



— YOUTUBE RESEARCH SUMMARY

Research Summary: Histamine Intolerance

As featured in Dr. Kenny Mittelstadt's video: [Histamine Intolerance: Why Diet Isn't Enough](#)

— Research Context

Histamine intolerance is shaped by how the body's capacity to clear histamine, and the internal sources that generate it, determine where your threshold actually sits. Three studies connect the key pieces of that picture: the enzyme systems responsible for clearance, the role of gut bacteria in manufacturing histamine internally, and what the current evidence can and cannot yet tell us about treating this condition in sequence. Understanding all three together reframes why dietary restriction alone so often falls short as a standalone strategy.

— Key Findings from the Research

STUDY 1 · PMID 8645981

Jarisch and Wantke (1996) investigated the relationship between histamine, the enzyme diamine oxidase (DAO), and symptoms like headache in people who reacted to wine and other histamine-containing foods. DAO is the gut's primary histamine-clearing enzyme, sitting in the lining of the small intestine and breaking down histamine as food moves through. People experiencing these reactions showed significantly lower DAO activity compared to those who did not react. Their gut-level clearance capacity was already running at a meaningful deficit before any food was consumed. The threshold at which the body begins reacting is set by available clearance capacity, and restricting dietary histamine without investigating that enzyme deficit addresses the volume entering the sink without asking why the drain is blocked.

STUDY 2 · PMID 37394958

Fiorani and colleagues (2023) reviewed the role of specific gut bacteria in histamine production inside the intestine. Certain bacterial species carry an enzyme called histidine decarboxylase, which converts the amino acid histidine, found in many ordinary proteins, directly into histamine inside the gut. The source of histamine is sometimes the microbial environment processing food rather than the food itself. An overgrowth of these histamine-producing species connects to digestive disorders and to patterns of histamine excess that persist despite careful dietary restriction. When histamine-producing bacteria are active in the gut, the internal load continues regardless of what is eaten, because that production occurs downstream of everything swallowed. Which organisms are present, and what conditions allowed them to thrive, becomes a more clinically meaningful question than the histamine content of any single food.

STUDY 3 · PMID 39796463

Duelo and colleagues (2024) published the protocol for a prospective, double-blind, randomized, placebo-controlled trial examining whether a low-histamine diet combined with DAO enzyme supplementation produces measurable benefit in people diagnosed with histamine intolerance. The publication of this protocol signals that researchers recognize real gaps in the existing evidence base. Around twenty prior studies on this topic showed promising results, but most involved small groups, lacked control groups, and ran for short periods. The robust outcome data this trial is designed to generate does not yet exist. The clinical reasoning behind addressing DAO clearance and dietary histamine together is logical and the early signals are encouraging, and intellectual honesty about what has and has not yet been demonstrated in large, well-controlled trials matters for how clinicians and patients weigh the framework.



— Functional Medicine Connections

The gut and liver form a two-stage filtration system for histamine. DAO handles it at the gut level before it enters circulation. A second enzyme called HNMT (histamine N-methyltransferase) handles circulating histamine at the liver level. When both are working well, the body has genuine redundancy. When one is underperforming, the other takes on more load. When both are compromised, even a modest load can overflow the system entirely.

Layered on top of that clearance picture is the internal production question. When histamine-producing bacteria are overrepresented in the gut, they contribute a continuous internal load that restriction cannot reduce. When the combined load, dietary plus microbial plus any internally generated sources, crosses a threshold, the immune system's mast cells can enter a feedback loop. Mast cells release histamine as part of their response, which can trigger further activation and generate more histamine independent of anything in the diet. This is why reactions can feel disproportionate to the food that preceded them, and why enzyme support alone can produce real relief and then hit a ceiling. That ceiling exists because enzyme support addresses the gut-drain level but does not interrupt the loop once internal amplification is running.

The nervous system also connects here in a way that is easy to oversimplify. Chronic activation of the body's stress response appears to destabilize mast cells, reduce the immune regulation that would otherwise help contain reactivity, and worsen the gut immune environment that allows histamine-producing organisms to thrive. Nervous system load is one concurrent factor in a system with multiple concurrent failure points. Addressing one leg of a stool with three legs still leaves the stool unsteady.

— Practical Reflections & Takeaways

Has the range of foods that feel safe to you grown or shrunk over the time you have been restricting? If it has shrunk, that progression may be telling you something about a shifting threshold rather than about the foods themselves.

Are there other aspects of your health, your digestion, your stress load, your sleep, your hormonal patterns, that have been present throughout this picture but have not yet been part of the conversation? Those patterns are meaningful data and may be pointing toward the terrain conditions that are sustaining the underlying problem.

— References

Jarisch, R., & Wantke, F. (1996). Wine and headache. *International Archives of Allergy and Immunology*, 110(1), 7-12. PMID: 8645981.

Fiorani, M., Del Vecchio, L. E., Dargenio, P., et al. (2023). Histamine-producing bacteria and their role in gastrointestinal disorders. *Expert Review of Gastroenterology and Hepatology*, 17(8), 793-803. PMID: 37394958.

Duelo, A., Sanchez-Perez, S., Ruiz-Leon, A. M., et al. (2024). Study protocol for a prospective, unicentric, double-blind, randomized, and placebo-controlled trial on the efficacy of a low-histamine diet and DAO enzyme supplementation in patients with histamine intolerance. *Nutrients*, 16(1), 119. PMID: 39796463.

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