



Research Summary: Histamine #1

As featured in Dr. Kenny Mittelstadt's video:
Why Histamine Keeps Coming Back After You Fix Your Diet
Date of Publication: 06/20/2026

Research Context:

This week's topic explores how histamine intolerance isn't just about what you're eating. It's about whether your body can actually clear histamine efficiently, and what happens when the systems responsible for that clearance get suppressed. Most conversations about histamine stop at the input side: the foods, the triggers, the elimination lists.

But histamine intolerance is a two-sided equation, and when the clearance side breaks down, restriction becomes a management strategy rather than a lasting resolution. The ceiling never changes. Only the pressure underneath it does.

Key Findings from the Research:

Study 1 (PMID 17490952):

This foundational 2007 review by Maintz and Novak laid out how histamine intolerance works at the biochemical level. The key insight: histamine problems aren't just about how much comes in from food. They're about the balance between input and your body's clearance capacity. Two enzymes handle most of that work. DAO (diamine oxidase) works in the gut lining, catching histamine before it crosses into the bloodstream. HNMT (histamine N-methyltransferase) works inside cells, in the liver, lungs, and brain, tagging histamine for breakdown through methylation. When either enzyme is impaired, histamine builds up and symptoms appear. Critically, the review found that DAO activity directly reflects intestinal lining health. When that lining is inflamed or damaged, DAO output drops in real time, meaning your clearance capacity is a live readout of your gut.

Study 2 (PMID 30552302):

This 2018 study by Schink and colleagues compared the gut microbiome of people with histamine intolerance to healthy controls. They found that people with histamine intolerance showed signs of a more permeable gut lining, measured by elevated zonulin, a marker of gut barrier disruption, as well as reduced microbiome diversity and a higher proportion of Proteobacteria, bacteria often associated with gut inflammation. Healthy participants had higher levels of Bifidobacteriaceae, a family linked with gut protection. This was an observational study, meaning we're looking at patterns rather than confirmed cause and effect. But it's consistent with what the first study outlined: a disrupted gut environment appears to go hand in hand with impaired DAO function and histamine buildup, reinforcing the idea that gut lining health is a central part of the picture.

Study 3 (PMID 35565742):

This 2022 study by Sanchez-Perez and colleagues went further, looking specifically at which bacterial species were present in people with histamine intolerance versus healthy individuals. They found that histamine-secreting bacteria, including Staphylococcus, Clostridium perfringens, and Enterococcus faecalis, were significantly more abundant in the histamine intolerance group. At the same time, bacteria associated with gut protection, including Faecalibacterium, Ruminococcus, and Prevotella, were notably lower. This matters because dysbiosis appears to work against you in both directions at once: bacteria producing more histamine from inside the gut, while an impaired lining simultaneously reduces your ability to clear it. This was also an observational study, and the authors note that more research is needed to confirm the direction of causation. But taken together with the prior two studies, the pattern becomes harder to ignore.



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Functional Medicine Connections:

Here's how these pieces fit together. Your gut lining is where your first line of histamine defense lives. When that lining is inflamed or compromised, the enzyme that catches histamine at the door produces less of what it needs to do its job. At the same time, an imbalanced microbiome adds to the histamine load from the inside, creating more of it while your clearance capacity is already down. That gap between input and clearance is where most people's symptoms live.

The second clearance pathway, the HNMT enzyme, brings a different set of dependencies into this picture. It draws from your methylation cycle, which runs on B vitamins and is shared with detoxification, mood chemistry, hormone breakdown, and DNA repair. When chronic stress, gut dysfunction, or inflammation depletes those shared resources, HNMT becomes a bottleneck even when the gut lining is in better shape.

This is why two people can have the same histamine symptoms and a completely different picture underneath. And it's why the investigation worth doing goes beyond a food list, toward the gut terrain, the microbiome balance, and the functional status of the methylation cycle as a whole.

Practical Reflections & Takeaways:

When you think about when your histamine symptoms got worse, was there something happening in your life at the time? A stressful period, an illness, a major change? Your body's inflammatory load and stress load shape how well these clearance systems work, and that timeline is often where the real pattern starts to become visible.

If you've tried a low-histamine diet and found some relief, then hit a ceiling or started reacting again, it may be worth asking: what did I give my clearance system to work with? Restriction reduces input, but it doesn't rebuild a disrupted gut lining, rebalance a dysbiotic microbiome, or replenish a depleted methylation pool.

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