance and immune system responses in IBD patients is poorly understood, although researchers have been aware of the need for more data for years (Smolinska, Jutel, Crameri, and O'Mahony, 2014)[1]. Consequently, most clinicians are likely to feel obligated to deny that IgA reactions triggered by excess histamine is even possible, because there's no published medical research to support it.

It's very likely, however, that histamine intolerance can trigger IgA reactions.

It's very likely, however, that histamine intolerance can trigger IgA reactions.

If it walks like a duck, and quacks like a duck . . . If IBD patients can experience the same symptoms that are caused by typical IgA-based food sensitivity reactions, as a result of a histamine reaction, why wouldn't it be due to an IgA reaction?

IgA is the dominant immunoglobulin in mucosal immunity, and it plays a critical role in maintaining gut homeostasis. It's well established that excess histamine can disrupt the gut barrier by causing increased intestinal permeability (leaky gut). This allows food antigens, bacterial components, and histamine itself to enter the lamina propria (the layer immediately beneath the epithelia, containing the blood vessels that absorb nutrients through the tight junctions of the epithelia), where immune cells reside. Obviously, in IBD patients, a compromised gut barrier could lead to increased antigen exposure, stimulating the same type of IgA response that MC and other IBD patients experience if their diet includes a food which triggers a reaction.

Histamine can influence gut inflammation.

Mast cells store and release histamine in response to immune stimulation.

Histamine intolerance is associated with mast cell overactivation, leading to:

- Increased histamine release
- Enhanced cytokine secretion (IL-6, IL-4, and IL-13), which promote B-cell differentiation into IgA-secreting plasma cells
- Increased IgA production, particularly in response to dietary antigens and microbiota dysbiosis.
- Mast cell-derived histamine may amplify IgA-mediated immune responses, which could be heightened in IBD.

Furthermore, histamine intolerance is linked to gut microbiota imbalances.

Histamine-secreting bacteria (for example, Proteobacteria, Enterobacteriaceae, and Clostridium perfringens) are increased in IBD and histamine intolerance. This microbial imbalance could lead to increased antigenic stimulation, triggering IgA overproduction as a protective immune response. IBD increased antigenic stimulation, triggering IgA overproduction as a protective immune response. IBD patients already have an increased mucosal IgA response to gut microbiota, which could be further amplified by histamine intolerance.

So it's very likely true that:

Histamine intolerance can indirectly trigger an IgA immune system reaction in IBD patients through increased gut permeability, mast cell activation, dysbiosis, and immune cell modulation.

What's the solution?

Since there are no dedicated research data regarding this issue, we have to look "outside the box" for solutions. For many of us, minimizing (or totally avoiding) high histamine foods is sufficient to prevent reactions. Some patients claim success by using DAO supplements, or antihistamines. And research data are available suggesting that vitamin or mineral deficiencies may play a major role.

This may be a symptom of mast cell activation syndrome (MCAS).

The research article by Yip et al. investigates the role of vitamin D3 metabolites, particularly 25-hydroxyvitamin D3 (25OHD3) and 1α,25-dihydroxyvitamin D3 (1α,25[OH]2D3), in regulating IgE-mediated mast cell activation, a key factor in allergic reactions (Yip, et al., 2014)[2]. The researchers discovered that mast cells, both in humans and mice, can convert the inactive precursor 25OHD3 to its active form, 1α,25(OH)2D3, via the enzyme CYP27B1. This conversion plays a vital role in regulating mast cell activity. Both 25OHD3 and 1α,25(OH)2D3 were shown to suppress IgE-dependent mast cell degranulation and the release of proinflammatory and vasodilatory mediators in vitro. This suppression occurred in a vitamin D receptor (VDR)-dependent manner, indicating that mast cells' responsiveness to vitamin D is mediated through VDR signaling. Although this wasn't part of the study, it's highly likely that IgA-modulated mast cell activation (or suppression) is also mediated by a similar mechanism involving VDR signaling.

The researchers noted that when applied topically to the skin, vitamin D3 metabolites significantly reduced the severity of skin swelling in IgE-mediated passive cutaneous anaphylaxis (PCA) reactions. This effect was also dependent on the presence of functional mast cell-VDRs and CYP27B1, suggesting that vitamin D3 metabolites can dampen allergic responses through direct effects on mast cells. By demonstrating that mast cells can metabolize 25OHD3 to suppress IgE-mediated activation, the study supports the idea that vitamin D may have a therapeutic role in modulating mast cell-driven inflammatory conditions, suggesting that maintaining adequate vitamin D levels may be beneficial for individuals prone to mast cell-related disorders.

How is vitamin B12 is connected with histamine?

A website known as Cancer Center for Healing states that recent research has highlighted a vital link between vitamin B12 and histamine metabolism, particularly in individuals with histamine intolerance and related inflammatory conditions (although they don't cite a reference) (Cancer Center for Healing, 2023, August 12)[3]. As they point out, histamine plays a vital role in immune response, but excessive levels can lead to allergic reactions, digestive issues, and systemic inflammation. Understanding how vitamin B12 supports histamine breakdown can provide valuable insights into managing histamine-related disorders.

> Vitamin D3 plays an important role in regulating mast cell activity.

> Vitamin B12 plays a key role in reducing histamine.

Vitamin B12 supports DAO, the key enzyme responsible for degrading histamine in the gut. B12 deficiency impairs DAO activity, leading to elevated histamine levels and worsening symptoms of histamine intolerance. Additionally, methylation, a biochemical process required for histamine breakdown, is heavily dependent on B12, folate, and other B vitamins. Low B12 levels can reduce methylation efficiency, causing histamine accumulation and exacerbating inflammatory responses.

Vitamin B-12 is absorbed in the terminal ileum.

The journey of vitamin B12 absorption begins in the stomach, where gastric acid and enzymes release B12 from food. Once freed, it binds to R-protein (haptocorrin) found in saliva and gastric fluids. As digestion continues into the small intestine, pancreatic enzymes degrade R-protein, allowing B12 to bind with intrinsic factor (IF), a protein secreted by specialized parietal cells in the stomach.

The IF-B12 complex is then absorbed in the terminal ileum, the last section of the small intestine. This absorption is dependent on calcium, which is supplied by the pancreas. While vitamin B12 can also be absorbed through passive diffusion, this method is highly inefficient, accounting for only 1% to 2% of the vitamin B12 absorbed orally.

But vitamin B12 absorption's can be compromised by:

- Low stomach acid levels (often due to acid-suppressing medications)
- Gastrointestinal conditions (e.g., inflammatory bowel disease, leaky gut)
- Vegan or vegetarian diets (which lack sufficient B12 sources)
- Surgical removal of stomach or intestines

Regarding the second item in this list, it's worth noting that the inflammation that causes MC is typically more intense (more inflamed epithelial cells) in the terminal ileum, than any other section of the intestinal tract, making it very likely that MC patients will experience compromised vitamin B12 absorption.

To overcome absorption issues, individuals may benefit from:

- Sublingual B12 supplements (absorbed under the tongue)
- B12 injections, particularly for individuals with severe deficiency or malabsorption disorders
- Addressing underlying conditions, such as gut inflammation or low stomach acid

---

Additional vitamins and minerals that support histamine regulation include:

- Vitamin C, which lowers histamine levels and stabilizes mast cells
- Magnesium, which helps regulate histamine release
- Vitamin B6, which supports the proper functioning of DAO
- Folate (vitamin B9), which works alongside B12 in methylation pathways

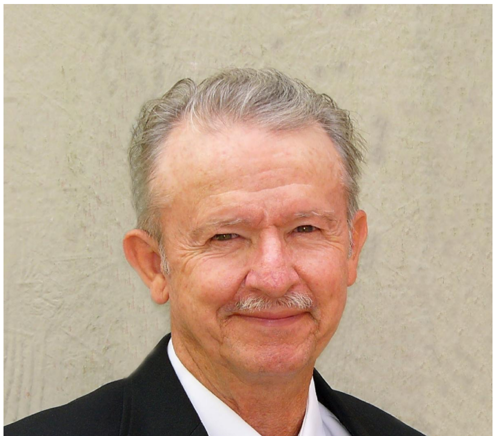
The Take-home Message

Histamine intolerance often develops as a side effect of MC, and it can often result in a confusing pattern of symptoms that make dealing with the syndrome especially difficult. But the good news, is that we can indeed do something about it to minimize and control the symptoms, because histamine intolerance is often associated with vitamin or mineral deficiencies that can be corrected to resolve, or at least minimize the symptoms.

If you're following our general recommendations, you're probably already taking magnesium and vitamin D supplements, because they're so important for proper healing. And if you can't tolerate oral magnesium, you're probably following our suggestions regarding the use of magnesium oils and lotions, or baths or foot soaks in water in which Epsom salts have been dissolved. And if that's the case, but you're still having symptoms, a vitamin B12 supplement might be in order.

It's challenging to find a multivitamin that doesn't have some issue for us, since we are all different, and at different points in our MC journey. So we are hesitant to suggest a particular product. But after an extensive search, a member of our Board of Directors has been satisfied with Manna Multivitamins. She is gluten, dairy and soy sensitive, and doesn't react to the product. It uses the forms of vitamins and minerals that we have recommended as working best. Since it is in a liquid form, when starting, you can try a partial dose to check how it is tolerated by you. The flavor is quite palatable. It does contain almonds, a mix of fruit extracts, and a few other inactive ingredients to check out for individual sensitivities.

Check Out Wayne's Blog



He posts a new blog about once a week. Here are the titles of the most recent. Click the button at the top of the newsletter to access.

SURPRISING STUDY RESULTS REGARDING SPENDING TIME ONLINE

FEW THINGS ARE MORE ELUSIVE THAN PUBLIC BATHROOMS, WHEN WE DESPERATELY NEED ONE

SHOULD INSURANCE COMPANIES BE CONTROLLING

SHOULD INSURANCE COMPANIES BE CONTROLLING OUR HEALTHCARE?

TREATING MC WITH DIET CHANGES MAY BE INCREASING OUR LONGEVITY, AND IMPROVING OUR QUALITY OF LIFE

The Microscopic Colitis Foundation Website is Undergoing an Update

If you visit our website, you will no doubt notice that it is in the middle of a renovation, and looking messy. You can still find Wayne's blogs, and back issues of the newsletters. We hope to have it completed soon, but web design changes always seem to take longer than planned.

References

1. Smolinska, S., Jutel, M., Crameri, R., and O'Mahony, L. (2014).Histamine and gut mucosal immune regulation. Allergy, 69(3), pp 273–281. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24286351/
2. Yip, K-H., Kolesnikoff, N., Yu, C., Hauschild, N., Taing, H., Biggs, L, . . . Grimbaldeston, M. A. (2014). Mechanisms of vitamin D_3 metabolite repression of IgE-dependent mast cell activation. The Journal of Allergy and Clinical Immunology, 133(5), pp 1356–64, 1364.e1-14. Retrieved from https://pubmed.ncbi.nlm.nih.gov/24461581/
3. Staff. (2023, August 12). B12 Histamine: Uncovering the Connection and Benefits. Cancer Center for Healing, Retrieved from https://cancercenterforhealing.com/b12-histamine/

Contact Us: Wayne Persky: wayne@perskyfarms.com
Rosalyn Upson (Newsletter Editor): rosalyn.upson@gmail.com