SCIENTIFIC VIEWPOINT

Histamine Intolerance

In a world that has become oversensitive to just about everything, people are looking to minimize the symptoms of what they think are histamine reactions—headaches or migraine, nasal congestions or sinus issues, fatigue, hives, digestive issues such as diarrhea, irregular menstrual cycles, nausea, vomiting, and skin issues such as eczema, etc. We have all heard about antihistamines. One article by Cleveland Clinic lists over eighteen treatments targeting different histamine receptors, and there are currently more than one hundred such over-the-counter and prescription medications available on the market.

So what is the big deal? Roughly 1% of the US population has histamine intolerance, and of those three million people, 80% are middle-aged. In the pediatric community, there seems to be a demand for non-histamine producing products as well. Is this something to be concerned about? Or is this just another fad to push certain products, diets, or lifestyle packages. To answer this question, we need to look at how the body works and try to figure out where the glitch lies in order to be respectful to our physiology and biochemistry before putting ourselves through unnecessary regimens.

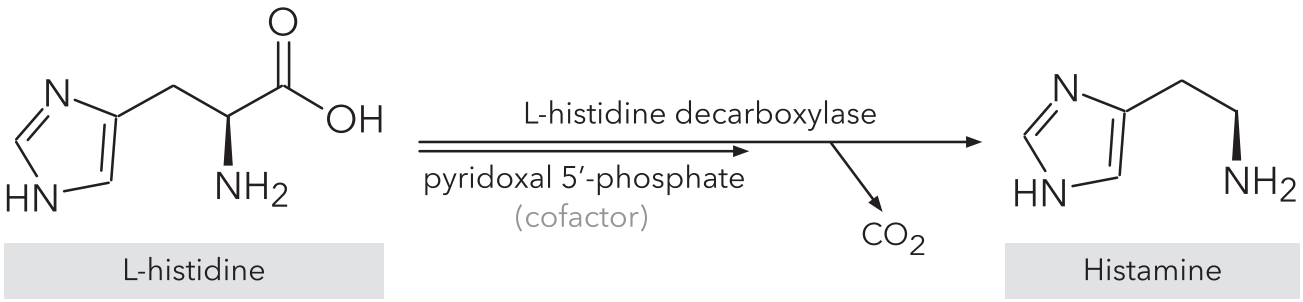

Figure 1. Synthesis of histamine by decarboxylation of its precursor amino acid.

What is histamine? Histamine is a potent mediator of a number of biological reactions. It is produced in mast cells, basophils, platelets, and some neurons, where it is stored intracellularly in vesicles and released on stimulation, when it is converted from histidine by way of the enzyme histidine decarboxylase with the help of vitamin B6 (see ***Figure 1***). In addition to mast cell degranulation, which occurs via cross linking of IgE antibody on the cell surface following binding of the allergen, histamine release can occur independently of IgE. It is a biogenic amine, which means your body makes it for a reason. We can liken it to inflammation—the body makes it because it needs it, but when it gets out of hand it can become a nuisance. The reason the body makes it is because it is involved in many biological reactions. For example, it is a mediator of inflammation and IgE (allergic) reactions,

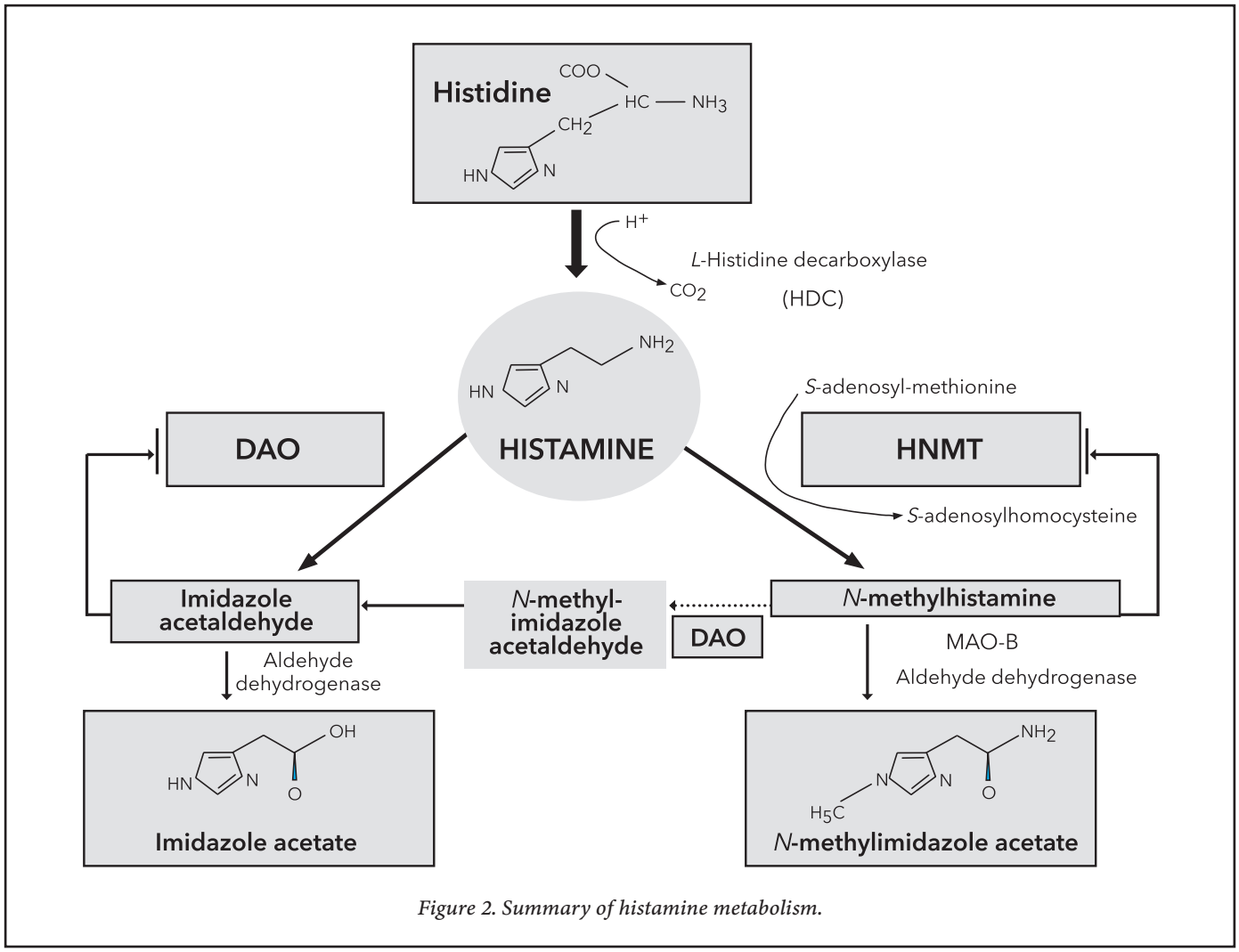

Figure 2. Summary of histamine metabolism.

contracts smooth muscle, is involved in gastric acid secretion, is a vasodilator, is a neurotransmitter in the central nervous system, is involved in tissue growth and repair, and is involved in cytokine production among other functions.

Histamine intolerance (HIT) results from an imbalance of accumulated histamine and the body's capacity to degrade it. Histamine occurs to various degrees in many foods, usually due to decomposing of food that is improperly stored, left over, or fermented by way of bacteria that possess the enzyme histidine decarboxylase. In healthy individuals, dietary histamine can be rapidly metabolized by diamine oxidase (DAO) which is the main enzyme responsible for breaking down ingested histamine. Conversely, histamine N-methyltransferase, the other important enzyme inactivating histamine, is a cytosolic protein that can convert histamine only in the intracellular space of cells (see ***Figure 2***).

An impaired histamine degradation based on reduced DAO activity and the resulting histamine excess may cause numerous symptoms mimicking an allergic reaction. The ingestion of histamine-rich food or alcohol or drugs that release histamine or block DAO may provoke diarrhea, headache, asthma, hypotension, arrhythmia, urticaria, pruritus, flushing, and other conditions in patients with histamine intolerance. These symptoms are expressed depending on the interaction between histamine and one of four receptors (H1R, H2R, H3R, and H4R) in the body (see ***Figure 3***).

It is important to understand that only approximately 5% of the total amount of histamine enters the body ready-made with food and is synthesized by intestinal microorganisms (the so-called exogenous histamine). Bacterial and human decarboxylases are activated under the influence of an increased demand for histamine. For example, it is necessary to regulate the intraplasmic pH under conditions of lactic acidosis, and this is only one of the reasons why histamine is not all bad. Another example where histamine is beneficial is when mast cells of the gastrointestinal tract and the histamine they produce have an anti-carcinogenic effect. It has been experimentally established that the deficiency of bacterial histidine decarboxylase promotes the development of inflammation and tumors in the intestine, combined with a defect in myelopoiesis and overproduction of pro-inflammatory cytokines. Administration of hista-

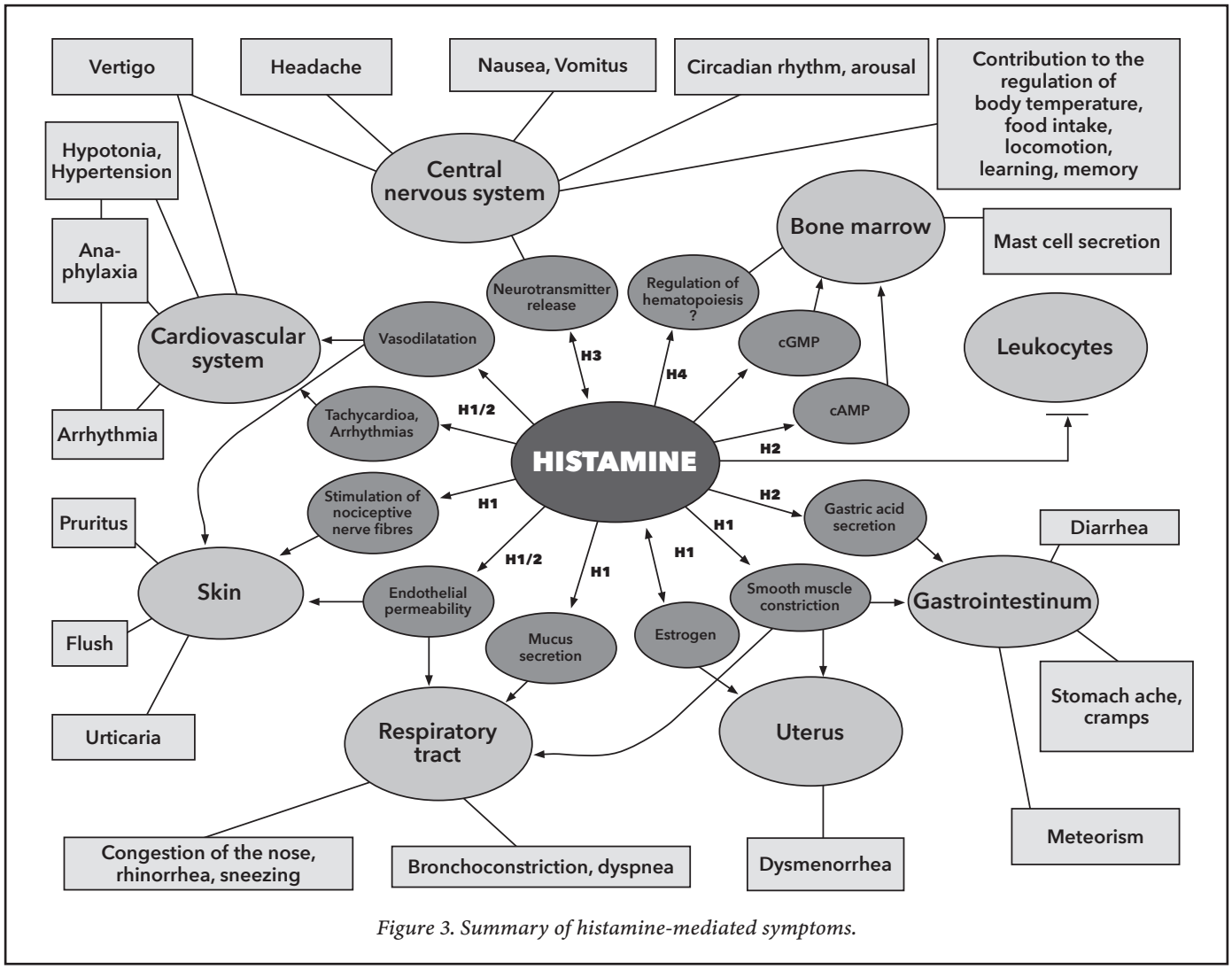

Figure 3. Summary of histamine-mediated symptoms.

mine-producing L. reuteri promotes the regression of these disorders through its anti-inflammatory effect when histamine binds to the H2 receptor.

In cells, histamine is concentrated mainly in the microsomes and the nucleus. The main depot cells of histamine are basophils and mast cells in the endoplasmic granules, which accumulate in significant amounts (>90% of the total intracellular pool). In other words, the body makes a lot more histamine than what we consume through our food. In the human body, there are two main pathways for the degradation of histamine which involve DAO (or histaminase, which metabolizes histamine outside the cell) or histamine-N-methyltransferase (metabolizes histamine inside the cell). DAO is mainly synthesized in the mucous membrane of the placenta, kidneys, and small and ascending colon (activity increases in the distal direction). Accumulating in intracellular vesicles, DAO then enters the extracellular space, where it degrades histamine. DAO performs a "barrier function," thereby limiting the passage of histamine from the intestines into the blood.

It is very important to understand that DAO is synthesized by mature intestinal enterocytes, is located in the intestinal villi, and is constantly released from the intestinal mucosa into the gut as well as into the blood circulation during digestion. Why is this important? Because histamine intolerance originates in the gut! As a matter of fact, the more destruction of enterocytes is occurring, as in GI disease, the more histamine intolerance is observed. This is why the most common and most severe symptoms indicated by HIT patients in more than 90% was bloating. Other very commonly related GI symptoms include postprandial fullness and diarrhea (both in >70% of patients), abdominal pain (>65%), and constipation (55%). This should prompt any practitioner attempting to address HIT in their practice to primarily look at healing the gut, evaluating medications taken by their patients as these are also a major source of inhibitors of DAO activity (see ***Table 1***) as well as diet as there are certain foods that liberate histamine (see ***Table 2***).

Another source of decreased DAO activity are genetic SNP's, but these are not as common as the first two sources. These SNP's are not a death sentence however—most merely interfere with DAO's kinetic activity by decreasing the enzyme's binding affinity.

Substance class	Active agents
Radiological contrast media	
Muscle relaxants	Pancuronium, Alcuronium, D-Tubocurarin
Narcotics	Thiopental
Analgesics	Morphine, pethidine, NSAR, ASS, metamizole
Local anesthetics	Prilocaine
Antihypotensives	Dobutamine
Antihypertensives	Verapamil, alprenolol, dihydralazine
Antiarrhythmics	Propafenon
Diuretics	Amiloride
Motility agents	Metoclopramide
Antibiotics	Cefuroxime, cefotiam, isoniazid, pentamidine, clavulanic acid, chloroquine
Mucolytics	Acetylcysteine, ambroxol
Broncholytics	Aminophylline
H2 receptor antagonists	Cimetidine
Cytostatics	Cyclophosphamide
Antidepressants	Amitriptylline

Table 1. The commonest histamine liberating or DAO inhibiting medications.

DAO is so dependent on a healthy GI tract that it has been proposed as a marker of the integrity of intestinal mucosa. A recent study analyzed the molecular effects of histamine in human ileac neuroendocrine tumor cells, which are a model for gut enterochromaffin cells. The results indicated that enterochromaffin cells participate in intestinal intolerance or allergic reactions to food constituents associated with elevated histamine levels. In inflammatory bowel diseases, reduced DAO activity was related to the degree of mucosal damage. In Crohn's disease, DAO was discussed as a marker for disease assessment. Moreover, histamine content and secretion were found to be significantly increased in affected mucosa in Crohn's disease and in ulcerative colitis. Intestinal mucosa DAO activity was shown to reflect intestinal involvement in Crohn's disease. Additionally, histamine was concluded to contribute to the mucosal reactions in the intestine and to reflect the degree of colonic inflammation. Measurement of gut DAO activity was stated as a biologic marker of colorectal proliferation and histamine catabolism was reported to be lower in the colonic mucosa of patients with colonic adenoma. According to reports, in oncologic patients receiving chemotherapy, DAO activity may be a predictor of intestinal mucosal damage. Serum DAO activity was reported to be a predictor of GI toxicity and malnutrition due to anticancer drugs. Some results in children support the hypothesis of DAO being a marker of small intestinal functional integrity.

All of these findings in the literature points to DAO being highly dependent on a healthy GI tract and an optimal structural integrity of the enterocytes where it is formed. Without GI health there is suboptimal DAO activity and therefore any amount of histamine present whether internal or from exogenous sources, i.e., ingested food or bacterial-derived, will bring about an intolerance. Besides an impaired degradation of orally supplied histamine due to DAO deficiency, a deranged gut flora may also contribute to elevated histamine levels. In a study that observed microbial patterns in

Vegetable	Animal
• Citrus fruits	• Fish
• Papaya	• Shellfish
• Strawberries	• Pork
• Pineapple	• Egg white
• Nuts	**Other**
• Tomato	• Additives
• Spinach	• Liquorice
• Chocolate	• Spices

Table 2. Foods with potential histamine releasing effect.

patients with HIT, researchers concluded that the altered occurrence of proteobacteria and bifidobacteriaceae, reduced alpha-diversity, and elevated stool zonulin levels suggest a dysbiosis and intestinal barrier dysfunction in HIT patients, which in turn may play an important role in driving disease pathogenesis. In other words, it is the dysbiosis, the lack of diversity, and the deranged intestinal barrier that drives the intolerance and not a specific histamine-producing strain.

As a matter of fact, studies have demonstrated that certain strains that produce histamine suppressed TNF production via activation of the H2 receptor. Specifically, a component of the gut microbiome, *L. reuteri*, is able to convert a dietary component, L-histidine, into an immunoregulatory signal, histamine, which suppresses pro-inflammatory TNF production by binding to the H2 receptor which has anti-inflammatory benefits. We must keep in mind that our intestinal flora not only produces histamine but is also in need of other biogenic amines (BA's). BA's such as histamine are immune mediators and neurotransmitters, whereas others such as putrescine, spermidine, and spermine are needed for optimal cell growth and differentiation, stabilization of the DNA negative charge, RNA transcription, protein synthesis, apoptosis, and regulation of the immune response. In bacteria, BA's are also essential for growth and proliferation, so giving histamine a bad rap when we know it has a place in our well-being is not respecting our physiology and biochemistry.

Conclusion

When dealing with histamine intolerances, practitioners need to focus on healing the gut where the real problem lies. It is important to remember that DAO is produced in the enterocytes, is present at the villi, and is secreted into the intestinal mucosa. HIT is not a deficiency of DAO supplementation just as high cholesterol is not a deficiency of statins. Any condition or disease that disrupts the structural integrity of the GI tract will put DAO production at risk and limit its normal function of metabolizing ingested or microbial-derived histamine, resulting in HIT. Focusing only on histamine-rich foods, histamine-producing strains, genetic SNP's, or DAO-blocking drugs is not addressing HIT at the root cause. Rather, a multi-factorial approach should include diet and lifestyle modification, balancing the intestinal flora, and healing the gut so that DAO production could run at optimal levels.

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