

Histamines and Mental Health

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Inner Source Health
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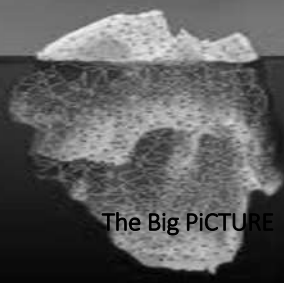
disclosures

- Owner: Inner Source Health – New York City and Huntington (Long Island), NY
- Formulator and Consultant: Douglas Laboratories



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- INTAKE
- LABS
 - BLOOD WORK, URINE,
 - GENETICS
- Rx:
- SLEEP
- EXERCISE
- THOUGHTS / PASSIONS
- NATURE
- FOODS
- DETOX
- SUPPLEMENTS
- OTHER MODALITIES



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Case – anxiety – 23 yr old

- Male
- Severe anxiety
- Multiple psychiatrists
- No improvement



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History

- 1910: physiologic actions of histamine identified
- New Jersey Psychiatric Institute in 1966 Dr. Carl Pfeiffer (1908 – 1988)
- assaying histamine content in blood
- Found blood of schizophrenics contained abnormal levels of histamine
- Treated patients for both low and high histamine levels



For every drug that benefits a patient, there is a natural substance that can achieve the same effect.

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What Is Histamine?

- Produced by:
 - Basophils, eosinophils and mast cells to increase capillary permeability to WBC's
 - Gut microbiota
- released when the immune system feels "under attack"
- Causes immediate inflammatory response
- Biogenic amines like histamine are produced by bacterial decarboxylation in foods
- neuromodulator, neurotransmitter

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Receptors

H1 – smooth muscle, endothelium, airway, some CNS, some intestines, mast cells: asthma mediation, ocular allergy

H2 – Gastric acid production, intestinal tract, blood vessels, mast cells

H3 – CNS homeostasis, Peripheral NS, vasodilates nasal cavities

H4 – basic inflammatory responses: intestinal tissue, bone marrow, spleen, thymus and immune active cells (T cells, mast cells, neutrophils and eosinophils)

* Allergies and IBS patients : have higher #'s of H1 and H2

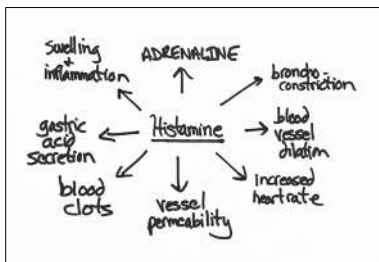
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Histamine - effects

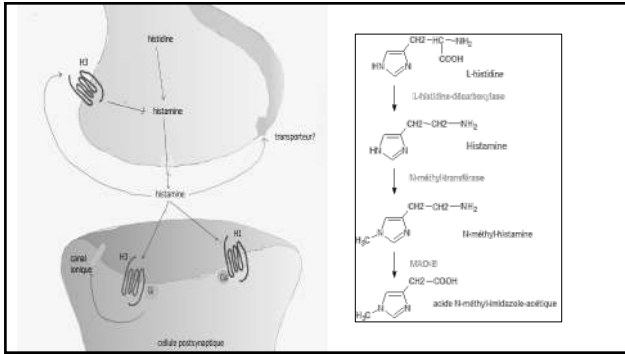
- vasoactive → leakage and edema
- bronchial smooth muscle constrictor → asthma
- stimulates nociceptive / itch neurons
- proinflammatory actions → allergy, atopy
- Higher epinephrine → stress and anxiety
- regulates anterior pituitary hormones

World J Gastroenterol. 2005 May 21; 11(19): 2851–2857.

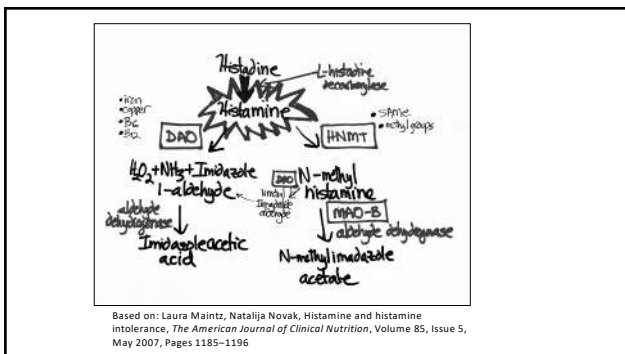
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Brain and Histamine

- histaminergic neurons originate from the **tubermamillary nucleus of the posterior hypothalamus (TMN)** – these send projections to most parts of the brain


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CNS histamine

is involved in many brain functions:


- arousal, control of pituitary hormone secretion, suppression of eating and cognitive functions, pain perception
- increases wakefulness / prevents sleep
- During REM and non REM sleep, histamine stops firing completely

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Sleep, 2019 May, 42(5): zsz031.
Published online 2019 Feb 5.
doi: 10.1093/sleep/zsz031

PMCID: PMC6519916
PMID: 30722053



Genetic lesioning of histamine neurons increases sleep-wake fragmentation and reveals their contribution to modafinil-induced wakefulness

Xiao Yu,¹ Yina Ma,¹ Edwint C. Harding,¹ Baoxue Yufan,¹ Alexei L. Vyssotski,² Nicholas P. Franks,^{1,3} and William Wadsworth^{1,3}

- Murine studies
- histamine receptor knockouts
- fragmented sleep and decreased Non-REM sleep.
- mice were slower to wake up.

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Diphenhydramine

- (Benadryl, night sleep aids) a commonly used antihistamine, make the user sleepy
- This is due to the actions against histamine in the brain



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Too much, or too little?



- **Xs histamine in brain** →
 - xs epi/ norepinephrine, lower GABA
 - over stimulation, aggressiveness, compulsivity, and a racing brain
- **Low histamine in thalamus** →
 - depression, hallucinations

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Psychiatric and Neurologic Illness



- Alterations in histaminergic system are found in the brain per post mortem studies

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Brain histamine levels

- Alzheimer's disease – decreased H
- Parkinson's disease - abnormally high H
- Schizophrenic patients – high levels, or can be low
- convulsions and seizures - low H levels
- Ischemia – high level of H release
- Depression – high or low levels

18

frontiers
in Systems Neuroscience

Front Syst Neurosci. 2012; 6: 51. PMID: PMC3389384
 Published online 2012 Jul 4. PMID: 22753171
 doi: 10.3389/fnsys.2012.00051

Histamine and motivation
 Fernando Torrealba,^{1,2,*} Maria E. Rivas,^{1,2} Marco Contreras,^{1,2} and Jose L. Valdes²

- A **reduction in H1R ligand binding** in the frontal lobe of depressed patients and schizophrenic patients and the frontal and temporal regions of Alzheimer's disease patients has been observed
- chronic schizophrenic patients have **increased levels of histamine metabolites** in their cerebrospinal fluid

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C.C. Pfeiffer. **Nutrition and Mental Illness: An Orthomolecular Approach to Balancing Body Chemistry.** Healing Art Press, Rochester VT (1988), pp. 24–32

- depression, bipolar disorder, schizophrenia, and drug abuse are associated with abnormal histamine levels, in some instances in as many as 20% of cases

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Alerts | About | Author Instructions | Submit

Int J Neuropsychopharmacol

pyv045

- "histaminergic neurotransmission is indispensable for behavioral and neurochemical responses to acute administration of SSRIs"

- TCAs and Noradrendrenergics worked fine

- Histapenic patients – may not respond

Stefano Provensi, PhD, Maria Beatrice Passani, PhD, Tommaso Cassano, PhD, Fernando Benetti, MD, and Patrizio Blandina, MD

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High Histamine Levels (Histadelia, Histemia)

- headaches / migraines
- nasal congestion or sinus issues
- fatigue
- hives
- digestive issues
- irregular menstrual cycle
- Seasonal allergies
- Nausea, Vomiting
- increased mucus and saliva production tendency
- Flushing
- HTN
- Feeling hot or cold
- Cold hands / feet

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Histadelia and Psychiatry

- Anxiety
- Schizophrenic
- Hyperactivity
- compulsions
- Obsessions
- inner tensions
- phobias
- Chronic depression
- Suicidal tendencies
- Pain sensitive
- High metabolism (lean)
- Sweats
- Addictions (work, sex, drugs, sugar, etc...)

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Interactions with NT's

- Histamine increases dopamine
- elevated histamine also results in low serotonin
- Histamine levels decrease with adequate GABA levels

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Histapenia and Psychiatry

- Could be schizophrenic too
 - Chronic depression
 - Often doesn't show signs of sickness or allergies
- According to Carl Pfeiffer:
- canker sores
 - difficult orgasm with sex
 - no headaches or allergies
 - heavy growth of body hair
 - ideas of grandeur
 - Paranoia
 - racing thoughts
 - Sense their mind is being controlled
 - seeing or hearing things abnormally
 - ringing in the ears,

26



symptoms

- Will vary greatly from person to person

27

Review > Biomed Pharmacother. 2000 Jun;54(5):263-7.
doi: 10.1016/S0753-3322(00)80069-4.

The role of brain histamine in acute and chronic stresses

C. Ito ¹

- Anxiolytic drugs also decrease brain histamine
- acute stresses increase brain histamine
- psychostimulants also increase the striatal histamine release

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Histadelic Kids and Teens

- self-motivated and achievement-oriented but may have learning issues
- can't stand being told what to do
- "oppositional defiant disorder"
- Obsessively hooked on activities
- Greater drug use, chain smoking in teens



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Causes of High Histamine

1 - Overproduction:

- stress
- allergy
- histamine rich foods
- toxins, drugs
- intestinal lining damage, gut dysbiosis

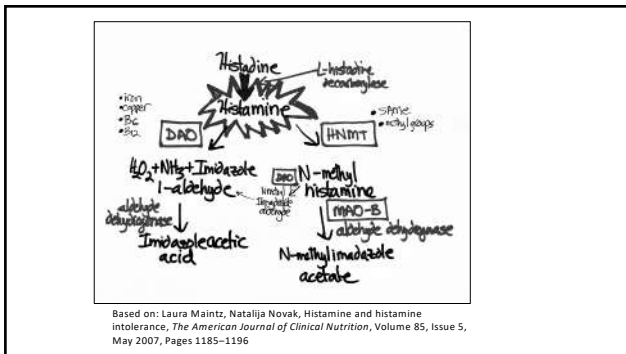
2 - poor break down:

- diamine oxidase (DAO) deficiency
- HMNT gene issue, poor methylation
- MAO b gene issue

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DAO

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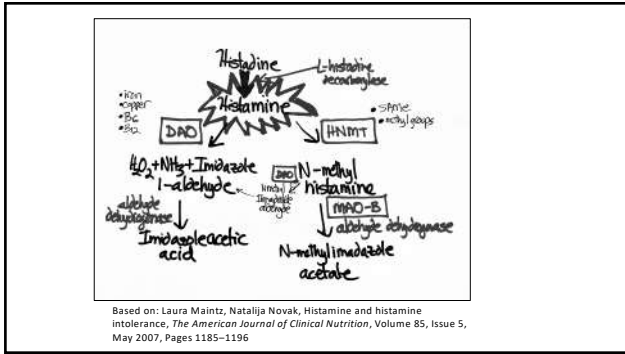
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DAO (diamine oxidase)

- It degrades histamine from foods.
- synthesized by apical enterocytes located in the intestinal villi and is released from the mucosa for digestion and into the blood circulation
- **AOC1 gene** codes for DAO enzyme production
- Genetic variants in AOC1 can increase or decrease the production of the enzyme.

Am J Physiol. 1998 Oct; 275(4):R969-75.

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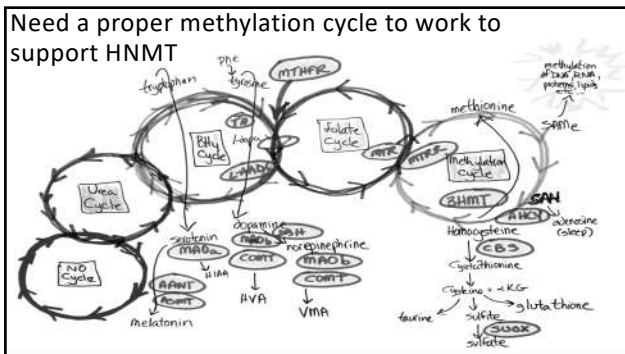


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HNMT (Histamine n-methyltransferase)

- HNMT is the enzyme that regulates histamine in the body via converting it from histamine into N-methylhistamine, which can then be eliminated from the body.

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Drugs , Toxins

- amitriptyline blocks the production of DAO in the gut (controversial)
- nitrite poisoning, alcohol abuse
- Smoking
- alcohol

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Damage to the Intestines

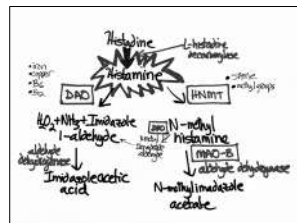
- damage or inflammation of the wall of the small intestine raise histamines
- Operation
- Viruses
- Candida / yeast
- food allergy and intolerance)
- SIBO
- Inflammation: ulcerative colitis and Crohn's disease



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Causes of Low Histamine

- 1 – over-methylation
- 2 – excess copper (Cu stimulates histamine breakdown)
- 3 – Low Protein



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Testing

- 1 – Low Histamine Diet Therapeutic Trial
- 2 – Plasma / Whole Blood Histamine
- 3 – DAO serum test
- 4 – Serum Tryptase
- 5 - 24 Hour Urine Histamine or Methylhistamine
- 6 - also test: zinc, copper, iron, vitamin B6, homocysteine,
- 7 - Genetic tests: SNPs for DAO, MTHFR, MTRR
- 8 - Blood type - A is more likely to sequester copper

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Lab Testing : Histamine

- histamine content can be measured in plasma, serum or whole blood
- Whole blood may be best

Other Tests
 Histamine, Plasma 1.10 H <1.00 ng/mL -4

Results for this test are for research purposes only by the assay's manufacturer. The performance characteristics of this product have not been established. Results should not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

41

Clin Transl Allergy. 2011; 1(Suppl 1): P115. PMID: PMC3354134
 Published online 2011 Aug 12.
 doi: 10.1186/2045-7022-1-S1-P115

Serum diamine oxidase (DAO) activity as a diagnostic test for histamine intolerance

Erna Music,^{1,2} Mira Silar,¹ Peter Korosec,¹ Mitja Kosnik,¹ and Matija Rijavec¹

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If DAO is high
 - then overproduction of histamine is the issue. Work on factors

If DAO is low
 - and histamine levels are normal, then supplement may be needed

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Serum Tryptase

> J Allergy Clin Immunol. 2000 Jul;106(1 Pt 1):66-71. doi: 10.1007/s12200-000-1076-0.

Histamine and tryptase levels in patients with acute allergic reactions: An emergency department-based study

R Y Lin T, L B Schwartz, A Curry, Q B Press, R J Knight, H S Lee, L Sakakibara, C Terentium, R E Wenzel

- enzyme that is released, along with **histamine** and other chemicals, from mast cells when they are activated
- "Raised histamine and, less commonly, raised tryptase levels are observed in almost 50% of patients presenting to emergency departments with acute allergic reactions."

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blood histamine:
 marker of methylation

- low histamine = over-methylation
- High histamine = undermethylation

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DAO - AOC1 (rs10156191):

- **AOC1(rs10156191):** Diamine oxidase (DAO), encoded by the AOC1 gene, is one of the enzymes that metabolizes dietary histamine
- Individuals with this genotype may have reduced DAO activity and a reduced capacity to metabolize dietary histamine.

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AOC1 (rs10156191):

- C' = Normal production of diamine oxidase (DAO)
- 'T' = Reduced production of DAO, increased risk of histamine intolerance
- Other rs: **rs2052129, rs1049742, rs1049793**
- If risk allele, consider f/u leaky gut (lactulose mannitol) or Zonulin testing

47

PLoS One. 2012; 7(11): e47571. PMCID: PMC3495953
 Published online 2012 Nov 12. PMID: 23152756
 doi: [10.1371/journal.pone.0047571](https://doi.org/10.1371/journal.pone.0047571)

The Diamine Oxidase Gene Is Associated with Hypersensitivity Response to Non-Steroidal Anti-Inflammatory Drugs

José A. G. Agúndez,¹ Pedro Ayuso,² José A. Cornejo-García,³ Miguel Blanca,⁴ María J. Torres,⁴ Inmaculada Doña,⁴ María Salas,⁴ Natalia Blanca-López,⁵ Gabriela Canto,⁵ Carmen Rondon,⁴ Paloma Campo,⁴ José J. Laguna,⁶ Javier Fernández,⁷ Carmen Martínez,¹ and Elena García-Martín^{2,*}

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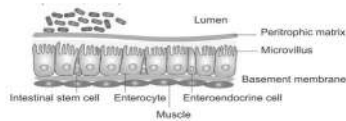
Leaky Gut Test

- **Test:** a person drinks a solution contain both mannitol (easy to absorb) and lactulose (hard to absorb). Collect urine
- **normal:** shows high levels of mannitol and low levels of lactulose.
- **high levels of both molecules** are found, it indicates a leaky gut condition.
- **low levels of both molecules are found,** it indicates general malabsorption of all nutrients.

| INTESTINAL PERMEABILITY (IP) REPORT | | | |
|-------------------------------------|--------------------|----------------------|--------------------------------|
| | With Ref. range | Output Ref. range | Ref. Range |
| LACTULOSE RECOVERY | | 1.52 % | Leaky Gut < 0.2% |
| MANNITOL RECOVERY | | 30.4 % | Leaky Gut 9.3 - 25.0 |
| LACTULOSE/MANNITOL RATIO | | 0.052 | Increased Pore Size < 0.055 |

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ZONULIN test for leaky gut



- **Zonulin** – Zonulin is a protein that opens intercellular tight junctions in the gut lining (*the connections between epithelial cells that make up the gastrointestinal lining*). Zonulin increases intestinal permeability in the jejunum and ileum and is considered a biomarker for barrier permeability.

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Treatment for High Histamine:

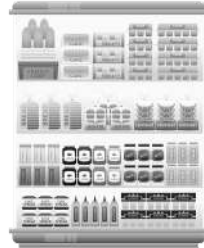


- 1 – Diet restrictions and additions
- 2 – DAO
- 3 – Other Supportive Supplements
- 4 – Avoid drugs, toxins that reduce DAO
- 5 – Air filtration indoors
- 6 – Fix gut / microbiome

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1 – Diet Changes

- Low histamine diet
- Add pea shoots
- Avoid gluten
- Food preparation

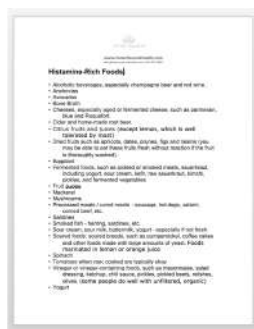


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Low Protein and Low H Diet

- talk to your patient about considering a low histamine diet.
- Limit: meats, fermented foods, canned items, poultry, fish, tomatoes, chocolate, spinach, eggplant, avocado, and nuts
- Review other foods (see sheet) as needed

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- microorganisms also convert histidine to histamine by decarboxylation (probiotics and treat gut)
- Avoid leftovers too!



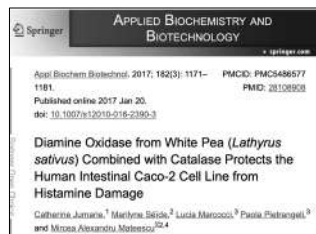
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Add Pea Shoots

- *Lathyrus sativus*
- Early Spring plant
- Naturally rich in DAO



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Review > Inflamm Res. 2018 Apr;67(4):279-284. doi: 10.1007/s00011-017-1117-4. Epub 2017 Nov 27.

Non-celiac gluten sensitivity: people without celiac disease avoiding gluten—is it due to histamine intolerance?

Wolfgang J Schnedl ^{1, 2}, Sonja Lackner ³, Dietmar Enko ⁴, Michael Schenk ⁵, Harald Mangge ⁶, Sandra J Holasek ³

58

> Ann Dermatol. 2017 Dec;29(6):706-714. doi: 10.5021/ad.2017.29.6.706. Epub 2017 Oct 30.

Effect of Different Cooking Methods on Histamine Levels in Selected Foods

Bo Young Chung ¹, Sook Young Park ¹, Yun Sun Byun ¹, Jee Hee Son ¹, Yong Won Choi ¹, Yong Se Cho ¹, Hye One Kim ¹, Chun Wook Park ¹

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Food Preparation: AGES

LEAST AGES

- Raw
- Boiling or Crock Pot or Stewing
- Baking
- Sautee
- Sterilization
- pasteurization
- Fry
- Grilling*

MOST AGES

- Processed foods
- Avoid any "crispy" foods
- *marinating foods in lemon juice, vinegar or other acidic substances before cooking them with dry heat reduces AGE formation



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2 – Give DAO supplement

- **Diamine Oxidase enzyme:** primary defense against histamine produced by bacteria from our food
- Derived from pig kidney
- DAO deficiency is the primary cause of histamine intolerance
- *The American Journal of Clinical Nutrition*, Volume 85, Issue 5, May 2007, Pages 1185–1196

61

> Food Sci Biotechnol. 2019 May 24;28(6):1779-1784. doi: 10.1007/s10068-019-00627-3. eCollection 2019 Dec.

Diamine oxidase supplementation improves symptoms in patients with histamine intolerance

Wolfgang J Schnedl ¹, Michael Schenk ², Sonja Lackner ³, Dietmar Enko ⁴, Harald Mangge ⁵, Florian Forster ⁶

- Open label, 28 pts
- r/o: lactose intolerance, fructose malabsorption, *Helicobacter pylori* infection nor celiac disease.

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> Food Sci Biotechnol. 2019 May 24;28(6):1779-1784. doi: 10.1007/s10068-019-00627-3. eCollection 2019 Dec.

Diamine oxidase supplementation improves symptoms in patients with histamine intolerance

Wolfgang J Schnedl ¹, Michael Schenk ², Sonja Lackner ³, Dietmar Enko ⁴, Harald Mangge ⁵, Florian Forster ⁶

- 4 weeks on, then 4 weeks off
- All symptoms improved significantly, worsened without. DAO serum increased slightly

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3 – Other Supplements

- SAMe / Methionine
- Quercetin
- Pycnogenol

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3 – SAMe / Methionine

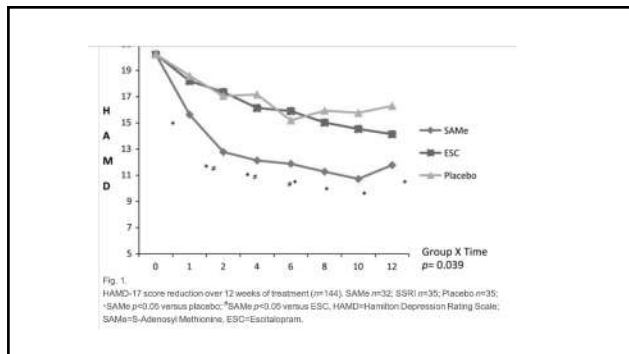
- detoxifies histamine by methylating the ring structure forming N-methyl-histamine
- Methionine 500mg QID
- SAMe – start with 400mg twice a day and increase slowly to 400mg four times a day

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- N = 144, double blinded, measured carnitine and histamine
- SAMe (1600–3200 mg/daily), escitalopram (10–20 mg/daily), or matching placebo for 12 weeks

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Journal of Affective Disorders
Volume 164, 1 August 2014, Pages 76–81

S-adenosyl methionine (SAME) versus escitalopram and placebo in major depression RCT: Efficacy and effects of histamine and carnitine as moderators of response

George I. Papadimitrakou^a, Dimitris Vlastakis^b, Marilena Fava^c, David Borch-Johnsen^d
^a The University of Melbourne, Department of Psychiatry, Australia
^b Monash University of Medicine, Centre for Human Psychophysiology, Australia
^c Psychiatry Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, United States

- HAMD: significant improvement in SAME group
- Response endpoint were 45%, 31%, and 26% for SAME, escitalopram, and placebo, respectively
- No correlation between baseline histamine or carnitine level and reduction of HAMD-17 score

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Journal of Affective Disorders
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^a The University of Melbourne, Department of Psychiatry, Australia
^b Monash University of Medicine, Centre for Human Psychophysiology, Australia
^c Psychiatry Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, United States

- sub-sample of 20 participants with a measurable level of histamine, mean average of 0.53 ng/mL (±0.34; reference range 0.5–1.4 nmol/mL) for the SAME group and 0.57 ng/mL (±0.43) for escitalopram.
- After SAME treatment, histamine levels were found to be non-significantly (p=0.21) reduced to 0.35 ng/mL (±0.36), while histamine slightly increased to 0.63 ng/mL (±0.51) in the escitalopram group.

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Quercetin

- The flavonoid quercetin has a variety of functions including the inhibition of histamine release from human basophils and murine mast cells
- quercetin is a potent anti-cytokine and chemokine generated from several cell types, which has an inhibitor effect in immunological and non-immunological conditions, mediated by mast cells

*Prog Clin Biol Res. 1986; 213(1):493-506.
 Peluso I, Miglio C, Marabito G, Ioannone F, Serafini M
 Crit Rev Food Sci Nutr. 2015; 55(3):383-95.*

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> *Phytother Res. 2003 Jan;17(1):66-9. doi: 10.1002/ptr.1240.*

Pycnogenol inhibits the release of histamine from mast cells

S C Sharma ¹, S Sharma, O P Gulati

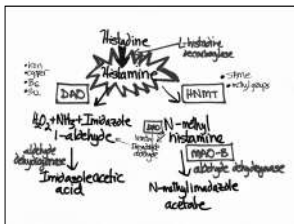
Affiliations + expand

PMID: 12557250 DOI: 10.1002/ptr.1240

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DAO – supportive nutrients

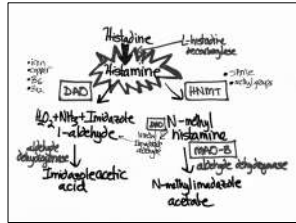
- Copper
- Iron
- Vitamin B6



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Methylation Supports

- SAME
- Methylfolate
- Methylcobalamin



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4 – Avoid certain drugs / supplements

- **Metformin:** inhibits intestinal amine transporters and DAO after therapeutic doses
- **Nicotinamide:** 100mg depletes methyl groups, serotonin and histamine levels significantly increased at 5hrs postload

X. J. Pharmacol. Ther. 2015; 148: 423-433. doi: 10.1016/j.pbr.2015.04.005

Prediction and validation of enzyme and transporter off-targets for metformin

Wang, Y., Li, Y., Lawrence, L., Mithani, M., et al. (2015) Prediction and validation of enzyme and transporter off-targets for metformin. *Journal of Pharmacology and Therapeutics*, 148(4), 423-433.

X. J. Pharmacol. Ther. 2015; 148: 423-433. doi: 10.1016/j.pbr.2015.04.005

Excess nicotinamide increases plasma serotonin and histamine levels

Wang, Y., Li, Y., Lawrence, L., Mithani, M., et al. (2015) Excess nicotinamide increases plasma serotonin and histamine levels. *Journal of Pharmacology and Therapeutics*, 148(4), 423-433.

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5 – Air filtration indoors

- remove indoor particles that can spur histamine reactions



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6 – Fix Gut

- Check SIBO
- Check Leaky Gut
- Proper probiotics:
 - Bifidobacter spp: bifidobacter infantis
 - Lactobacillus spp: particularly L. plantarum
 - Avoid: L. Bulgaricus, L. Casei, L. Delbrueckii, L. Lactis, and L. Reuteri , E. Faecalis



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Treatment for Low Histamine

- 1 – High protein / “histamine diet”
- 2 – Amino acid histadine supplement
- 3 – lower copper
- 4 – avoid methyl groups

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1 – Higher protein diet

- Remember to stay healthy



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2 – Amino acid histadine supplement

- Raises histamine levels
- Used for weight loss

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2 – Amino acid histadine supplement

Clin Cosmet Investig Dermatol. 2017; 10: 403–411. PMID: PMC5634381
 Published online 2017 Oct 5. PMID: 29042806
 doi: 10.2147/CCID.S146760

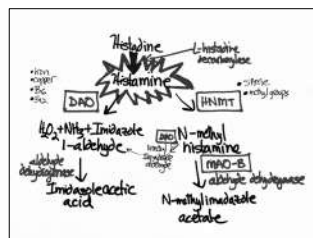
Feeding filaggrin: effects of L-histidine supplementation in atopic dermatitis

Siao Pei Tan,^{1,2} Simon B Brown,^{1,2} Christopher EM Griffiths,³ Richard B Weiler,^{1,2} and Neil K Gibbs^{3,4}

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3 – Lower copper

- Zinc
- Manganese
- niacin (B3)
- Vitamin C



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4 – avoid methylation support

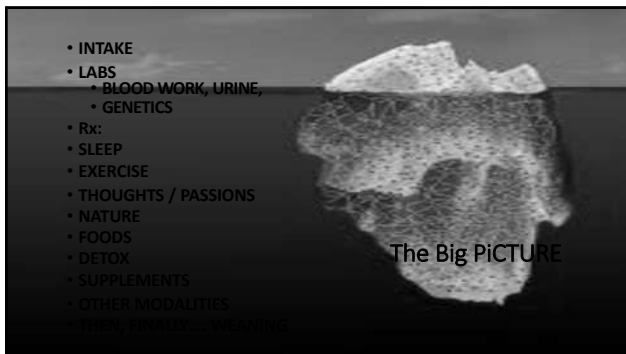
- Consider folinic acid (instead of methyl folate)
- Consider adenosyl cobalamin (instead of methyl cobalamin)

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REVIEW

- 1 – Abnormal histamine levels
- 2 – Treatment of high histamine
- 3 – Treatment of low histamine

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drpeter@innersourcehealth.com



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