



MAST Cell Activation: The Condition and cases

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BRB CE Group

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Disclosures

- on the Medical Advisory group for NFH. This is a paid position.
- a co-founder of Exceptional ND, an education platform for NDs. This is a for profit company
- a board member for Canadian Association of Naturopathic Doctors. Not for profit
- on the Membership Engagement Taskforce for the OAND. Not for profit

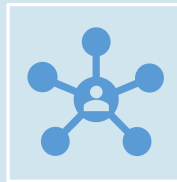
The Art and Science of Naturopathic Medicine



Connect with your patient using the lens they bring you. They like genetics, use genetics, they like inflammation etc.



Naturopathic Doctors need to acknowledge the art of sale in a treatment process. ENTHUSIASM.



If you don't connect with your patient, you are less likely to have clinical success

Histamine

- Histamine is a monoamine neurotransmitter and signalling compound
- Histamine increases vascular permeability
- One of its primary roles is to regulate other neurotransmitters and signal when something is wrong
- Histamine can also be made by microbes in the gut
- Histamine has a neuroinflammatory impact on CNS and a systemic impact on the rest of the body leading to allergies, skin reactions, joint pain and digestive disorders.

Histamine

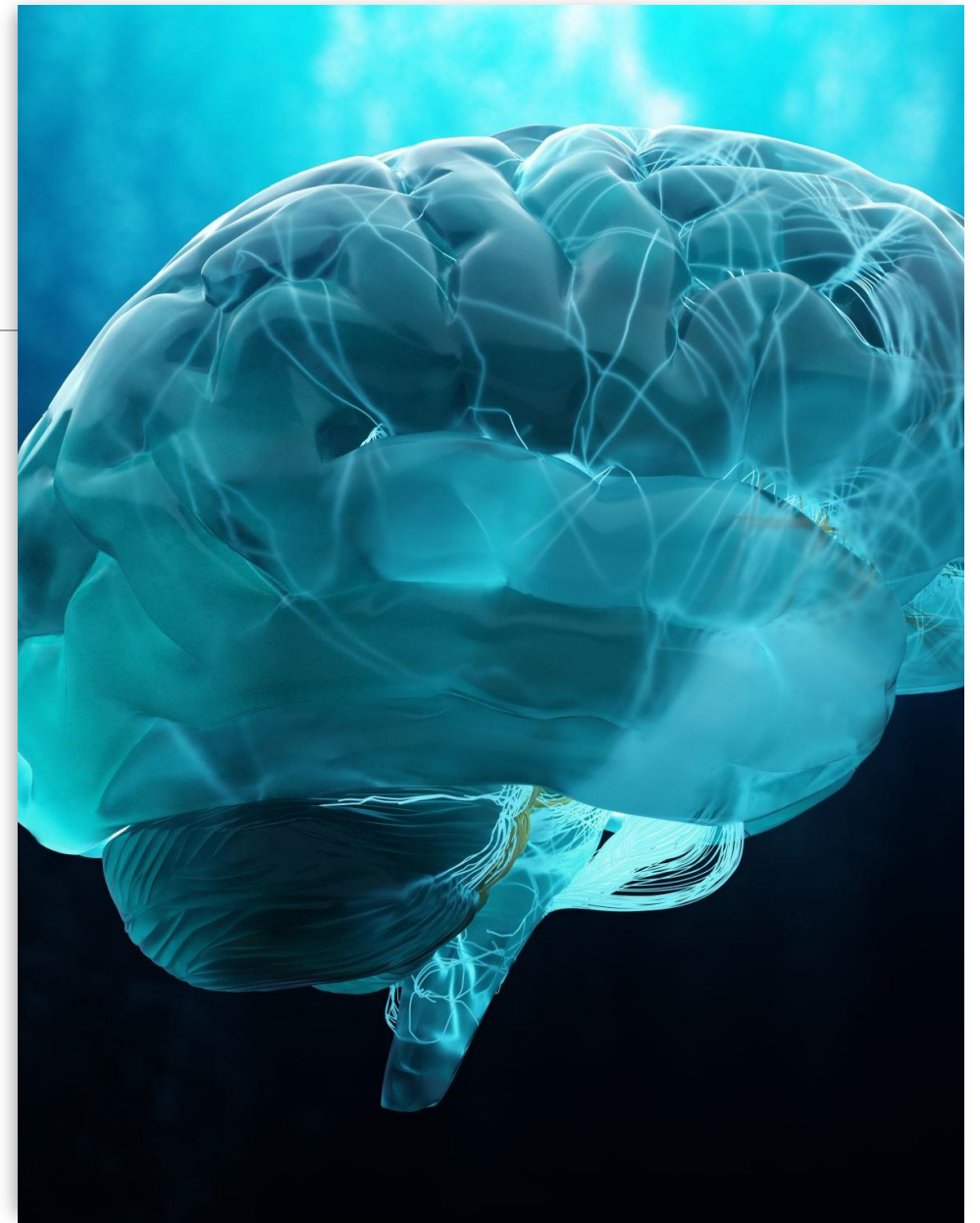
- Histamine is found in nearly all tissues, such as stomach mucosa lining, neurons, mast cells, and basophils
- It plays extensive roles in smooth muscle contraction, brain excitation, widening of blood vessels, and sensory system signaling in the brain
- This role in sensory signaling — specifically overactivation of the H1 histamine

Histamine Receptors

- H1 – mucosal inflammation, pro-inflammatory
- H2 – operates the “proton pump” regulating HCL for digestion
- H1 primarily (but potentially H1 and H2) are associated with respiratory mucosal inflammation and respiratory inflammation
- The GI tract and respiratory tract contain all the elimination pathways for histamine which reduces inflammation

Histamine in the brain

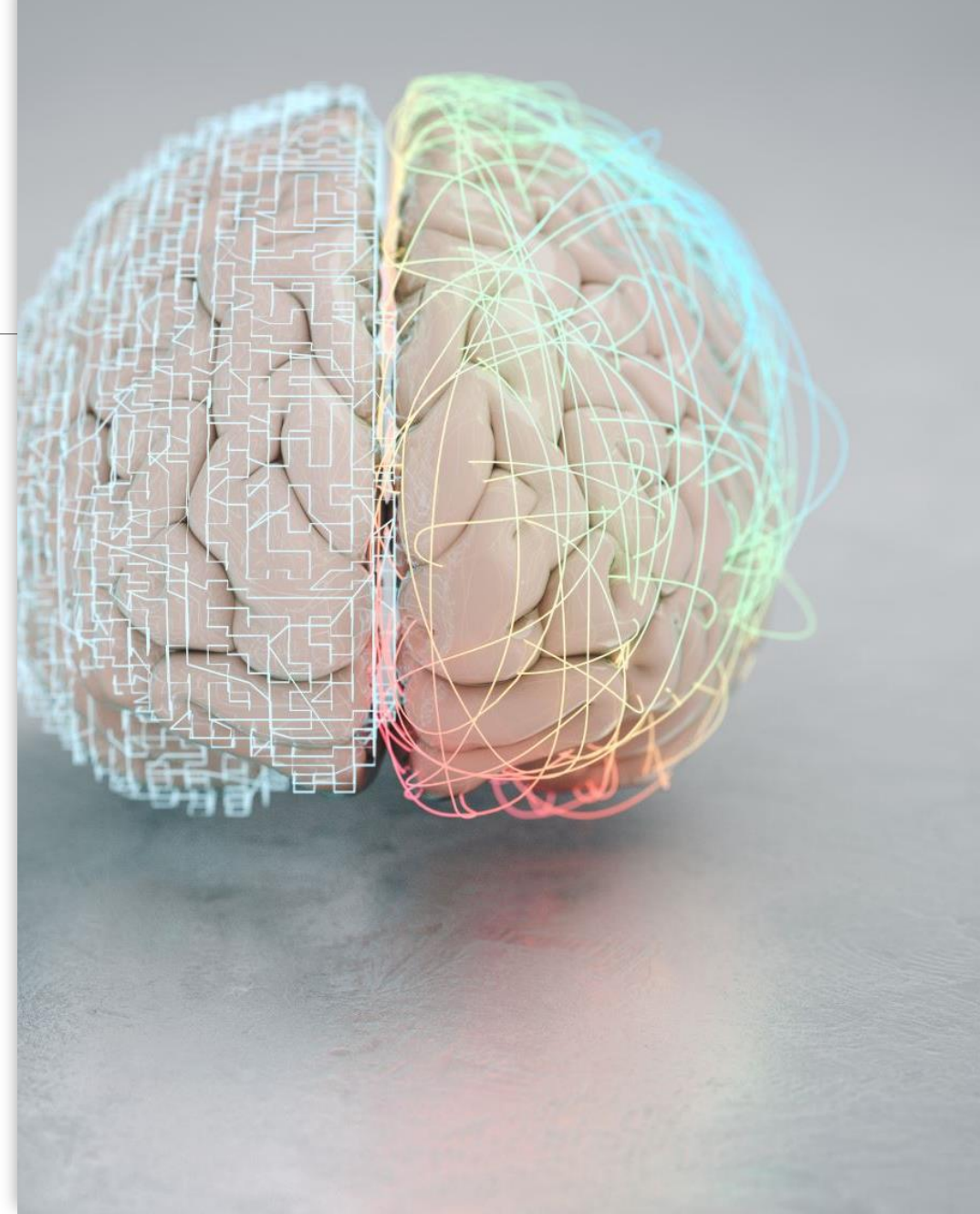
- H1 and H2 are stimulating
- H3 and H4 act weakly and are inhibiting
- In the brain – histamine plays a role in counter regulatory to keep all the other neurotransmitters regulated, histamine dysregulation leads to dysregulation of all other neurotransmitters
- Histamine is excitatory and its impact is on par with glutamate and epinephrine / norepinephrine



Histamine - gut brain axis

- Histamine impacts GI membranes, GI microbiota, GI integrity, GI neurotransmitters
- The brain is a mirror image of the gut
- GI inflammation leads to more brain inflammation which becomes a vicious cycle
- Histamine causes gut inflammation and brain inflammation by inflaming membranes
- Leaky gut = leaky blood brain barrier
 - **If non-sedating Rx cause sedation*

**Healing the gut – diet, healthy fats, manage dysbiosis, curcumin, quercetin, zinc, vitamin A*



Histamine and the brain

- High levels associated with rage, mania, agitation, anxiety, panic, sleep disorders, eating disorders, metabolic syndrome, neuroinflammation, migraines, dementia, epilepsy and vestibular disorders
- Low histamine associated with depression
- Does not cross the BBB
- Produced centrally by histidine (histidine converts to glutamate)
- Should be considered in all cases of extreme mania or depression or if the **obvious neurotransmitter doesn't help the patient**

Glutamate and histamine

- Histamine increases glutamate
- Glutamate is a byproduct of CNS neuroinflammation
- Glutamate is mopped up by supporting methylation

Histamine Symptoms

Digestive System: Bloating, abdominal discomfort, gas, nausea, vomiting and diarrhea, GERD, Food sensitivities

Skin: Hives (urticaria), intense itching, and flushing or redness (particularly on the cheeks), angioedema, dermatographia

Nervous System: Headaches, migraines, dizziness, fatigue, rage, anxiety, sleep disturbance, panic, irritability, autism symptoms, ADHD symptoms

Respiratory: Nasal congestion, a runny nose, sneezing, and wheezing, shortness of breath

Cardiovascular: Rapid heart rate (palpitations) or low blood pressure, fainting, POTS

Hormonal: Painful menstruation, Peri-menopausal symptoms, uterine cramping, bleeding, heavy periods, ovulation-related symptoms, cyclical migraines

Urinary: Interstitial cystitis, overactive bladder, urinary frequency

Musculoskeletal – Bone, muscle pain, osteosclerosis, osteopenia, osteoporosis, nerve sensitivity

Symptoms sometimes attributed to histamine intolerance.

Your symptoms may include:



Diarrhea.



Nausea or vomiting.



Headache.



Runny or stuffy nose.



Shortness of breath (dyspnea).



Itching.



Rash or hives.



Flushing.



Low blood pressure.



Irregular or fast heart rate.



Swelling of lips, tongue or throat.

What triggers HISTAMINE?

IgE, IgG4, IgA, IgG

Toxicants – chemical, heavy metal and mold

Microbiome microbes

Chronic infections / Biofilms

Inflammation

Oxidative stress

Autoimmunity

Glutamate

Endocrine - Adrenal fatigue, Thyroid, Metabolic, Hormones, Perimenopause

Mitochondrial dysfunction / Lipid peroxidation

Methylation impairment

Food

Foods that trigger HISTAMINE

Alcohol (wine, beer and champagne).

Processed meat.

Cheeses.

Sauerkraut.

Vegetables (tomatoes, eggplant and spinach).

Tropical fruit (pineapple, bananas, papaya and citrus fruits).

Fish (mackerel, tuna, sardines and herring) and shellfish.

Strawberries.

Nuts and peanuts.

Licorice.

Chocolate.

Pork.

Egg white.

Additives (like colorants and preservatives).

Diet	Core Principles	Why It Helps with Mast Cell Activation
Low-Histamine Diet	Avoid high-histamine and histamine-releasing foods (aged, fermented, processed)	Reduces direct triggers of mast cell degranulation and circulating histamine load
Anti-Inflammatory Diet	Emphasizes whole foods, healthy fats, fruits, vegetables, herbs/spices (like turmeric)	Lowers chronic inflammation that can trigger mast cells
Mediterranean Diet	Rich in olive oil, fish, greens, low in processed foods	Anti-inflammatory, antioxidant-rich, supports gut and immune balance
Paleo or Autoimmune Paleo (AIP)	Removes grains, dairy, legumes, processed foods; AIP also excludes eggs, nuts, nightshades	Eliminates many common triggers (like gluten and lectins), calms gut inflammation
Low FODMAP Diet (short-term)	Reduces fermentable carbs that feed gut bacteria	Can help in people with SIBO or IBS, where gut dysbiosis leads to mast cell activation
Elimination Diet (customized)	Temporarily removes potential triggers; reintroduce one at a time	Helps identify personal food triggers, including histamine liberators or allergens

<https://pubmed.ncbi.nlm.nih.gov/34618688/>

Foods that may help stabilize Mast Cells

Food	Why It Helps
Fresh, organic meats and fish (immediately frozen if not eaten)	Low in histamine if fresh and minimally processed
Leafy greens (except spinach)	Anti-inflammatory and generally low in histamine
Blueberries, apples, pears	Low-histamine fruits with quercetin (mast cell stabilizer)
Olive oil, flaxseed oil	Anti-inflammatory fats
Turmeric, ginger	Natural mast cell stabilizers and anti-inflammatory agents
Green tea (decaffeinated if sensitive)	Contains EGCG, helps stabilize mast cells
Foods high in Vitamin C and B6	Support histamine metabolism and mast cell balance

<https://tmsforacure.org/signs-symptoms-triggers/symptoms-and-triggers-of-mast-cell-activation>

Diets that decrease Mast cell activation

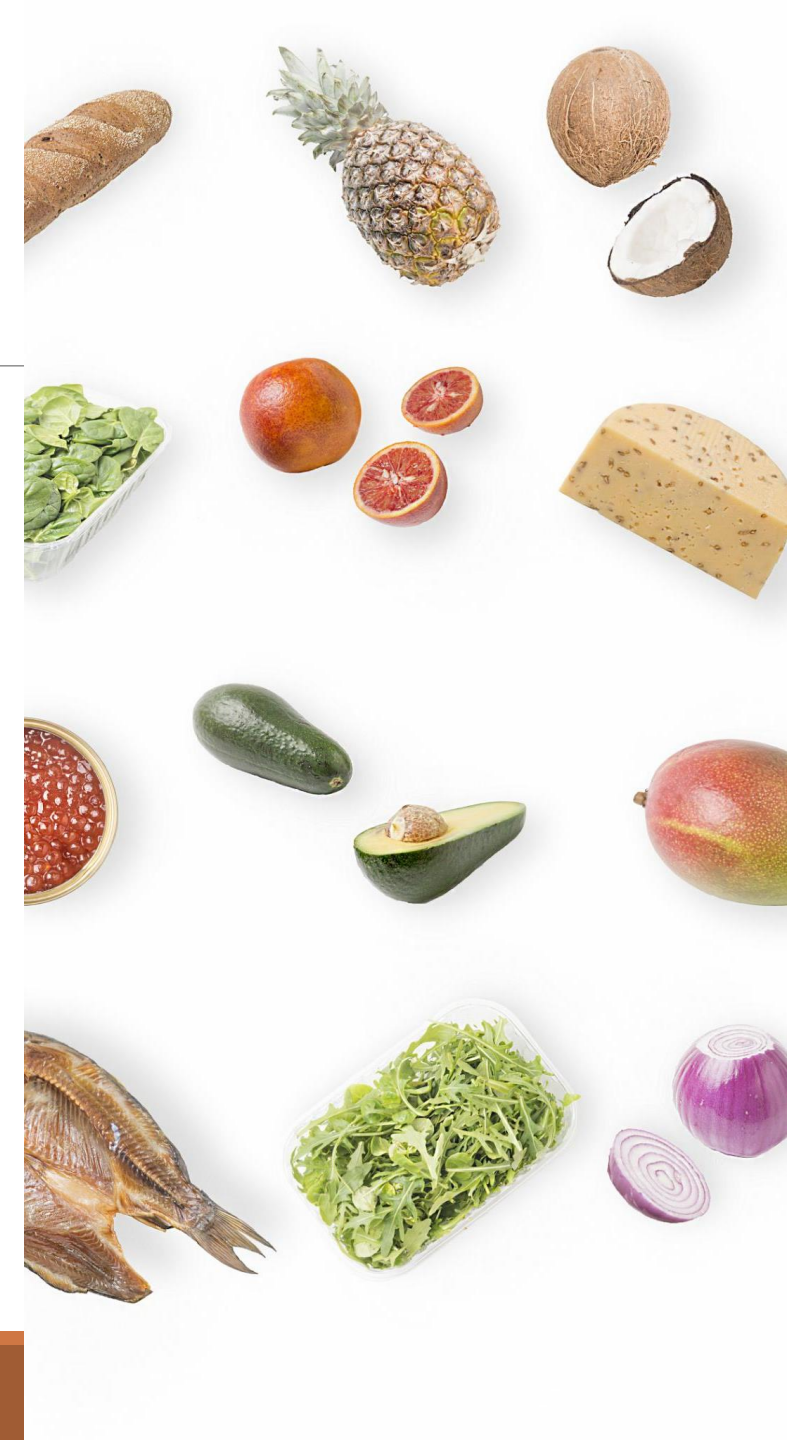
The **Six-Food Elimination Diet (SFED)**:

Eosinophilic esophagitis (EoE) diet research showed reduction of mast cell density; expression of mast cell proteases and associated chemokines declined.

Symptoms correlated with mast cell levels.

Those 6 foods are dairy, wheat, eggs, soy, peanuts and tree nuts, and seafood (fish and shellfish)

<https://pubmed.ncbi.nlm.nih.gov/25640519/>



Colonic mast cells are increased in obstructed defecation patients

> Dig Dis Sci. 2012 Jan;57(1):65-71. doi: 10.1007/s10620-011-1848-y. Epub 2011 Aug 4.

Increase of colonic mast cells in obstructed defecation and their relationship with enteric glia

Gabrio Bassotti¹, Vincenzo Villanacci, Riccardo Nascimbeni, Moris Cadei, Stefania Manenti, Elisabetta Antonelli, Lucia Fanini, Bruno Salerni

Affiliations + expand

PMID: 21814802 DOI: [10.1007/s10620-011-1848-y](https://doi.org/10.1007/s10620-011-1848-y)

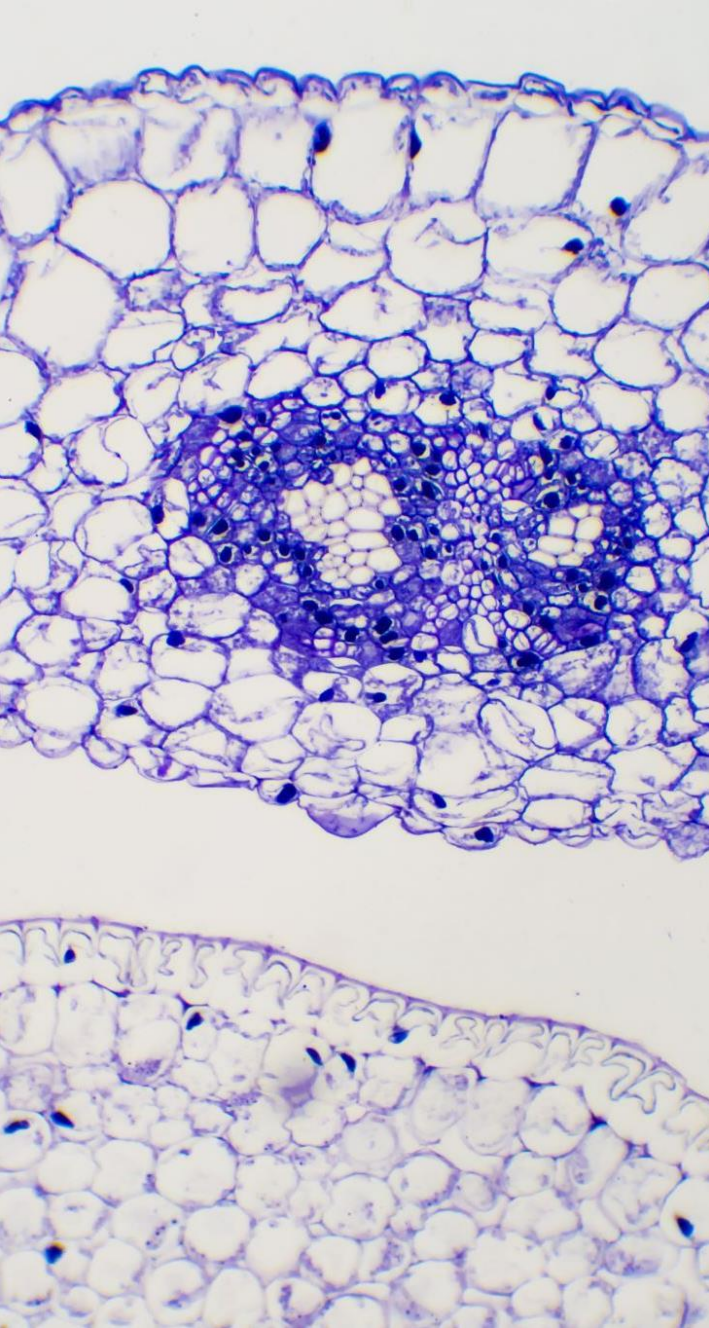
Abstract

Background: Mast cells are involved in visceral hypersensitivity and motor activity of the gastrointestinal tract. However, there is almost no information concerning mast cells in constipated patients.

<https://pubmed.ncbi.nlm.nih.gov/21814802/>



When in
doubt... clear
them out



Mast Cells: Body's Sentinels

Defense Against Pathogens

Mast cells act as an early alert system, responding to threats like viruses, bacteria, fungi, and toxins within body tissues.

Allergic Reaction Triggers

They can respond to harmless particles, triggering allergic reactions and releasing chemicals that cause symptoms.

Tissue-Based Sentinels

Unlike other white blood cells, mast cells remain in tissues, waiting for signals instead of directly destroying invaders.

<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.752350/full>

<https://pubmed.ncbi.nlm.nih.gov/21354470>

Mast Cell Activation Insights

Roles in Immunity and Healing

Mast cells are crucial for tissue repair, wound healing, and angiogenesis, acting as first responders in immune defense.

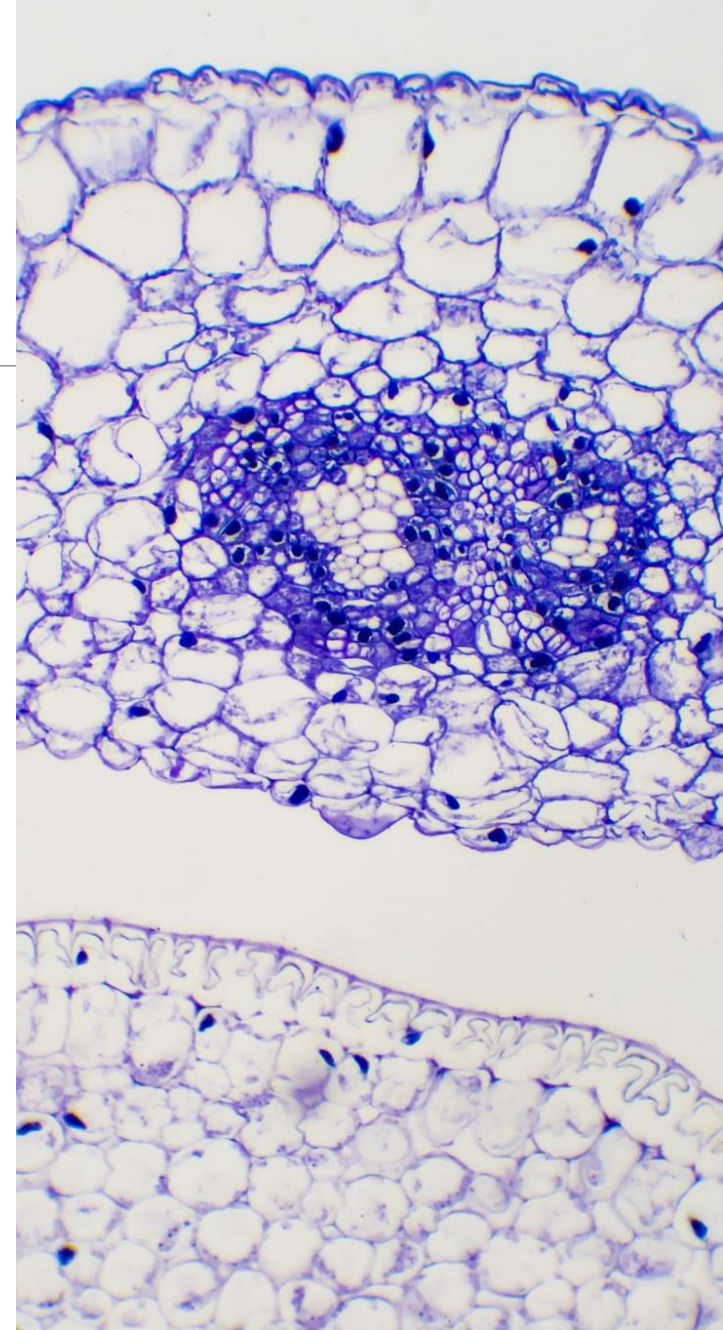
Inflammatory Mediator Effects

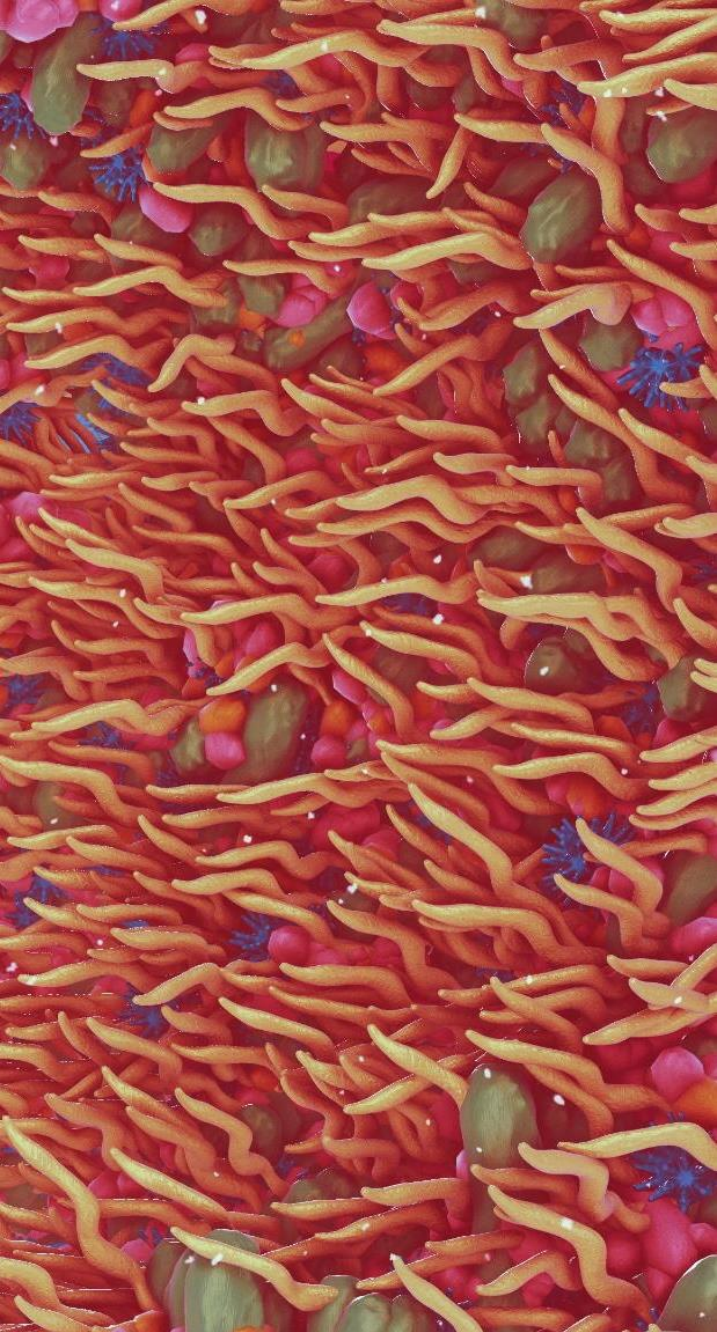
Mast cell inflammatory mediators protect tissues, but excessive activation can result in tissue damage and chronic inflammation.

Association With Autoimmune Disease

Overactive mast cells are linked to autoimmune diseases like rheumatoid arthritis, type 1 diabetes, and multiple sclerosis.

<https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.752350/full>
<https://pubmed.ncbi.nlm.nih.gov/21354470>





Mast Cells: Strategic Locations

Abundant in Connective Tissues

Mast cells are mainly located in connective tissues, providing a first line of defense at exposed body surfaces.

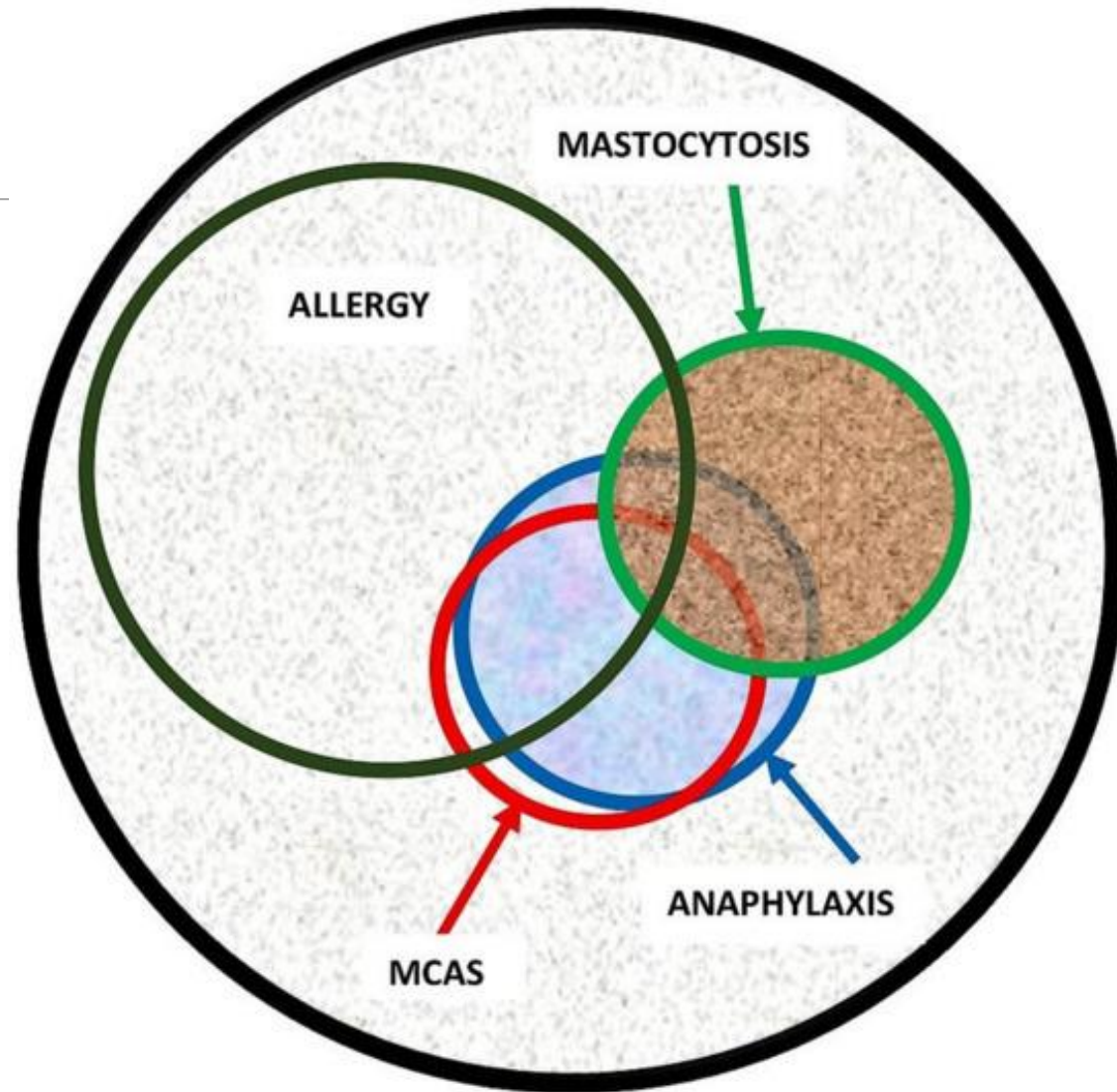
Near Blood Vessels and Nerves

Mast cells are strategically positioned near blood vessels, nerves, and lymphatic vessels to trigger rapid immune responses.

Scarce in Bloodstream

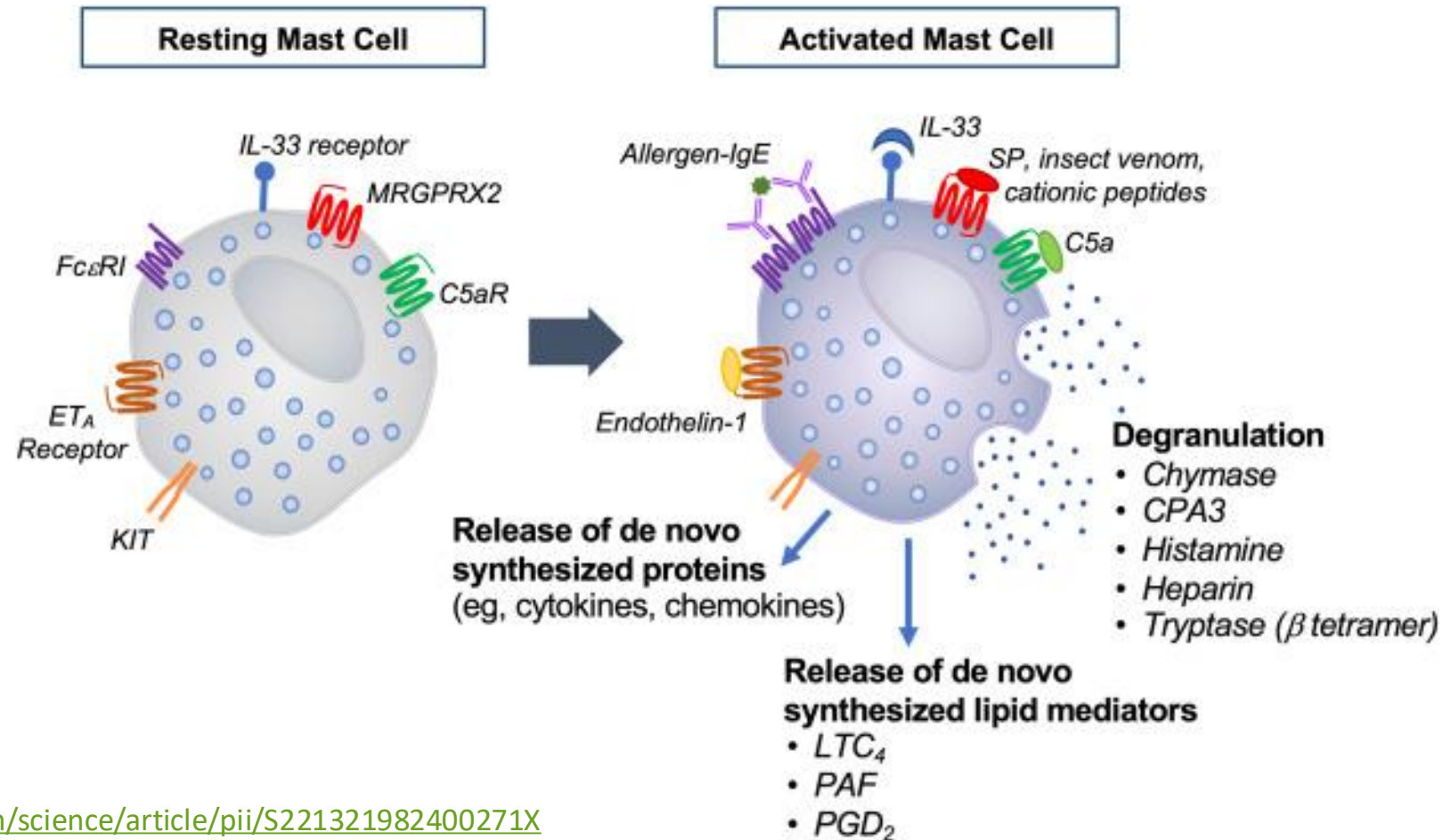
Very few mast cells circulate in the bloodstream, emphasizing their primary function within tissues rather than in circulation.

Disorders related to pathologic MAST cell activation



<https://www.mdpi.com/2075-4418/13/21/3307>

Activated Mast Cells



<https://www.sciencedirect.com/science/article/pii/S221321982400271X>

Systemic Mast Cell Activation

TRIGGERS

(such as food,
drug, insect
venom)

Rapid
Sec to min

Granule stored
(such as histamine,
tryptase, heparin,
TNF- α)

Rapid
< 15 min

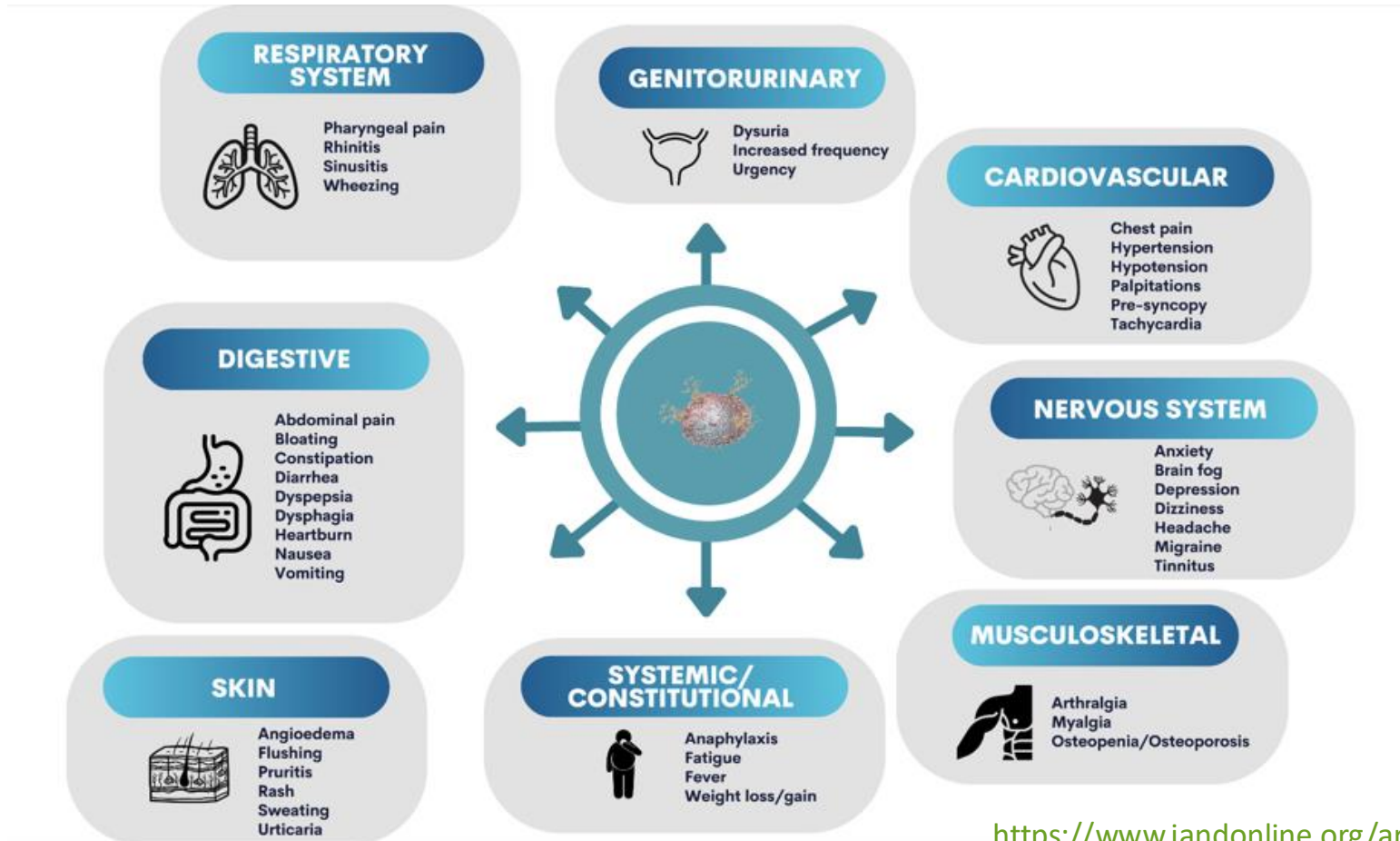
Lipid mediators,
such as leukotrienes
(LTB₄, LTC₄, LTE₄),
prostaglandins (PGD₂),
PAF

Delayed
> 3 hrs

Cytokines
Chemokines
Growth factors

<https://www.mdpi.com/2075-4418/13/21/3307>

MAST Cell Activation Symptom



[https://www.jandonline.org/article/S2212-2672\(24\)00221-1/abstract](https://www.jandonline.org/article/S2212-2672(24)00221-1/abstract)

MCAS Diagnostic Criteria Overview

Systemic Symptoms in Multiple Organs

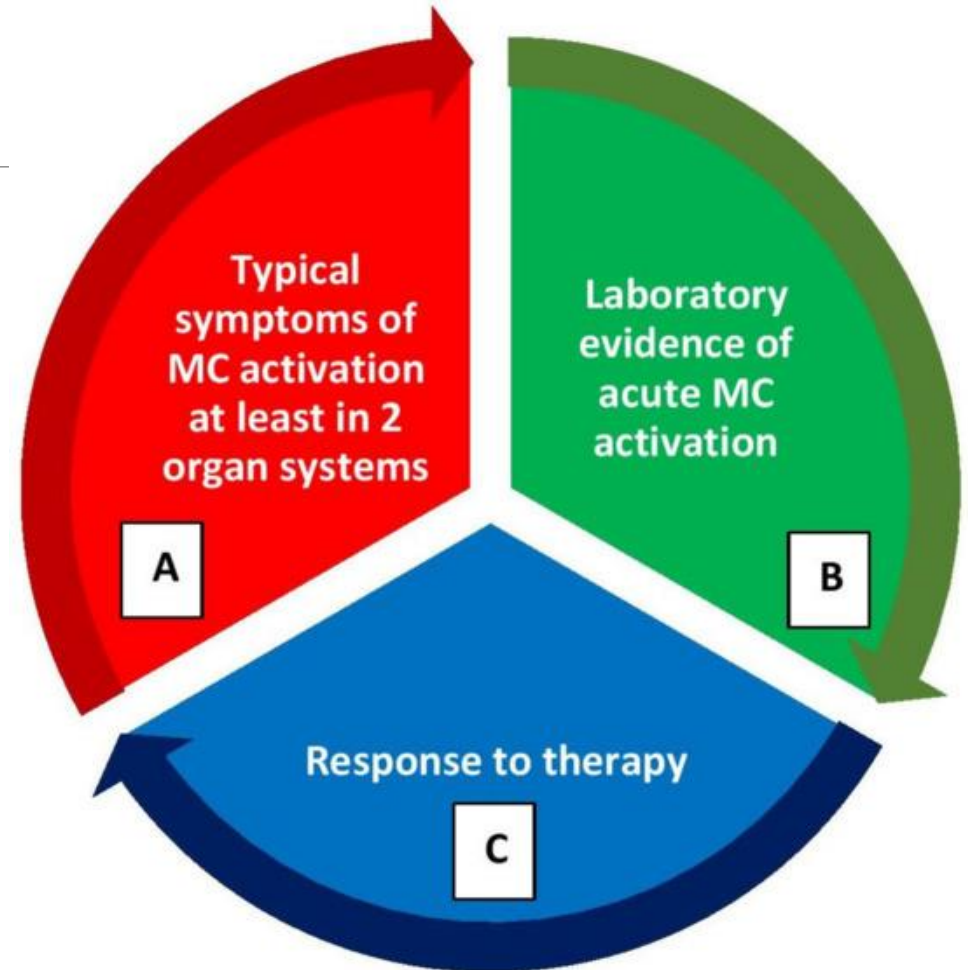
Diagnosis requires severe, recurrent symptoms that affect at least two different organ systems in the body.

Laboratory Confirmation

Elevated serum tryptase, histamine, or prostaglandin D2 compared to baseline is needed for laboratory confirmation of MCAS.

Response to Treatment

A favorable response to drugs that stabilize mast cells or block their mediators supports the diagnosis.



<https://www.mdpi.com/1648-9144/57/2/124>
<https://pubmed.ncbi.nlm.nih.gov/21035176/>
<https://www.mdpi.com/2075-4418/13/21/3307>

Mast Cells

Bioflavonoids inhibit
mast cell
degranulation which
reduces histamine
release



Natural Substances That May Stabilize Mast Cells

Substance	Mechanism / Notes	Effect on Mast Cells
Vitamin C	Natural antihistamine; antioxidant; lowers histamine; prevents degranulation	✅ Stabilizes mast cells
Vitamin B6 (P5P)	Cofactor for HNMT (histamine metabolism); supports methylation	⚠️ Indirect modulation of histamine levels
Magnesium	Regulates calcium influx; deficiency increases activation	✅ Reduces degranulation
Quercetin (2000 mg BID)	Flavonoid; inhibits histamine + cytokines; antioxidant	✅ Potent stabilizer
Zinc (30 mg to 300 mg?)	Immune modulator; supports histamine breakdown; antioxidant	✅ Stabilizes membranes, immune balance
Omega-3 Fatty Acids	EPA/DHA reduce inflammation; modulate immune response	⚠️ Indirect modulation of mast cell inflammation
Vitamin D	Immunoregulator; low levels linked to allergy, MCAS	⚠️ May reduce overactivation
Copper	Cofactor for DAO, HNMT (histamine enzymes); needs balance	⚠️ Supports histamine breakdown indirectly
NAC / Glutathione	Boosts glutathione; reduces oxidative stress	✅ Reduces mast cell-triggered inflammation
Resveratrol – 20 mg BID		

<https://tmsforacure.org/signs-symptoms-triggers/symptoms-and-triggers-of-mast-cell-activation>

> [Med Hypotheses](#). 1981 Nov;7(11):1359-76. doi: 10.1016/0306-9877(81)90126-2.

Vitamin C, titrating to bowel tolerance, anascorbemia, and acute induced scurvy

R F Cathcart

DOI: [10.1016/0306-9877\(81\)90126-2](#)

PMID: 7321921 [↗](#)

N-Acetyl- Cysteine

Rate limiting step to making glutathione

Improves pediatric OCD, autism

Improves hormone regulation

Mucolytic

Glutamate modulator - Reduces glutamate, reduces neuroinflammation

Substance	Mechanism / Notes	Effect on Mast Cells
Bromelain	Anti-inflammatory; proteolytic enzyme; reduces histamine	✓ Inhibits degranulation
Curcumin – 1-4 grams daily	NF-κB inhibitor; antioxidant; cytokine suppressor	✓ Inhibits mast cell activation
EGCG (Green Tea) – 100 to 200 mg of EGCG BID	Antioxidant; blocks IgE-induced activation	✓ Mast cell stabilizer
Luteolin (100 mg to 200 mg)	Flavonoid; inhibits cytokine release; antioxidant	✓ Potent mast cell stabilizer
Palmitoylethanolamide (PEA)	Activates PPAR-α; modulates immune + mast cell signaling	✓ Reduces degranulation
Rutin	Related to quercetin; antioxidant	✓ Mild mast cell stabilizer
Theanine (100 mg to 500 mg BID)	Green tea amino acid; anti-stress effects	⚠ Indirect modulation

Some natural MC stabilizers and doses:

- Silymarin – 500-1000 mg daily, doses divided
- Ellagic acid [red raspberries, strawberries, pomegranates, walnuts...] – 500 mg daily
- Pycnogenol – 500 to 1000 mg daily
- Magnolia/Honokiol – 200 to 250 mg twice daily
- Parthenolide (Feverfew) – 200 to 400 mg twice daily

(c) PS Anderson - www.ConsultDrA.com 2023



► Br J Pharmacol. 2013 Aug 15;170(1):23–37. doi: [10.1111/bph.12138](https://doi.org/10.1111/bph.12138) 

Twenty-first century mast cell stabilizers

[D F Finn](#)¹, [J J Walsh](#)¹

► Author information ► Article notes ► Copyright and License information

PMCID: PMC3764846 PMID: [23441583](https://pubmed.ncbi.nlm.nih.gov/23441583/)

<https://pmc.ncbi.nlm.nih.gov/articles/PMC3764846/>

EDUCATIONAL ARTICLE

An Orthomolecular Protocol for Long COVID

Michael J Gonzalez; Jorge R. Miranda-Massari; Charles Simone; Jose Olalde; Miguel J Berdiel; Jorge Duconge; Lourdes Amadeo; Jaime Claudio

Citation: Gonzalez MJ et al. (2023) An Orthomolecular Protocol for Long-COVID. *J Orthomol Med.* 38(1)

- <https://isom.ca/wp-content/uploads/2023/02/An-Orthomolecular-Protocol-for-Long-COVID-JOM-38.1.pdf>

Botanical Medicine in HISTAMINE management

Stinging Nettle: A plant leaf that blocks H₁ histamine receptors (the targets for allergy symptoms). Think of histamine like a lock and the receptor like a keyhole; nettle blocks the keyhole so histamine cannot enter.

Quercetin: A plant pigment found in many herbs and fruits. It acts like a shield. It keeps mast cells from opening and spilling histamine.

Butterbur: An herb used to treat seasonal allergies. It stops the release of histamine in the body. Note: Raw, fresh butterbur has toxins, so you must use processed "PA-free" supplements.

Turmeric: A bright yellow spice from a root. It lowers inflammation and keeps mast cells from releasing histamine.

Holy Basil: Also called Tulsi. It is a calming herb that lowers stress. Stress causes your body to release more histamine, so calming the body helps stop the release.

Bromelain: An enzyme from pineapples. It reduces swelling and helps your body absorb other natural herbs like quercetin.

Nigella Sativa: Also known as black cumin seed. It calms allergic responses and stops histamine pathways in your cells.

Probiotics and HISTAMINE

Mast cell supporting properties

Lowering inflammation

Binding mold toxins

Promoting digestion

Balancing your gut's microbiome

Improving nutrient absorption

Decreasing susceptibility to viral infections

Help improve your immune system

Help lower histamine levels

Help with leaky gut

Help with skin conditions like eczema and acne

Help your body produce vitamins such as: B1, B2 , B5, B12, Biotin, Folate, Vitamin K

Probiotics and HISTAMINE

Avoid:

Lactobacillus reuteri, Lactobacillus casei, Lactobacillus bulgaricus, Lactobacillus delbrueckii, and Streptococcus thermophilus.

- These strains possess the enzyme histidine decarboxylase, which converts the amino acid histidine into histamine.

► [Cureus](#). 2024 Mar 8;16(3):e55817. doi: [10.7759/cureus.55817](https://doi.org/10.7759/cureus.55817) 

Probiotics in Allergy and Immunological Diseases: A Comprehensive Review

[Swapna Vijayan](#)¹, [Venkataramana Kandi](#)², [Pratyusha S Palacholla](#)³, [Reshma Rajendran](#)⁴,
[Chandrasagar Jarugu](#)⁵, [Jayashankar CA](#)^{3,✉}, [Mundla Pravallika](#)³, [Shruthi C Reddy](#)³, [Atul S Sucharitha](#)³

Editors: Alexander Muacevic, John R Adler

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PMCID: PMC10999892 PMID: [38590477](#)

Probiotics to help metabolize HISTAMINE

Strains to Support Histamine Metabolism

The following strains are known to be helpful:

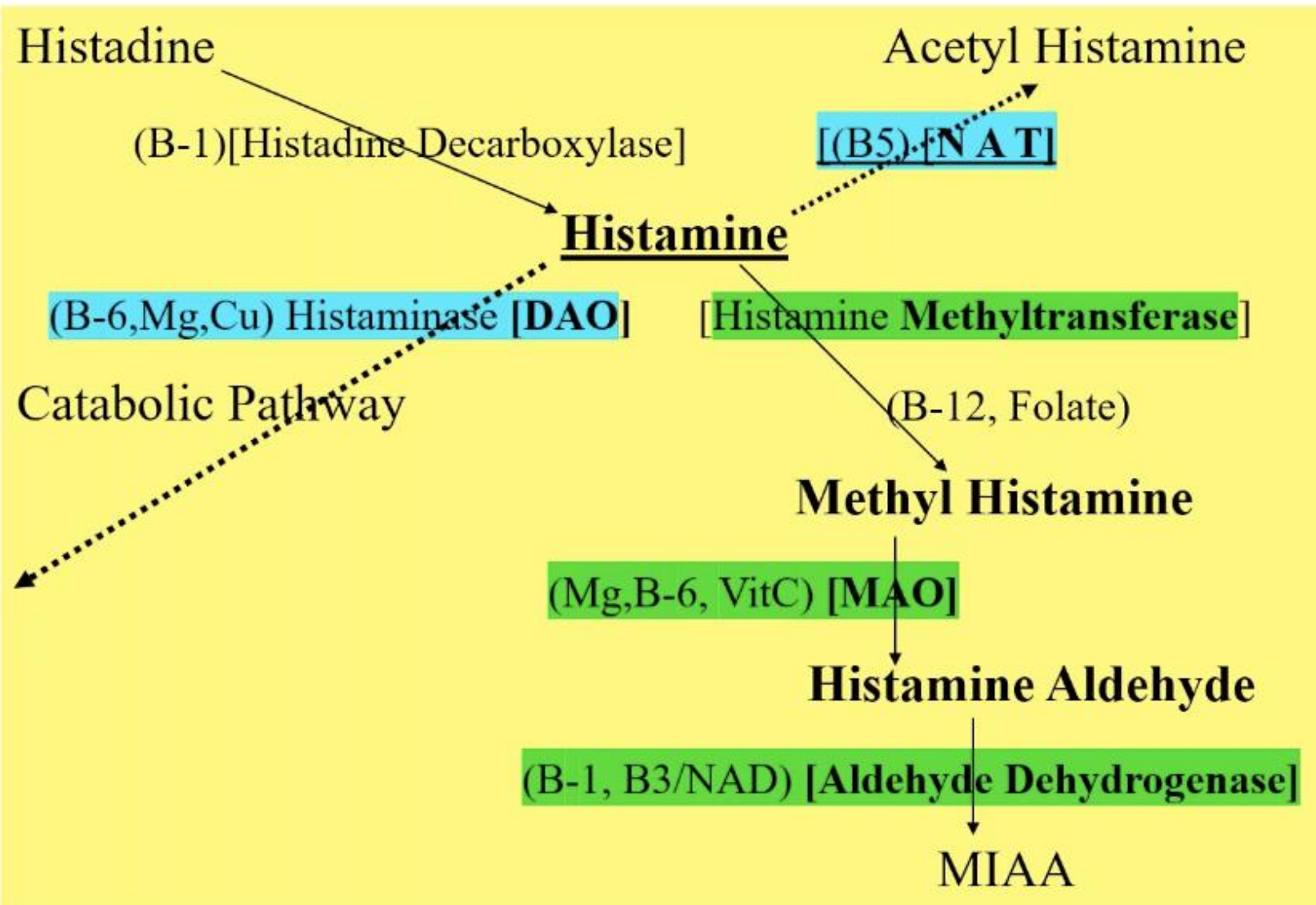
- *Lactobacillus plantarum* (LP-115): This strain increases the release of DAO. DAO is your main enzyme used to break down histamine in the gut.
- *Bifidobacterium longum*: This strain degrades histamine and keeps your gut barrier strong to prevent histamine from leaking into your blood.
- *Lactobacillus rhamnosus* (GG): This strain calms the immune cells (mast cells) that release histamine.
- *Bifidobacterium infantis*: This strain helps lower inflammation in the digestive tract.

Gut Microbiome Microbes

In the human gastrointestinal tract, an overgrowth of certain histamine-producing bacteria can contribute to conditions like chronic abdominal pain and irritable bowel syndrome (IBS)

- **Klebsiella aerogenes**
- **Morganella morganii**
- **Enterococcus faecalis**
- **E.Coli**
- *Clostridium*
- *Bacteroides*
- <https://healthsci.mcmaster.ca/histamine-producing-gut-bacteria-can-trigger-chronic-abdominal-pain/>

Histamine Metabolism



Histamine Breakdown Pathways

Enzyme	Pathway	Location	Co-factor Needed
DAO (Diamine Oxidase)	Oxidative deamination	Mainly in the gut, kidneys	Copper, Vitamin B6, Magnesium
HNMT (Histamine-N-methyltransferase)	Methylation pathway	Inside cells, especially in the liver, brain, lungs	Methyl donors: (B12, folate, SAMe, Betaine, Choline), B1, B6, Magnesium, Vitamin C,

<https://pubmed.ncbi.nlm.nih.gov/12692417/>
<https://pubmed.ncbi.nlm.nih.gov/19183150/>
<https://pubmed.ncbi.nlm.nih.gov/14988823/>

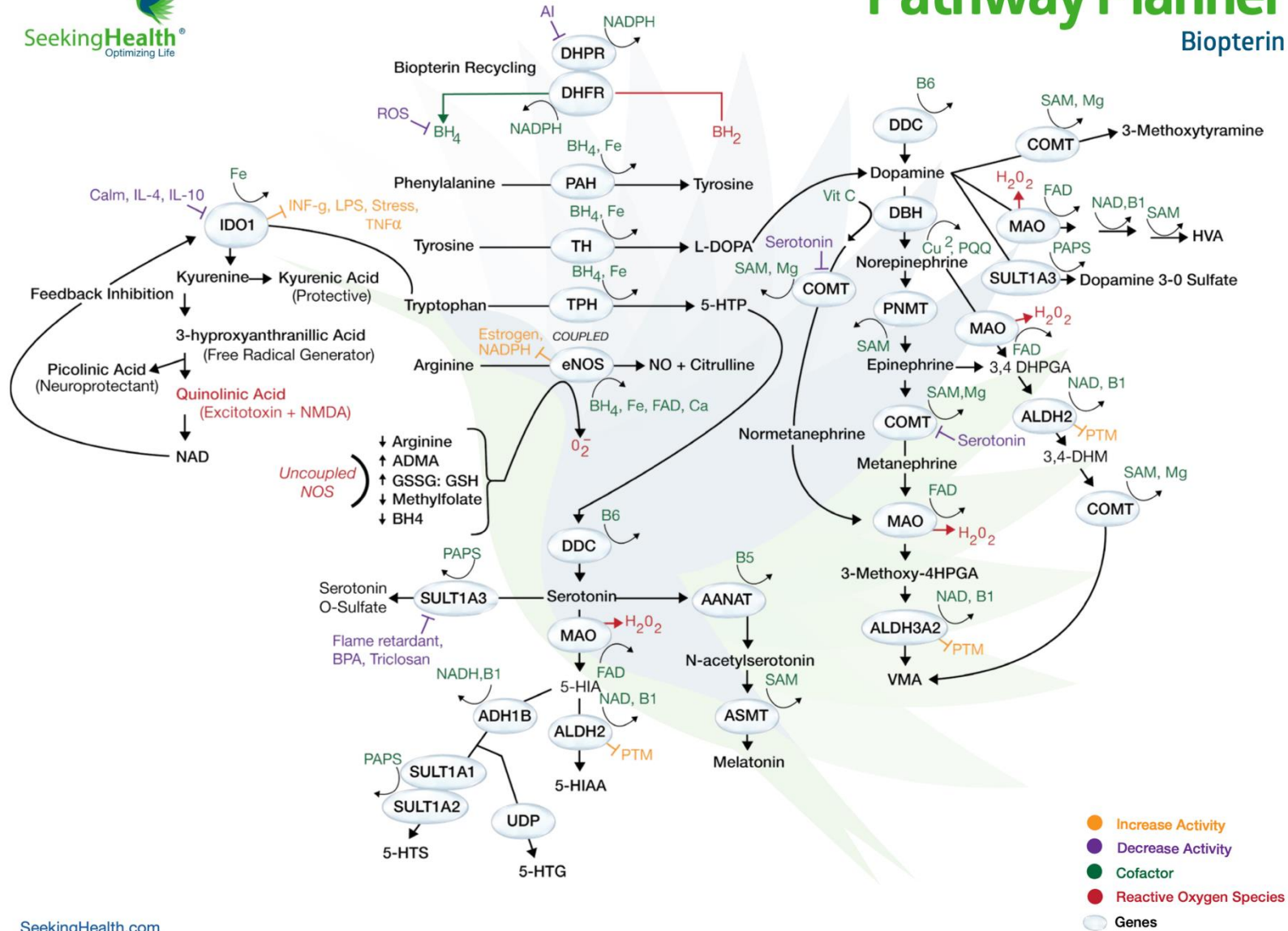
TABLE 1 | MC-secreted major mediators in immune regulation.

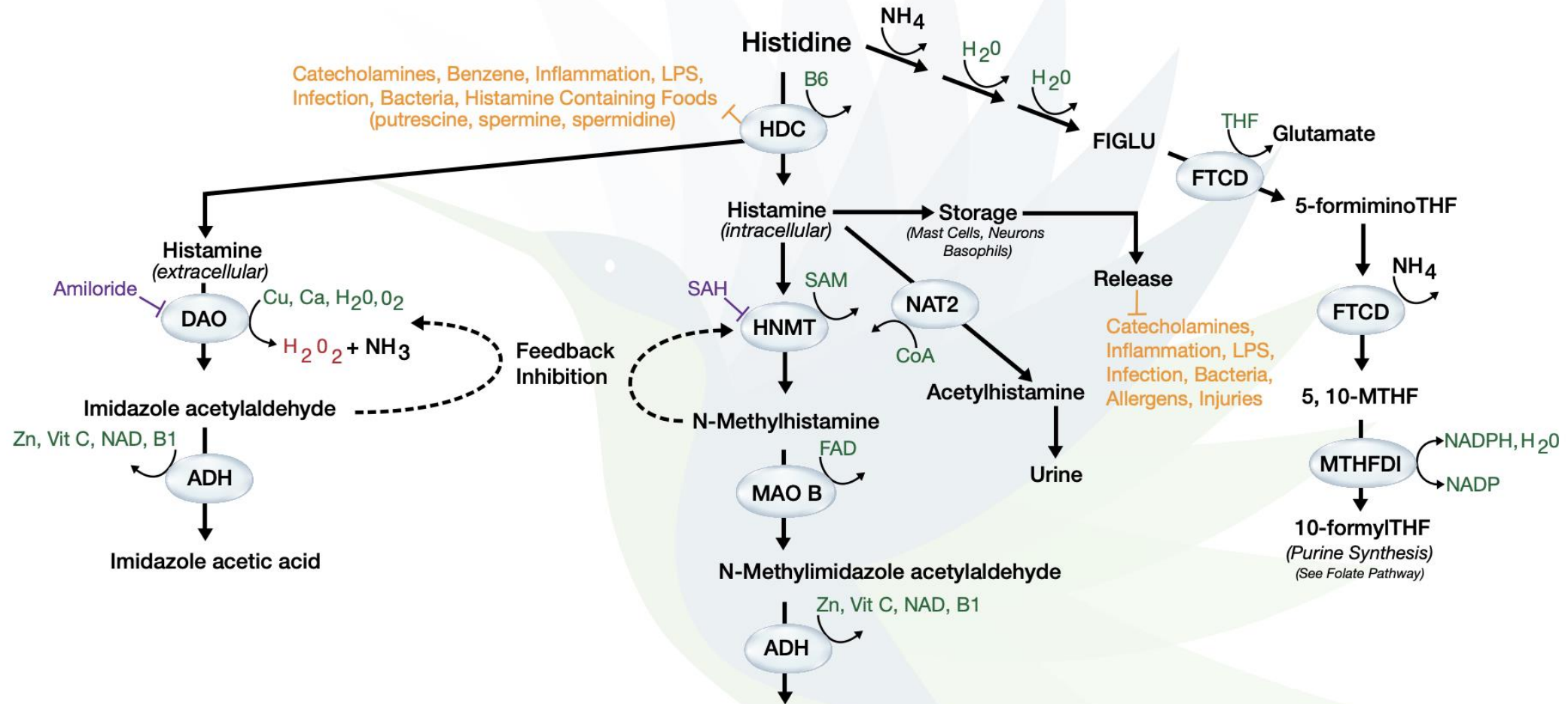
Mediators	Types of immune cell involved	Functions	References
TNF-alpha	Naive T cells Effector T cells Macrophages	Activation and proliferation of naive and effector T cells and suppression of T regulatory cell (Treg) activation, activation of macrophages	(48, 49)
Leukotrienes (LTB4, LTC4)	Neutrophils DCs	Recruitment and chemotaxis	(50–52)
IL12	Th1 cells	Initiation of a Th1 type response	(53, 54)
IL6	Neutrophils MCs Macrophages T helper cells	Regulation of inflammatory reactions, chemotaxis, macrophage M2 polarization, T helper cell polarization	(55–57)
CCL20	DCs	Recruitment to inflammatory site	(58, 59)
IFN Gamma	Th1 cells	Th1 response, migration and proliferation	(60)
Histamine	Th1 cells DCs	Cellular differentiation, chemotaxis	(61, 62)
Serotonin	T cells Monocytes Macrophages	Chemotaxis, proliferation, cytokine secretion	(63–65)
IL5	B cells	Terminal differentiation of activated B cells	(66, 67)
IL13	Fibroblasts	Facilitation of a Th2 type response	(67)
IL16	CD4+ T cells	T cell growth and chemotaxis	(68)
IL8 (CXCL8)	Neutrophils	Chemotaxis	(69)
IL1-beta	DCs and MCs	T cell-independent DC activation IL8 synthesis	(70–72)
MCP-1 (CCL2)	DCs, memory T lymphocytes, macrophages	Recruitment	(73, 74)
MC chymase	Neutrophils	Recruitment	(75)
RANTES/CCL5	Th2 cells	Polarization toward Th2 phenotype	(76)
MC tryptase	Neutrophils	Recruitment	(77)
IL4	Th2 cells B cells	Differentiation of naïve T cells to Th2 cells, migration of T cells and B cells B cell maturation, B cell survival signal	(67, 78, 79)
TGF beta	iTregs, Th2 cells, B cells	Development of T regulatory cells (Tregs), B cell apoptosis and maturation	(80, 81)
IL2	Th1 cells Tregs	Th1 and 2 differentiation, Treg survival and development	(82, 83)
IL10	T follicular helper cells	Downregulation of Th1 cytokines	(84)

B6 and the MICROBIOME

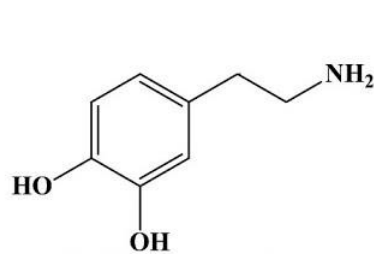
- You need enough B6 to maintain a healthy microbiome
- B6 – non-activated, pyridoxine
- P5P – phosphorylated B6 - ACTIVE
- B6 deficiency leads to systematic oxidative stress including oxidative stress in the microbiome
- Conversion of B vitamins can happen with opportunistic microbes leading to a pro-inflammatory metabolites which may explain some of the negative reactions to B6 / P5P



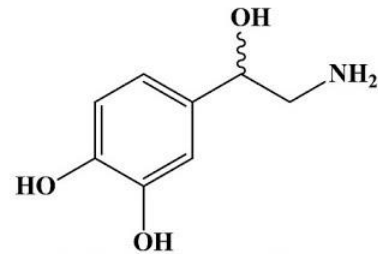




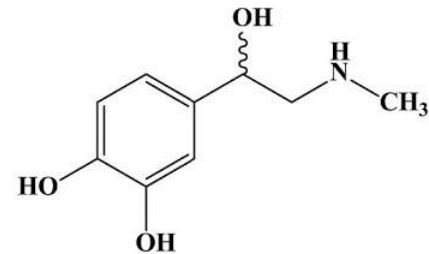
Metabolism of Catecholamines



Dopamine



Norepinephrine
(Noradrenaline)



Epinephrine
(Adrenaline)

Enzymes

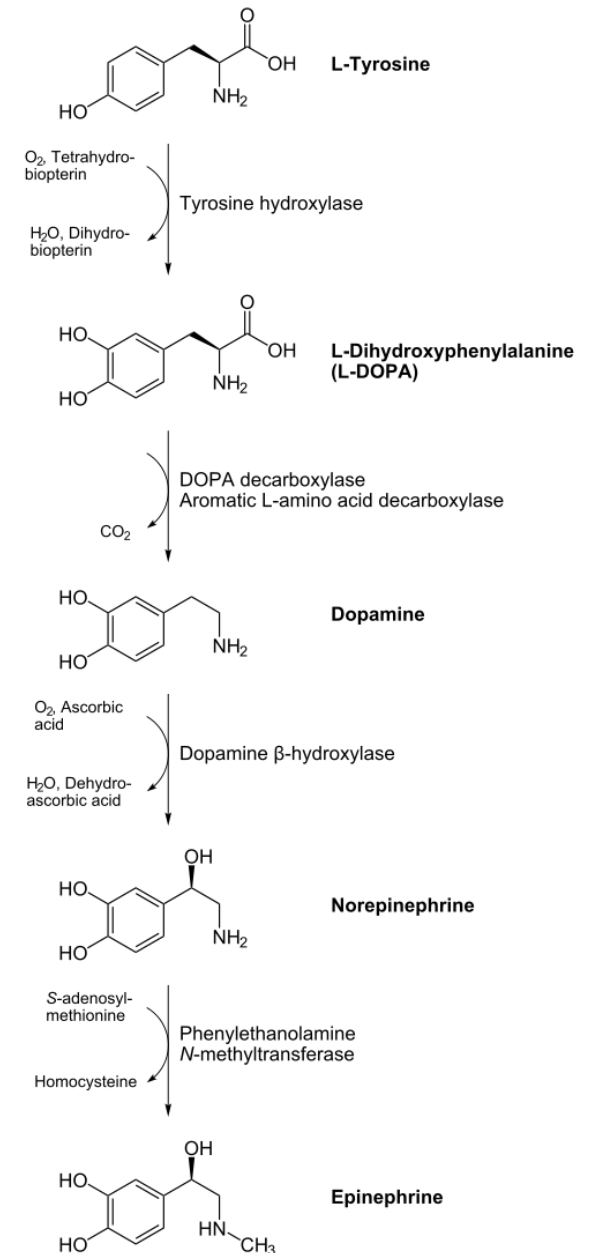
MAO: Mono Amine Oxidase

AD: Aldehyde Dehydrogenase

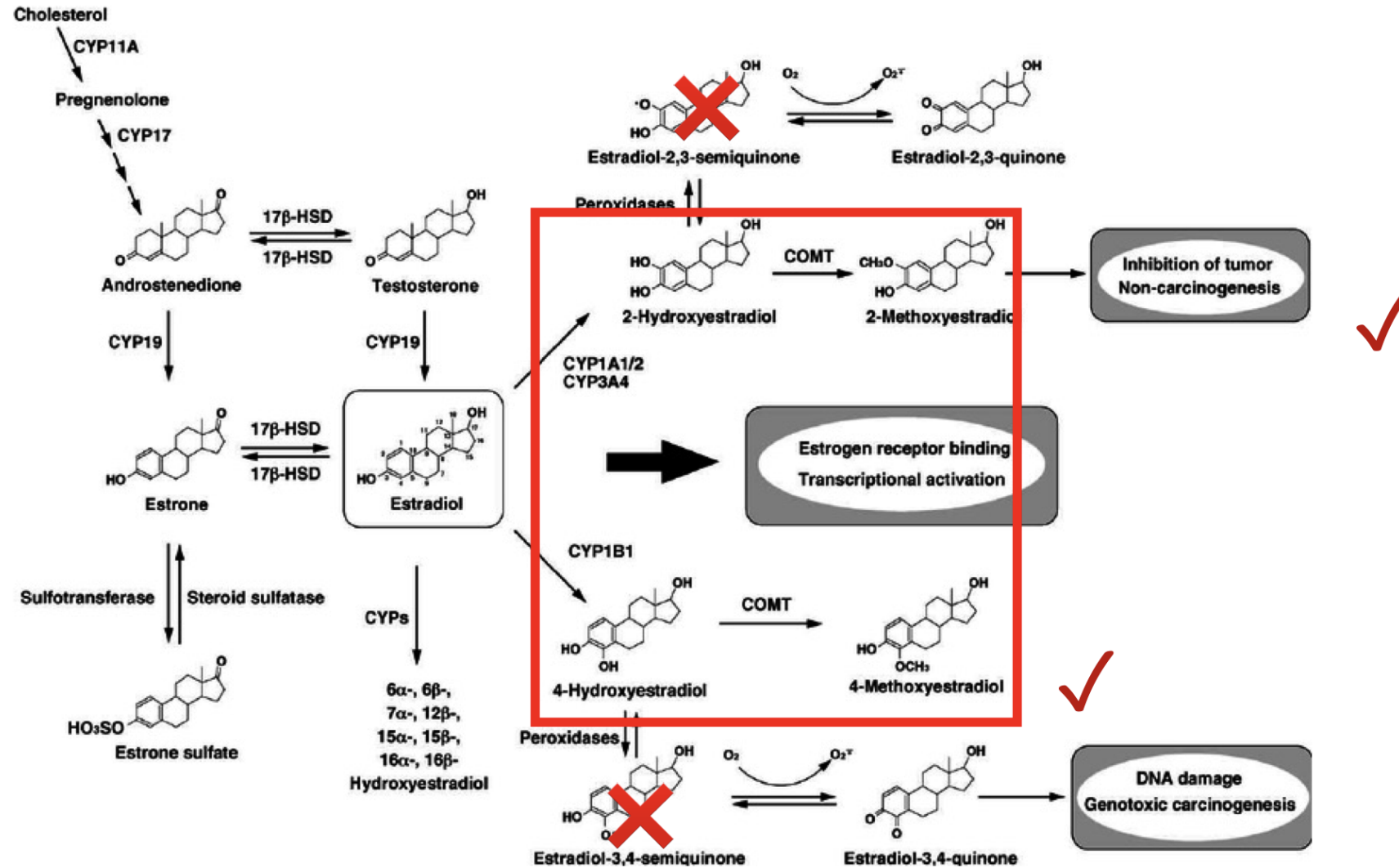
COMT: Catechol O-Methyl Transferase



<https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.13458>

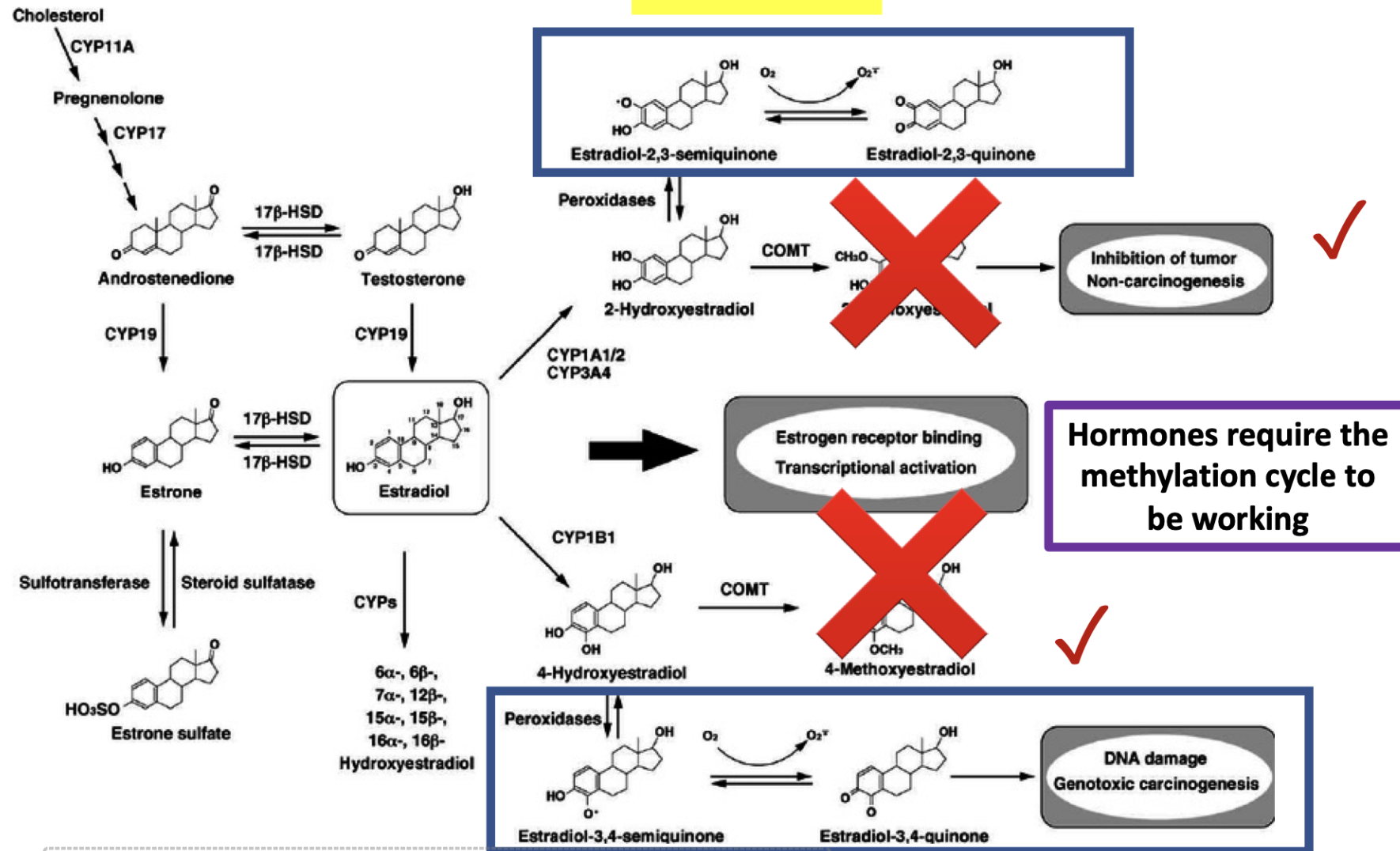


COMT: Catechol-O-methyltransferase



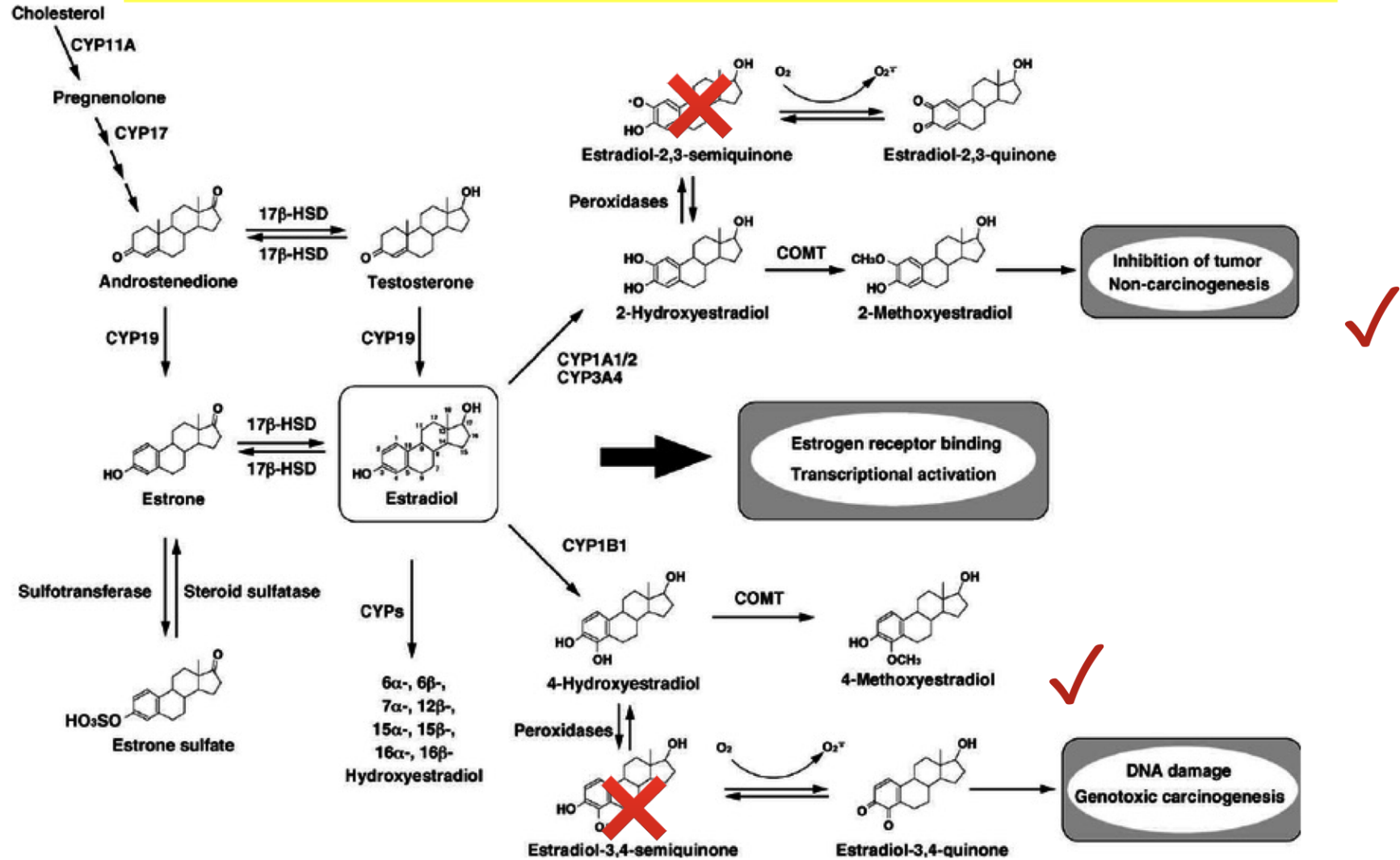
[http://www.cancerletters.info/article/S0304-3835\(04\)00802-X/fulltext](http://www.cancerletters.info/article/S0304-3835(04)00802-X/fulltext)

Estrogen Dominance? When hormones don't get detoxified

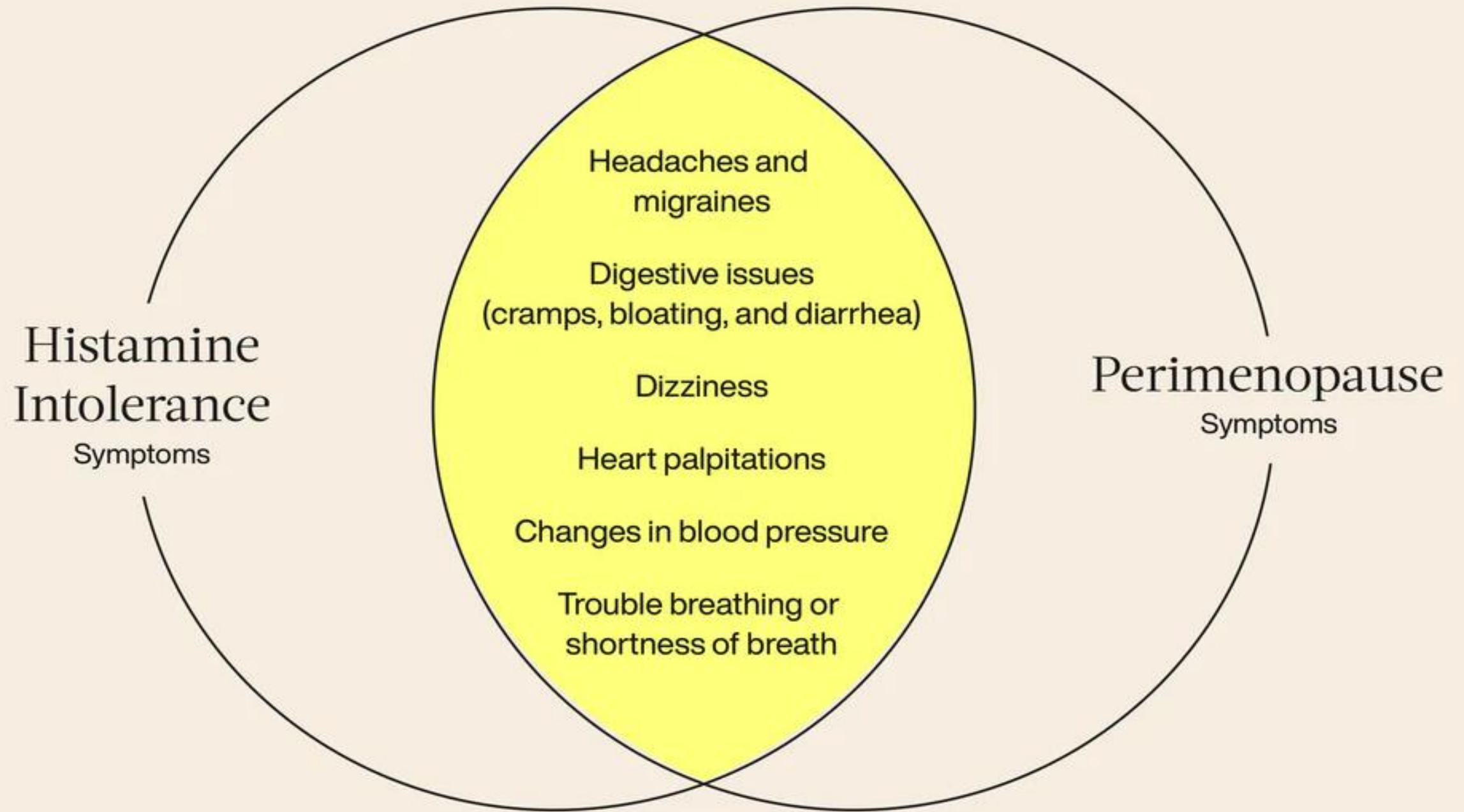


[http://www.cancerletters.info/article/S0304-3835\(04\)00802-X/fulltext](http://www.cancerletters.info/article/S0304-3835(04)00802-X/fulltext)

Making and breaking down hormones

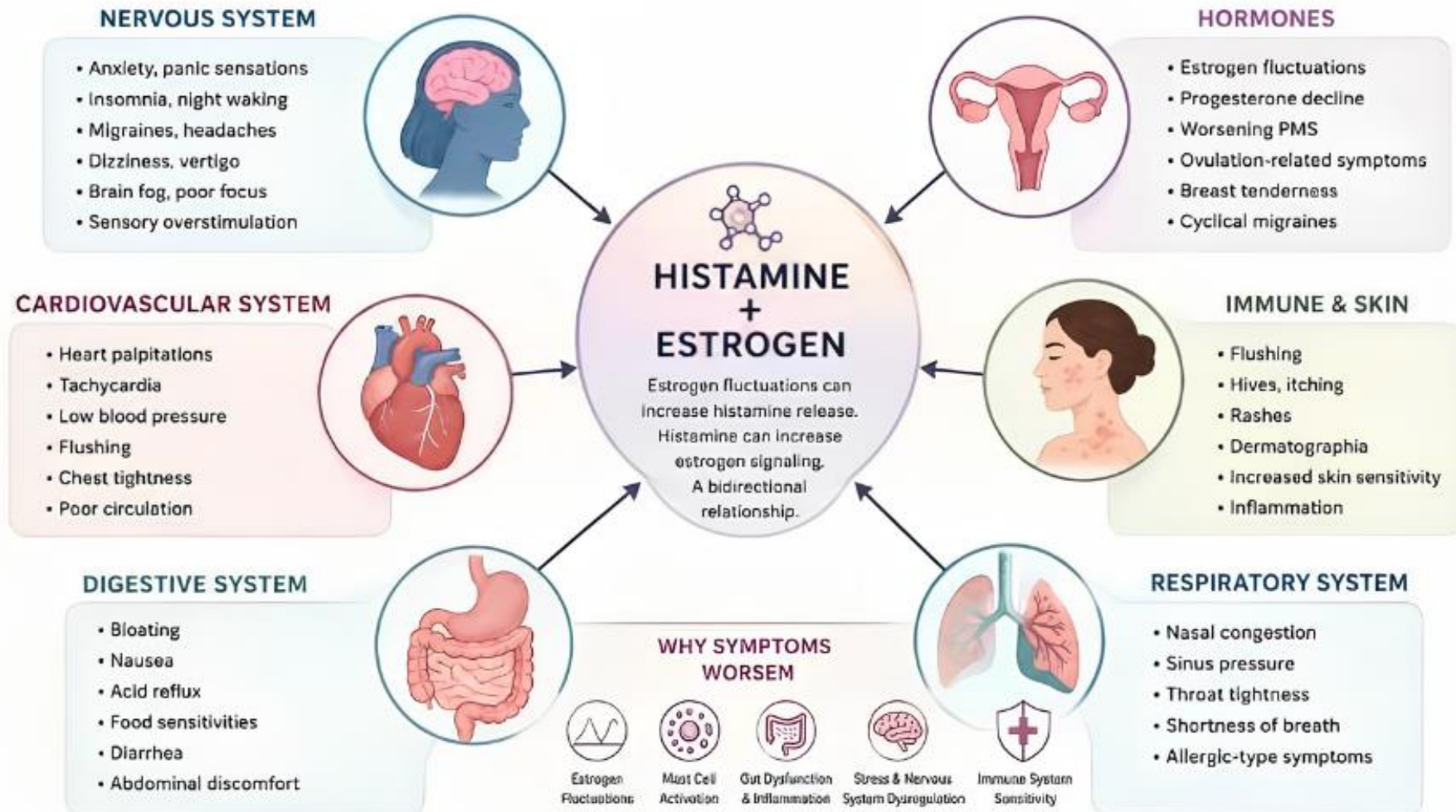


[http://www.cancerletters.info/article/S0304-3835\(04\)00802-X/fulltext](http://www.cancerletters.info/article/S0304-3835(04)00802-X/fulltext)



Histamine Symptoms During Perimenopause

THE ESTROGEN-HISTAMINE CONNECTION



KEY TAKEAWAY: Histamine intolerance during perimenopause is rarely caused by one factor alone. It reflects the interaction of hormones, immune signaling, gut health, inflammation, and nervous system regulation.

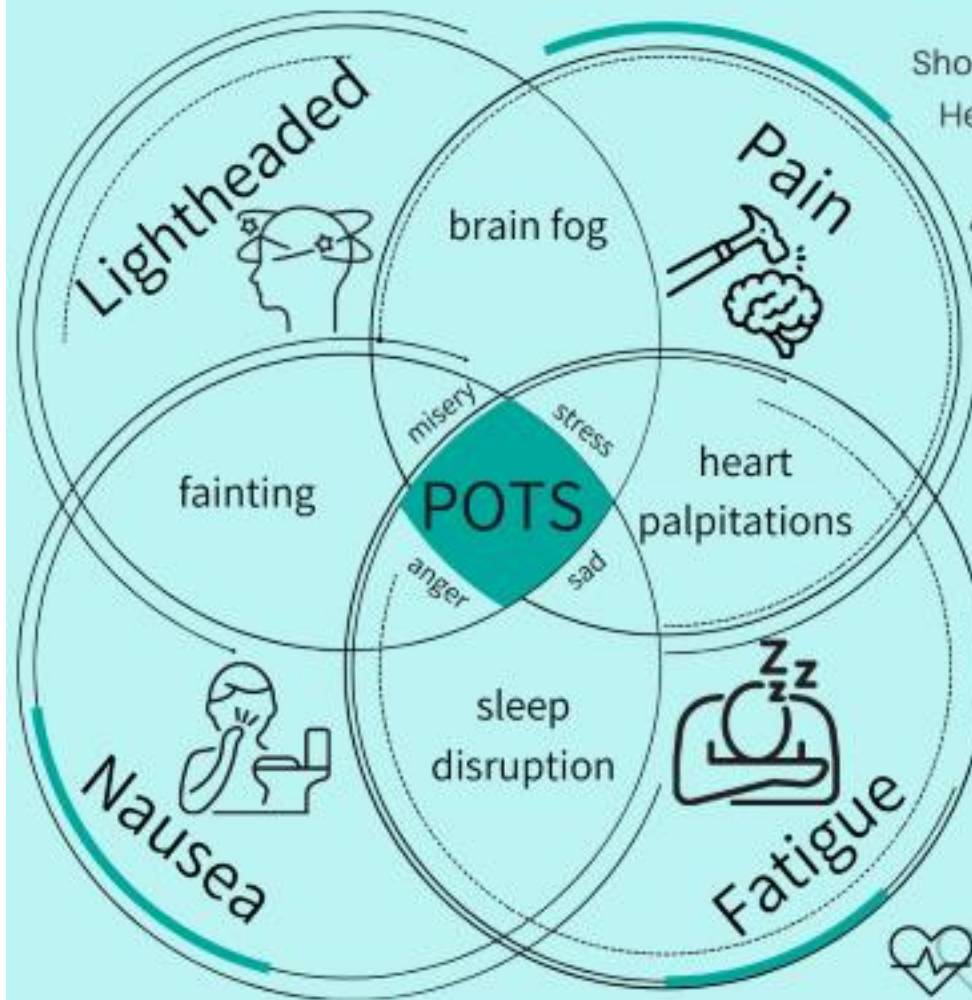
Effect of progesterone administration on tissue mast cell population and histamine content in mice uterus after ovulation induction

Negar Azadi¹, Nasim Beigi Boroujeni¹, Maryam Hormozi¹, Leila Narimani¹, Majid Tavafi¹, Khatereh Anbari², Mandana Beigi Boroujeni¹

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²Social Determinants of Health Research Center, School of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

Common POTS Symptoms



- Lightheadedness (99%)
- Tachycardia (97%)
- Pre-syncope (94%)
- Headache (94%)
- Difficulty concentrating (94%)
- Nausea (90%)
- Shortness of breath (88%)
- Heart palpitations (87%)
- Muscle pain (84%)
- Abdominal pain (83%)



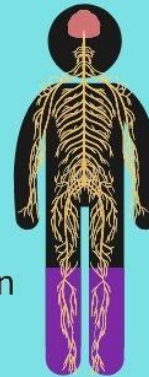
Shaw et al. (2019). J Intern Med. doi:10.1111/jcim.12895

POTS Subtypes

Neuropathic POTS

Characterized by decreased sympathetic innervation, particularly in legs

- Loss of sweating in extremities
- Blood pooling
- Blue/red/purple feet when standing or warm



Hypovolemic POTS

Characterized by low blood volume, both plasma and red blood cells

- Weakness
- Decreased exercise tolerance



Hyperadrenergic POTS

Characterized by elevated plasma norepinephrine and rise in systolic blood pressure when standing

- Extreme tachycardia
- Heart palpitations
- Tremor
- Migraine headaches
- Nausea/vomiting



Types of POTS Explained

Hypovolemic and Idiopathic POTS

Hypovolemic POTS is linked to low blood volume, while Idiopathic POTS presents with no clear cause, each offering unique treatment challenges.

Hyperadrenergic POTS

This subtype is characterized by excess norepinephrine, leading to symptoms like rapid heart rate and high blood pressure.

Neuropathic POTS

Neuropathic POTS results from nerve dysfunction, affecting blood flow regulation and causing symptoms like dizziness upon standing.



How do you know you have POTS?



Heart rate is how many beats per minute your heart beats. Check HR in each position. Normal is 55-75bpm. High heart rates should be considered as compensatory mode.

- Seated
- Lying down
- Standing

Heart rate should be the same in all positions. If there is an elevation in heart rate over 20-30 points when standing, that's POTS. Postural Orthostatic Tachycardia Syndrome.

Heart rate should go up 10-15 points on standing, and then acclimate to a resting heart beats after a few minutes.

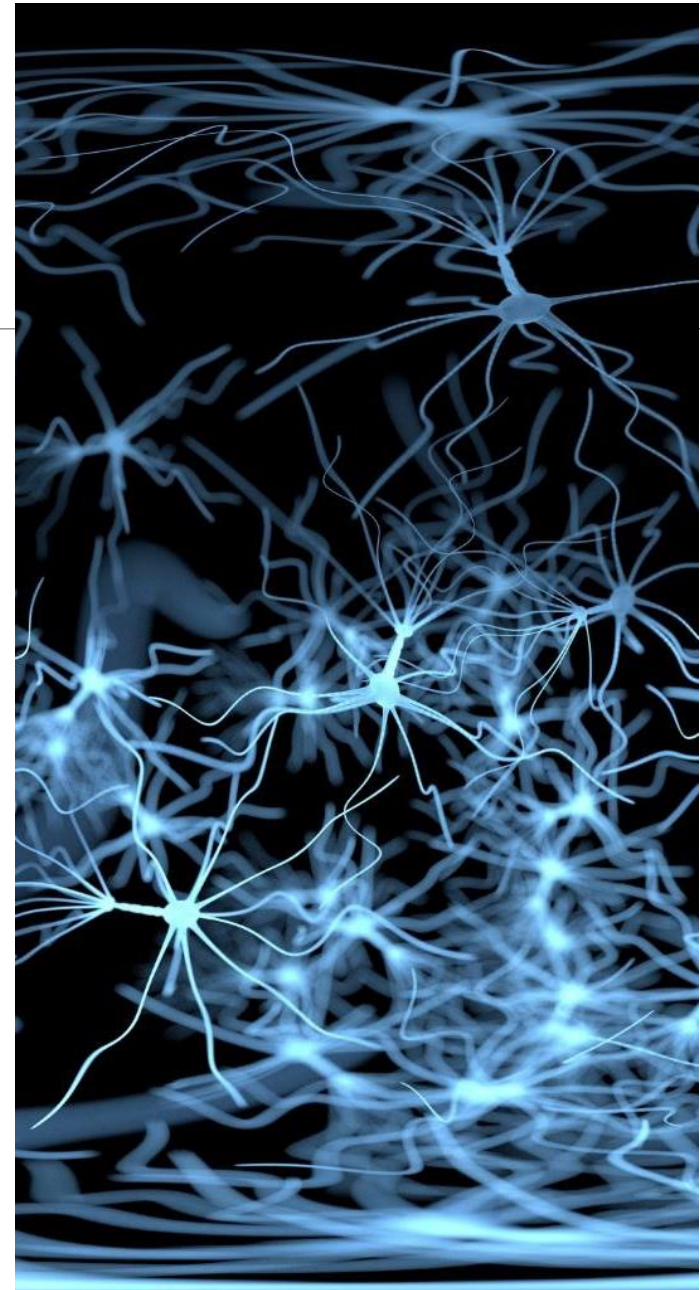
Clinical Definition of POTS

The physiological stress of having POTS may aggravate mast cell activity in people who already have MCAS or are predisposed.

The conditions may feed into each other, making symptoms worse or harder to treat unless both are addressed.

Make sure to treat POTS so the MAST cell Activation Syndrome treatments work

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5267948/>



A Tale of Two Syndromes – POTS and MCAS

🕒 February 17, 2015 📁 Uncategorized

by Dr. Andrew White

- <https://dysautonomiainternational.org/blog/wordpress/a-tale-of-two-syndromes-pots-and-mcas/>

MAST Cell Activation Tx

B12 injections

Cod liver oil

Multivitamin and mineral

Paleo or modified ketogenic diet

+ Clear outs with Magnesium until no fecal loading.....By Dr. Sonya Doherty ND





Vitamin B12 Deficiency Effects

Disrupted Methylation

Vitamin B12 deficiency impairs methylation, a crucial process for neurotransmitter synthesis and gene regulation.

Reduced Neurotransmitter Synthesis

Impaired methylation lowers neurotransmitter levels, decreasing hormone signaling and affecting mood and brain function.

Neurological and Hormonal Imbalances

Lower neurotransmitter and hormone levels cause neurological and hormonal imbalances, impacting overall health and well-being.

Methylcobalamin / B12 injections

James Neubrand Protocol:

- Concentration: 2500mcg/0.1ml or 25000mcg/1ml
- 65mcg/kg every 3 days (usually 0.05ml)
- Suggested syringes are BD Ultra fine 3/10th CC
- 30-31 Gauge subcutaneous*

*Ontario ND's cannot inject vitamin B12 subcutaneously



HISTAMINE MANAGEMENT

Methyl units to break down histamine. Methylation: primarily B12 injections away from ____ the GI system.

Nutrient cofactors including a lot of vitamin B6, in adults, even as high as 200mg-600mg

Vitamin C

Quercetin

Glutathione b/c addresses most of the possible roots

Diet

Cod Liver oil (to reduce cell dancer response)

Bowel Clear outs

Find the root. Mold? Viruses? Bacteria? Yeast? Toxicity?

<https://pubmed.ncbi.nlm.nih.gov/12692417/>
<https://pubmed.ncbi.nlm.nih.gov/19183150/>
<https://pubmed.ncbi.nlm.nih.gov/14988823/>

Did it help, did it hurt or did it stay the same?

ANTI-HISTAMINE TRIAL

H1 Blockers

Non-Sedating

- Loratadine (Claritin)
 - 5 and 10 mg
- Desloratadine (Clarinex)
 - 2.5 and 5 mg
- Cetirizine (Zyrtec)
 - 5 and 10 mg
- Fexofenadine (Allegra)
 - 30, 60 and 180 mg

Sedating

- Diphenhydramine (Benadryl)
 - 12.5, 25 and 50 mg
- Levocetirizine (Xyzal)
 - 5 mg
- Promethazine (Phenergan)
 - 12.5, 25 and 50 mg
- Cyproheptadine
 - 4 to 32 mg total daily dose divided: Q-8 hrs
 - **Also blocks some Serotonin receptors**

Types of H2 Antihistamines (H2 Receptor Antagonists)

Histamine H2 Receptor Blockers

Mechanism of Action:

- Block H2 receptors primarily on gastric parietal cells
- Reduce gastric acid secretion
- Also block H2 receptors on immune cells, vascular tissue, and the heart, providing modest systemic antihistamine effects

Types of H2 Antihistamines (H2 Receptor Antagonists)

Medication	Status	Primary Clinical Uses
Famotidine (Pepcid®)	 Commonly used	GERD, peptic ulcers, mast cell disorders (MCAS), adjunct allergy treatment
Cimetidine (Tagamet®)	Limited use	GERD, ulcers; significant CYP450 inhibitor with many drug interactions
Nizatidine (Axid®)	Less commonly used	GERD, gastric ulcers
Ranitidine (Zantac®)	 Withdrawn in Canada, U.S., and many countries	Removed due to NDMA contamination concerns

Types of H2 Antihistamines (H2 Receptor Antagonists):

Clinical Applications Beyond Acid Suppression

- Mast Cell Activation Syndrome (MCAS)
- Chronic urticaria (with H1 antihistamines)
- Allergic reactions (adjunctive therapy)
- Histamine intolerance
- Anaphylaxis (adjunct after epinephrine)

Types of H2 Antihistamines (H2 Receptor Antagonists): Clinical Pearls

H2 blockers are most effective when combined with H1 antihistamines for systemic histamine-mediated conditions.

Famotidine is the preferred H2 blocker because it:

- Has minimal CYP450 interactions

- Is generally well tolerated

- Is commonly used in MCAS and allergy protocols

Cimetidine should be used cautiously due to numerous drug interactions.

Take-Home Message:

H2 antihistamines reduce gastric acid production while providing additional blockade of histamine-mediated effects outside the stomach. Famotidine is currently the preferred H2 antagonist in both gastroenterology and integrative allergy practice.

> [Scand J Immunol](#). 1996 Dec;44(6):578-84. doi: 10.1046/j.1365-3083.1996.d01-351.x.

Vitamin A deficiency increases inflammatory responses

[U Wiedermann](#)¹, [X J Chen](#), [L Enerbäck](#), [L A Hanson](#), [H Kahu](#), [U I Dahlgren](#)

Affiliations + expand

DOI: [10.1046/j.1365-3083.1996.d01-351.x](#)

PMID: 8972739 [↗](#)

Vitamin A

Scavenges Peroxyl Radicals: Retinol directly neutralizes peroxyl radicals. This intercepts the destructive chain reaction before it destroys cellular lipids. [[1](#)]

Protects Cell Membranes: Vitamin A accumulates within the hydrophobic core of cell bilayers. This localization shields vulnerable membrane lipids from oxidative attacks. [[1](#), [2](#), [3](#)]

Suppresses Ferroptosis: Lipid peroxidation drives ferroptosis, a type of iron-dependent cell death. Vitamin A activates cellular pathways that stop this process. [[1](#), [2](#)]

Lowers Malondialdehyde (MDA): Studies show Vitamin A lowers MDA levels. MDA is the primary toxic byproduct used to measure active lipid destruction. [[1](#), [2](#), [3](#)]

Synergizes with Vitamin E: Vitamin A works alongside Vitamin E to reinforce the lipid barrier. Together, they provide much stronger protection than either vitamin does alone. [[1](#), [2](#), [3](#), [4](#), [5](#)]

Vitamin E (Mixed tocopherols)

Stabilizes Mast Cell Membranes: Mast cells store your body's histamine. Vitamin E accumulates directly in these cellular membranes, strengthening them so they do not leak or rupture easily. [[1](#), [2](#), [3](#), [4](#), [5](#)]

Suppresses Degranulation: It blocks the specific cellular signaling pathways (like protein kinase C) that trigger mast cells to burst open and release histamine. [[1](#), [2](#)]

Reduces Oxidative Stress: High levels of free radicals and lipid peroxidation trigger mast cells to dump histamine. As a major antioxidant, Vitamin E neutralizes this oxidative stress to prevent the cycle. [[1](#), [2](#), [3](#)]

Decreases Tissue Histamine Levels: Animal models show that consistent Vitamin E intake directly lowers overall histamine concentrations in highly sensitive tissues, including the skin and the lungs. [[1](#)]

Lowers Prostaglandins: Vitamin E suppresses the formation of inflammatory prostaglandins. These compounds typically work alongside histamine to worsen allergic reactions, swelling, and itching. [[1](#), [2](#)]

Carnitine

Powers Histamine-Degrading Enzymes: Breaking down histamine via Diamine Oxidase (DAO) and Histamine N-methyltransferase (HNMT) requires massive amounts of cellular energy (ATP). Carnitine transports long-chain fatty acids into your mitochondria, fueling the ATP production needed for these enzymes to work efficiently.

Protects Liver Detoxification Pathways: The HNMT enzyme processes histamine heavily inside the liver. Research shows that L-carnitine exerts a powerful hepatoprotective effect, reducing oxidative stress and liver inflammation so the organ can safely clear out metabolic waste and histamine.

Lowers Secondary Oxidative Stress: Accumulated histamine causes cellular inflammation and lipid damage. Carnitine functions as an antioxidant that scavenges free radicals, preventing the secondary tissue irritation that typically occurs during a histamine flare-up.

Reduces Toxic Byproduct Accumulation: Carnitine acts as an internal cellular broom, transporting toxic metabolic byproducts out of the cells. This keeps your cellular environment clean, preventing the systemic stress that causes mast cells to destabilize.

Protects Against Antihistamine Side Effects: If you take chronic pharmaceutical antihistamines, they can stress the liver. Studies indicate that supplementing with L-carnitine protects hepatic tissue from the oxidative strain caused by long-term allergy medication usage.

➤ [Allergy Asthma Proc.](#) 2021 May 1;42(3):243-246. doi: 10.2500/aap.2021.42.210022.

The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers–Danlos syndrome

[Edwin Wang](#)¹, [Tej Ganti](#)¹, [Eleni Vaou](#)¹, [Anna Hohler](#)¹

Affiliations + expand

DOI: [10.2500/aap.2021.42.210022](#)

PMID: 33980338 [🔗](#)

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DOI: 10.1002/hsr2.1109

PERSPECTIVE

Health Science Reports

Open Access

WILEY

Covid-19 Histamine theory: Why antihistamines should be incorporated as the basic component in Covid-19 management?

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LENSE – HISTAMINE

Methylation

Microbiome

Mitochondrial Function

Oxidative stress

IDO / Inflammation

The Methyl Cycle

Back bone of our physiology

Its functional status determines our resistance to environmental toxins and microbes

We can't CHANGE our DNA, but if we know your weak links, we can create “nutritional workarounds” to **optimize DNA methylation**

Methylation

Responsible for **OVER** 200 different processes

Turns on and off genes – usually **OFF**

Processes chemicals, endogenous **TOXINS**, xenobiotics

Builds and breaks down **NEUROTRANSMITTERS**

Processes **HORMONES**

Builds **IMMUNE** cells (T-cell, NK cells)

Makes DNA and **HISTONES**

Manages **GLUTAMATE** – glycine, NAC, glutamate = glutathione

Produces **ENERGY** (CoQ10, carnitine, creatine, cholesterol)

Produces **MYELIN**

Builds and maintains **CELL MEMBRANES**

Metabolizes **HISTAMINE** (intracellular)

Products of the methylation cycle

Glutathione – governs autoimmunity

Metallothioneins – cysteine rich proteins that protect against heavy metal toxicity, DNA damage and oxidative stress

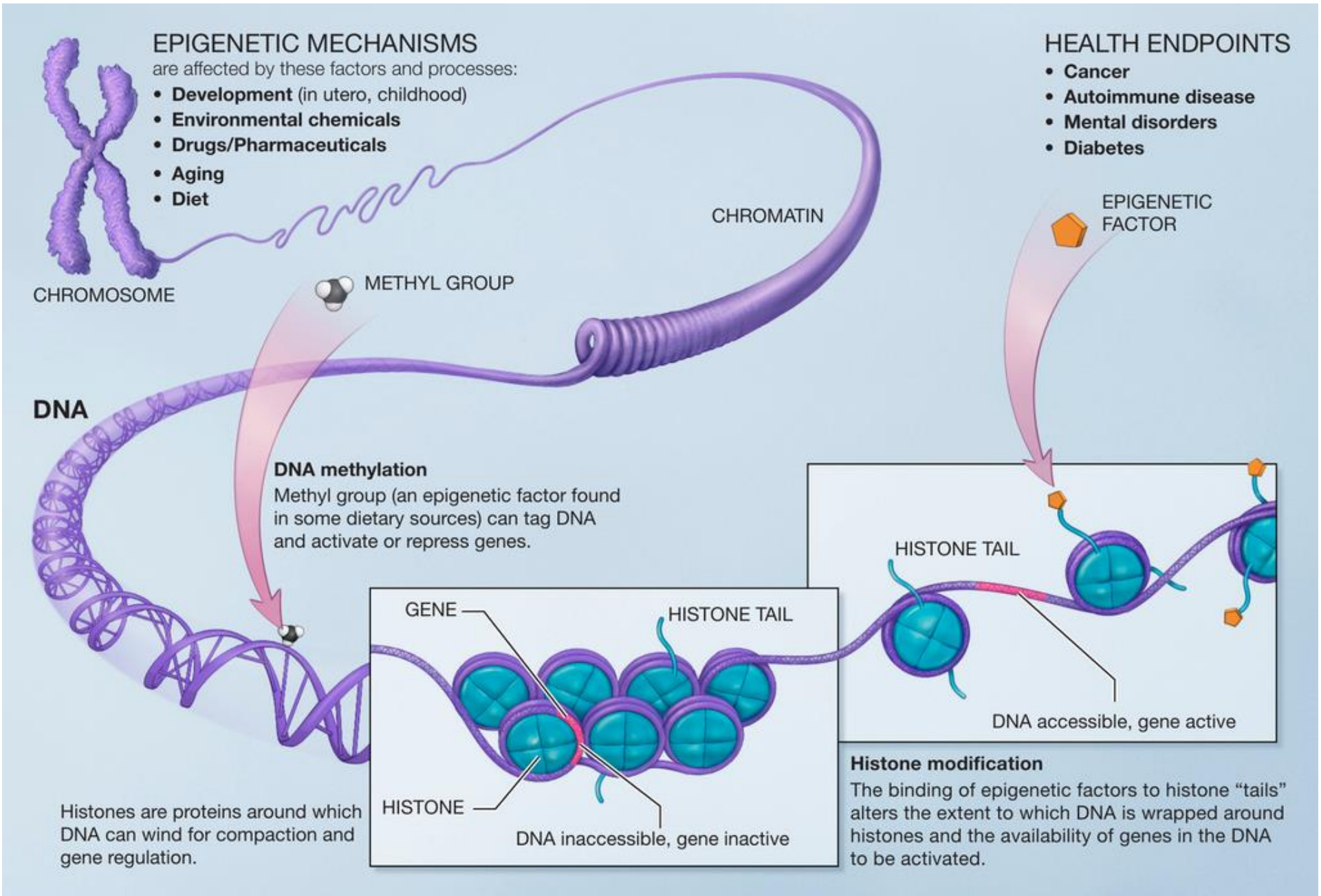
Cell membranes

Carnitine

*Creatine

*Phosphatidylcholine

Neurotransmitters



Basic Treatment Guidelines – Optimizing Methylation

- Methyl donor –
Methyl B12 injections, DMG, TMG, Choline, SAME, Methionine, Beet crystals
- Folate cycle –
Remove synthetic folic acid,
Add folate – greens, MTHF, folinic, B2
- Transulfuration (makes glutathione – enough B6!!!)
- Methylation cycle – zinc, zinc ionophores (quercetin, ECGC and Resveratrol)
- Cod liver oil (CLO) - Neurotransmitters are packaged in fat – the brain is 2.5 lbs of FAT!
- Reduce, remove and detoxify PPA

Basic Treatment Guidelines – Optimizing Methylation

- Methyl B12 injections – 25 mg per ml
- DMG – 400 mg BID
- TMG – 500 mg BID
- SAMe – 400 mg BID (Cell Danger Response (CDR) assessment)
- Methionine – 200-300 mg
- MTHF – 1-10 mg
- Folinic – 2 mg per kg
- B2 – 50 mg to 500 mg
- B6 – 10 mg to 300 mg
- Zinc – 10 mg to 100 mg, 300 mg?
- Quercetin – 500 mg to 2000 mg
- Cod liver oil (CLO) – 1 TBSP to 4 TBSP (avoid CLO in childbearing age)

- 
- 
1. Continue breastfeeding (WHO recommends 2 years)
 2. No grains, dairy, potatoes or processed food
 3. Maximum 3-6 tsp sugar daily (12-24 grams)
 4. Eat inulins and dihydrofolate
 5. Methyl and choline rich foods
 6. Uncooked green leafy vegetables
 7. Hormone, antibiotic free meat
 8. Fish, seafood with low mercury and PCBs
 9. Clean, filtered water
 10. Food without additives or chemicals (PPA, MSG, aspartame, food dyes, glyphosate)
 11. Maximize healthy fat, protein and antioxidant rich fruits and vegetables
 12. Avoid pesticides and other toxicants in food supply

PPA – Propionic Acid

PPA is a preservative in our food supply –
grains, dairy, processed foods

PPA is a short-chain fatty acid

PPA is made by microbes like clostridium, Bacteriodetes,
Desulfovibrio

PPA causes inflammation / neuroinflammation

PPA impairs mitochondrial production of ATP – like throwing
a wrench in your car engine

Binds carnitine leading to lower EFA status

PPA impairs methylation

PPA depletes glutathione

PPA is an intracellular toxin

PPA requires B12, biotin and carnitine to be toxified



What does optimizing methylation mean?

Optimal Glutathione

- Reduce exposure to toxicants
- Remove toxicants
- Regulate glutamate - a major cause of inflammation
- Protects mitochondria from lipid peroxidation

Healthy Cell membranes / Cell Danger Response (CDR)

- Oxidative stress
- Lipid peroxidation
- Impaired mitochondrial function

Effective Carnitine Shuttling

- Shuttles fats into mitochondria to make energy
- Damaged by toxicants, harmful microbes, oxidative stress

Intracellular Metabolism of

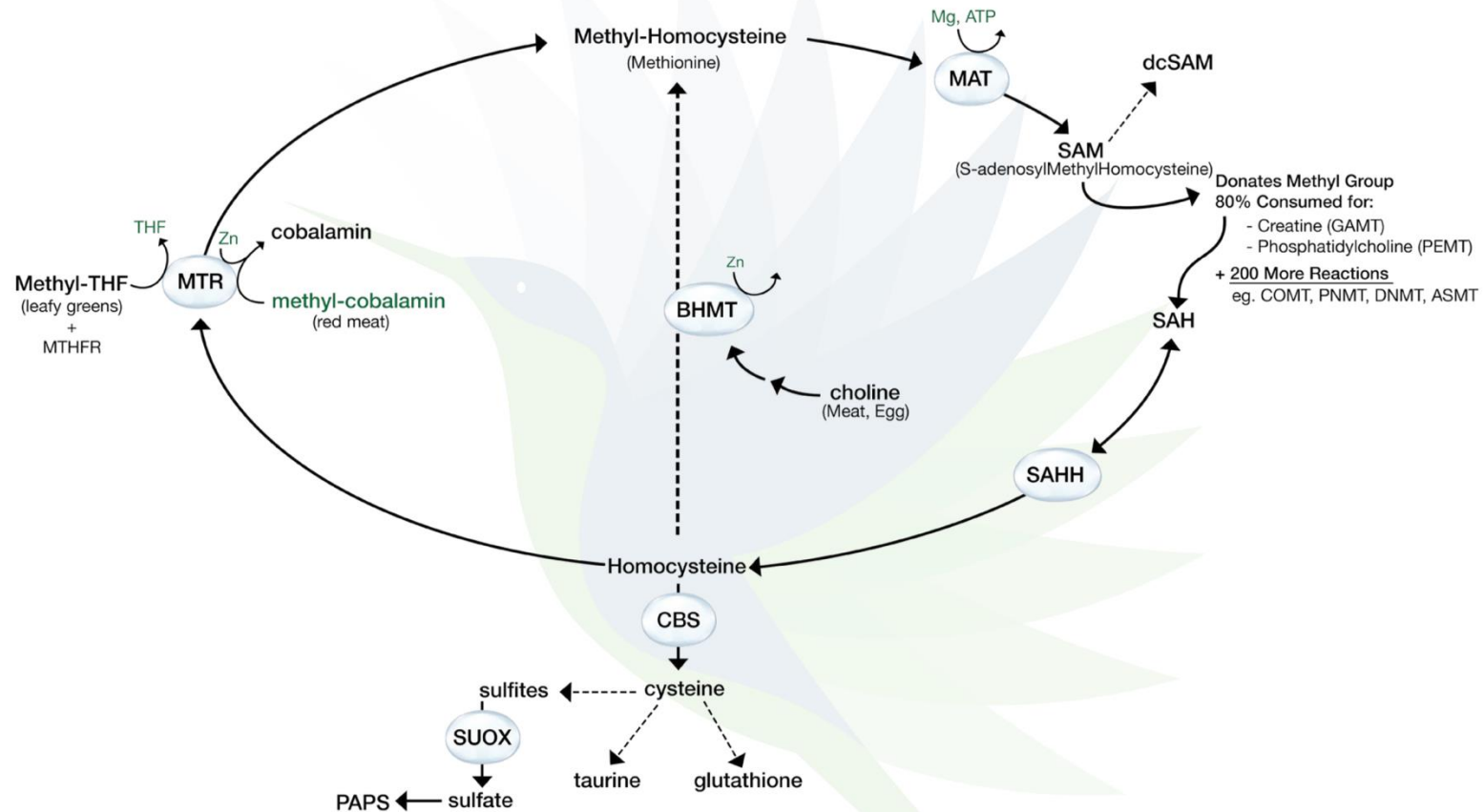
HISTAMINE



Effect of A1 vs A2 beta-casein containing diet on glutathione antioxidant status: Implications for inflammation and cognitive function via gut-brain axis

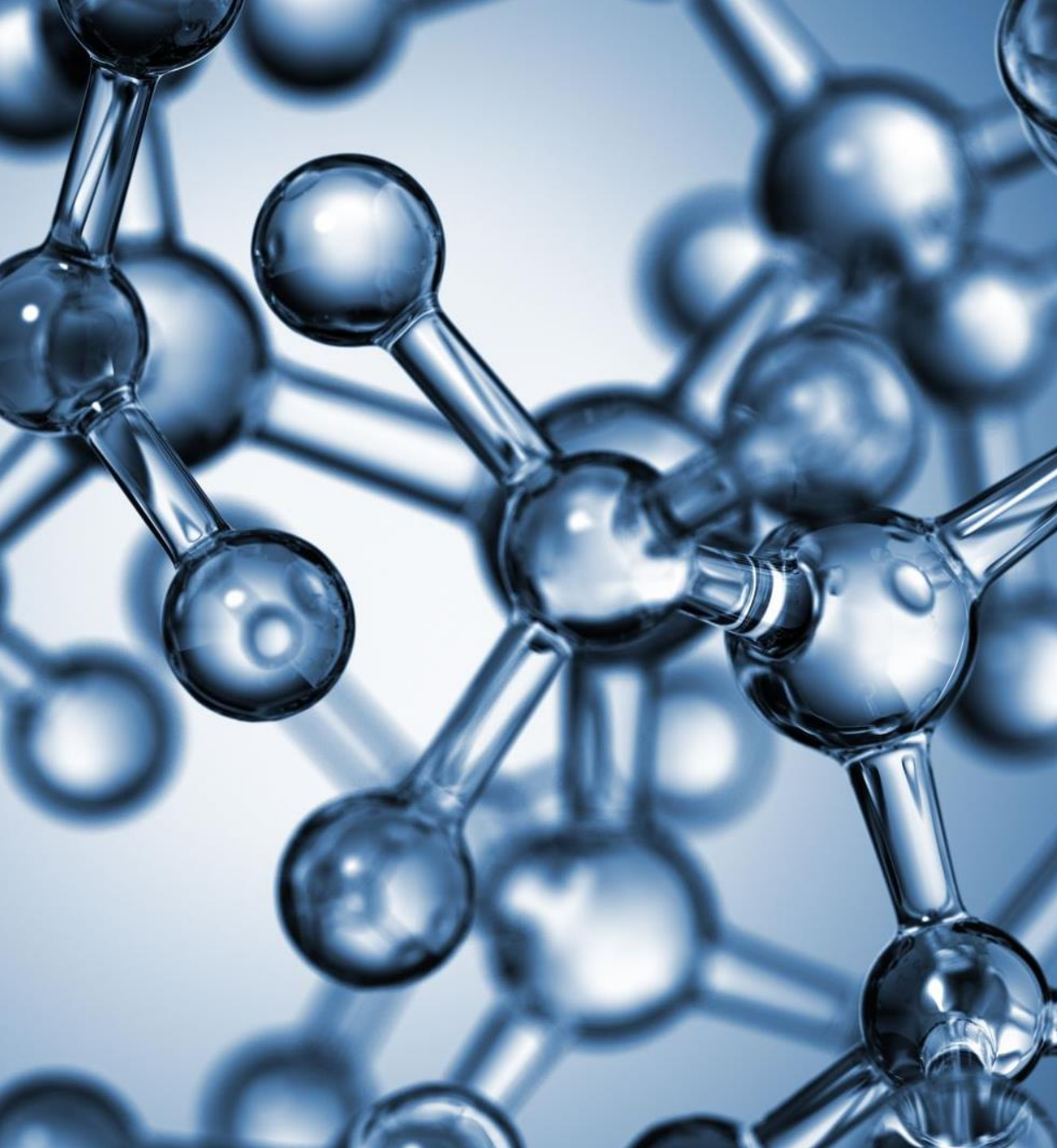
Malav Trivedi, Yiting Zhang, Richard Deth

First published: 03 October 2018 | https://doi.org/10.1096/fasebj.31.1_supplement.972.18



- Increase Activity
- Decrease Activity
- Cofactor
- Reactive Oxygen Species
- Genes





Autoimmunity, Inflammation and Histamine

Oxidative stress – ROS

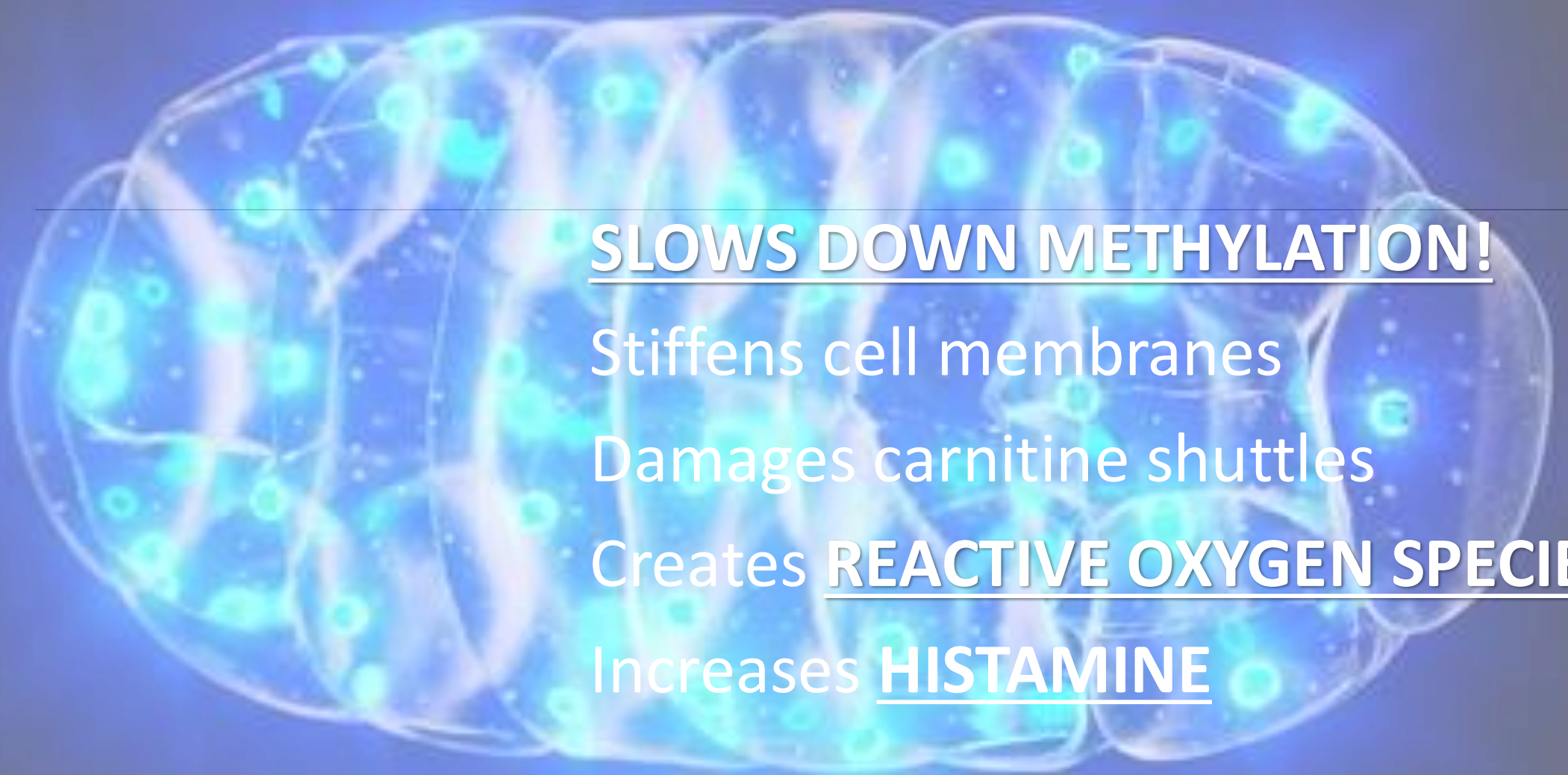
- Redox regulation of NLRP3 inflammasome
- MS sensitivity to oxidative stress upregulates transulfuration (but what happens when you run out of glutathione and co-factors for MS, MTR, MTRR and MTHFR?)

Inflammation - glutamate, histamine

DNA methylation

Epigenetics

Mitochondria – autophagy / ROS, CDR



SLOWS DOWN METHYLATION!

Stiffens cell membranes

Damages carnitine shuttles

Creates **REACTIVE OXYGEN SPECIES**

Increases **HISTAMINE**

Cell Danger Response



Journal of Allergy and Clinical Immunology

Volume 78, Issue 2, August 1986, Pages 308-314



Correlation between allergy and persistent Epstein-Barr virus infections in chronic-active Epstein-Barr virus-infected patients

Ph.D. George B. Olson^a, M.S. Moien N. Kanaan^a, M.S. Geoffrey M. Gersuk, Ph.D. Lee M. Kelley^a,
M.D. James F. Jones^{*}

CHAPTER 9

Histamine, Immune Cells and Autoimmunity

Elke Schneider, Maria Leite-de-Moraes and Michel Dy*

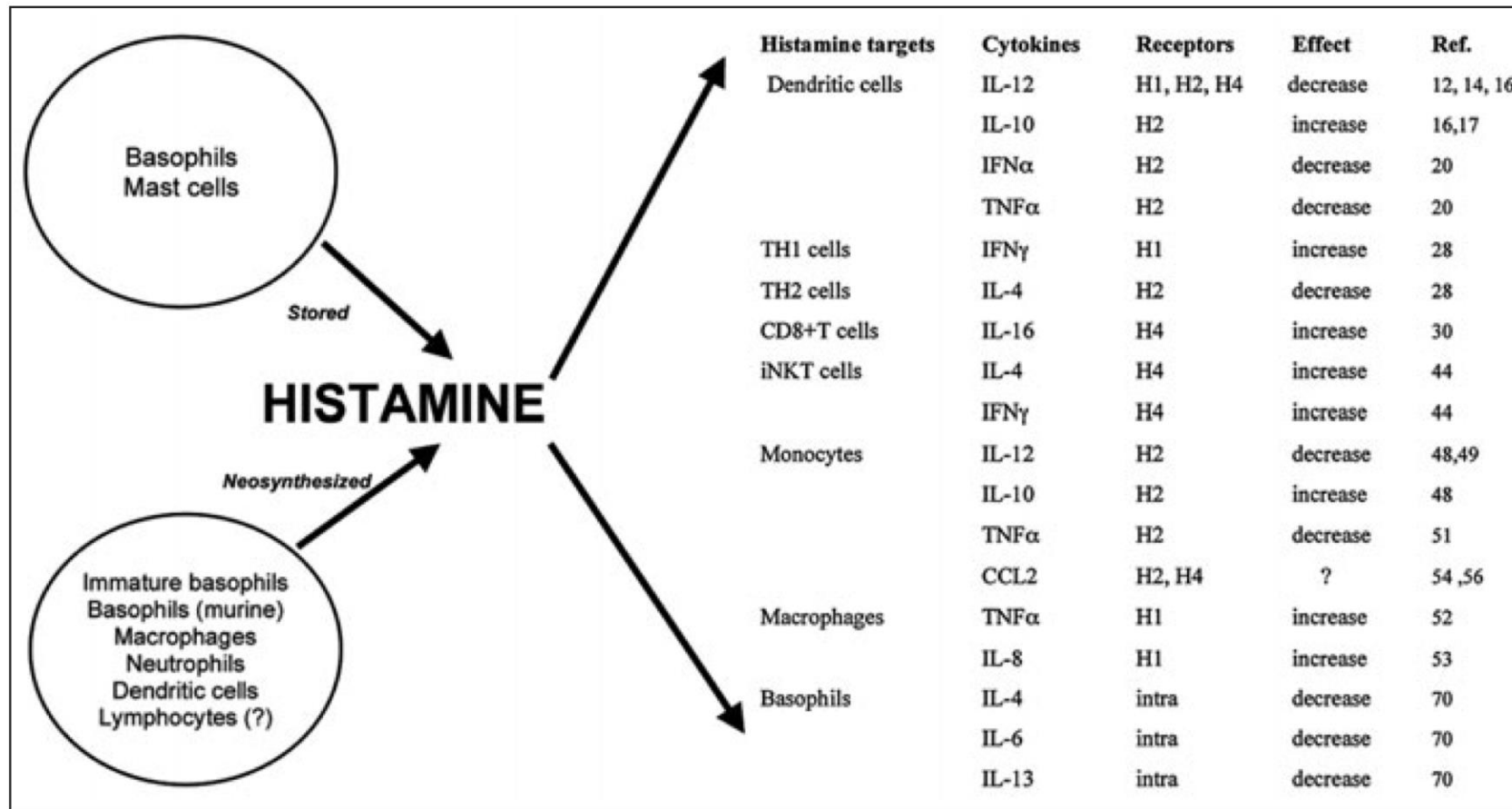


Figure 2. Histamine-cytokine connection in immune cells.

the histamine/cytokine network illustrated in Figure 2. These multiple biological activities are consistent with a major regulatory function of histamine during the immune response and in the emergence of pathologies resulting from immune disorders such as autoimmunity. In favor of a potential immunointervention, increased production of histamine occurs during diseases such as multiple sclerosis,⁸⁴ psoriasis,⁸⁵ Crohn's disease and ulcerative colitis^{86,87} in which histamine metabolite levels are correlated with disease severity. In the same line of evidence, the increase of mast cell numbers associated with autoimmune diseases argues in favor of the contribution of histamine during onset or effector phase of the pathology, even though it is quite evident that mast cells participate in various other ways in the autoimmune reaction, as summarized in a recent review.⁸⁸ For instance, mast cells are found in the brain of patients with multiple sclerosis associated with demyelinated plaques,⁸⁹⁻⁹¹ in the synovial fluid of rheumatoid arthritis patients,⁹³⁻⁹⁵ in the salivary gland of individuals suffering from Sjogren's syndrome,⁹⁶ in the



[Front Cell Dev Biol.](#) 2021; 9: 752350.

PMCID: PMC8546116

Published online 2021 Oct 12. doi: [10.3389/fcell.2021.752350](https://doi.org/10.3389/fcell.2021.752350)

PMID: [34712668](https://pubmed.ncbi.nlm.nih.gov/34712668/)

Mast Cells as Important Regulators in Autoimmunity and Cancer Development

[Christine N. Noto](#), * [Stella G. Hoft](#), and [Richard J. DiPaolo](#) *

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What is a histamine case?

Sudden anaphalaxis

Allergies

Oral allergy syndrome

FPIES/violent diarrhea

Cold induced urticaria

Exercise induced urticaria

Hives

Worse after hot shower

Itchy

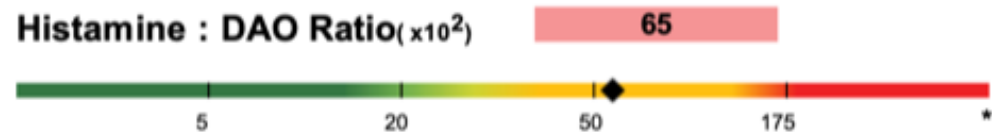
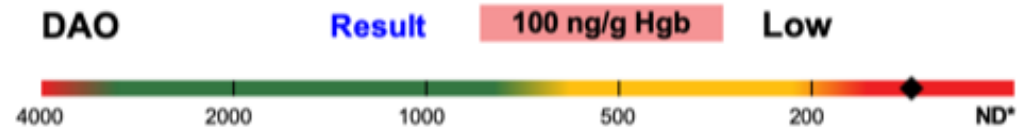
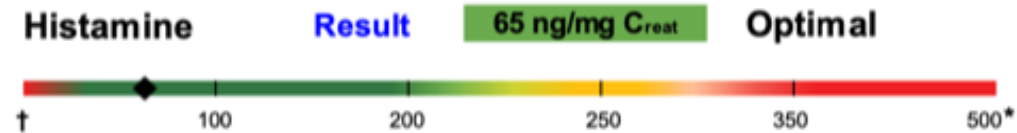
Some migraines

Adverse reaction to everything (esp B's, 5-HTP)

Aggressive anxiety

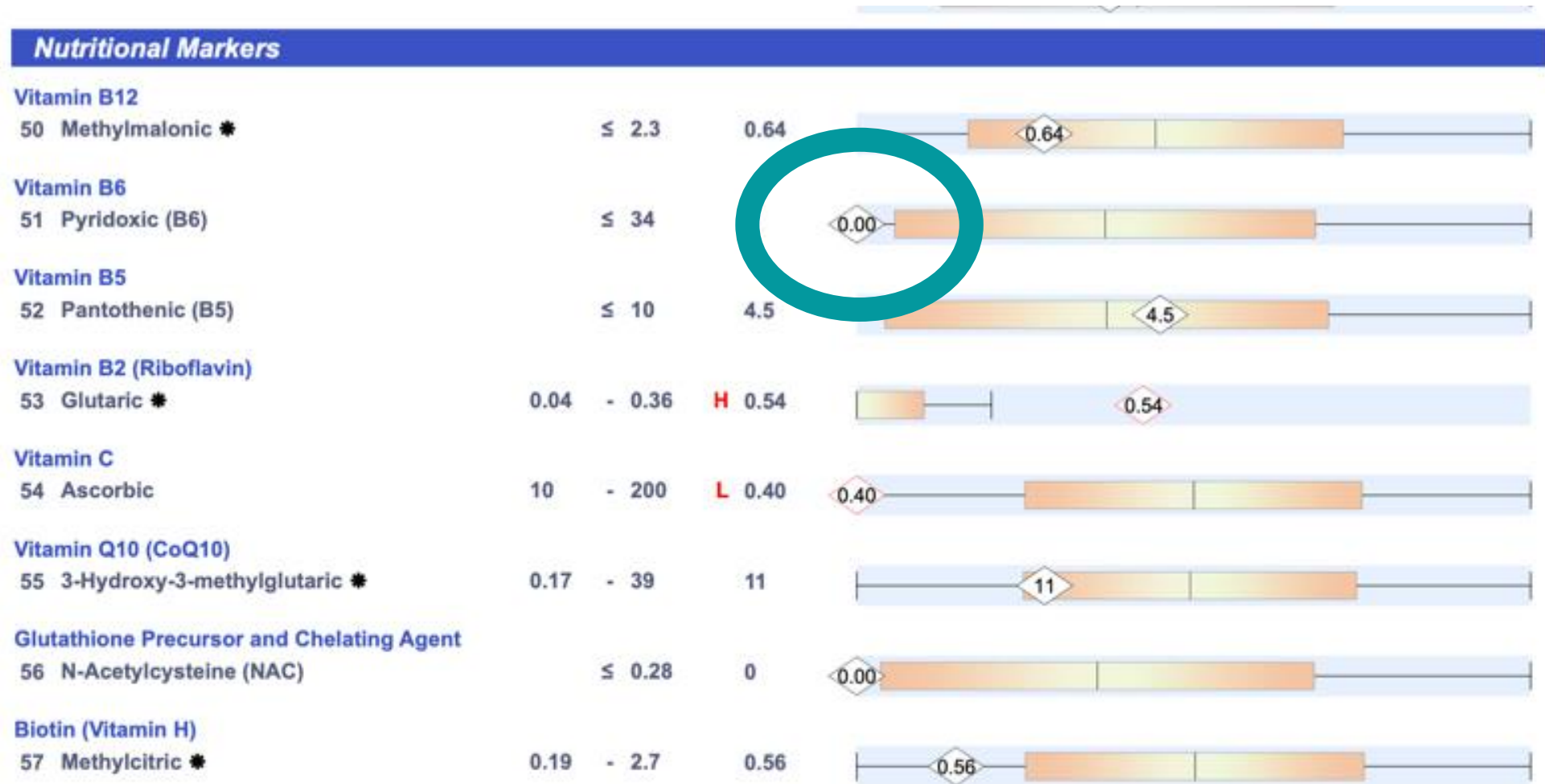
Non-responsive hormone case

ZONULIN FAMILY PEPTIDES (ZONULIN FP) + HISTAMINE : DIAMINE OXIDASE (DAO)

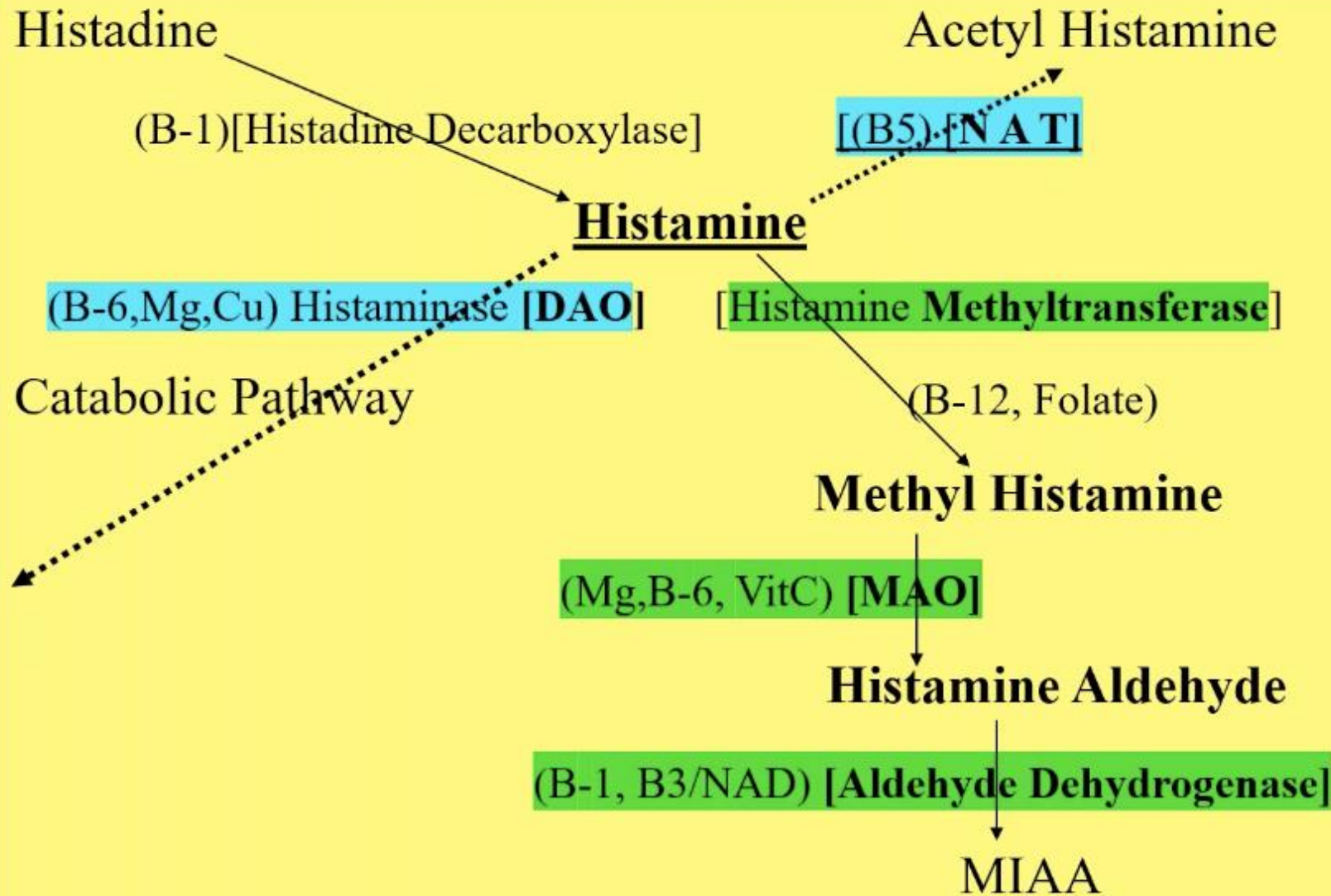


How to test?

OAT: Organic Acid Test:



Histamine Metabolism

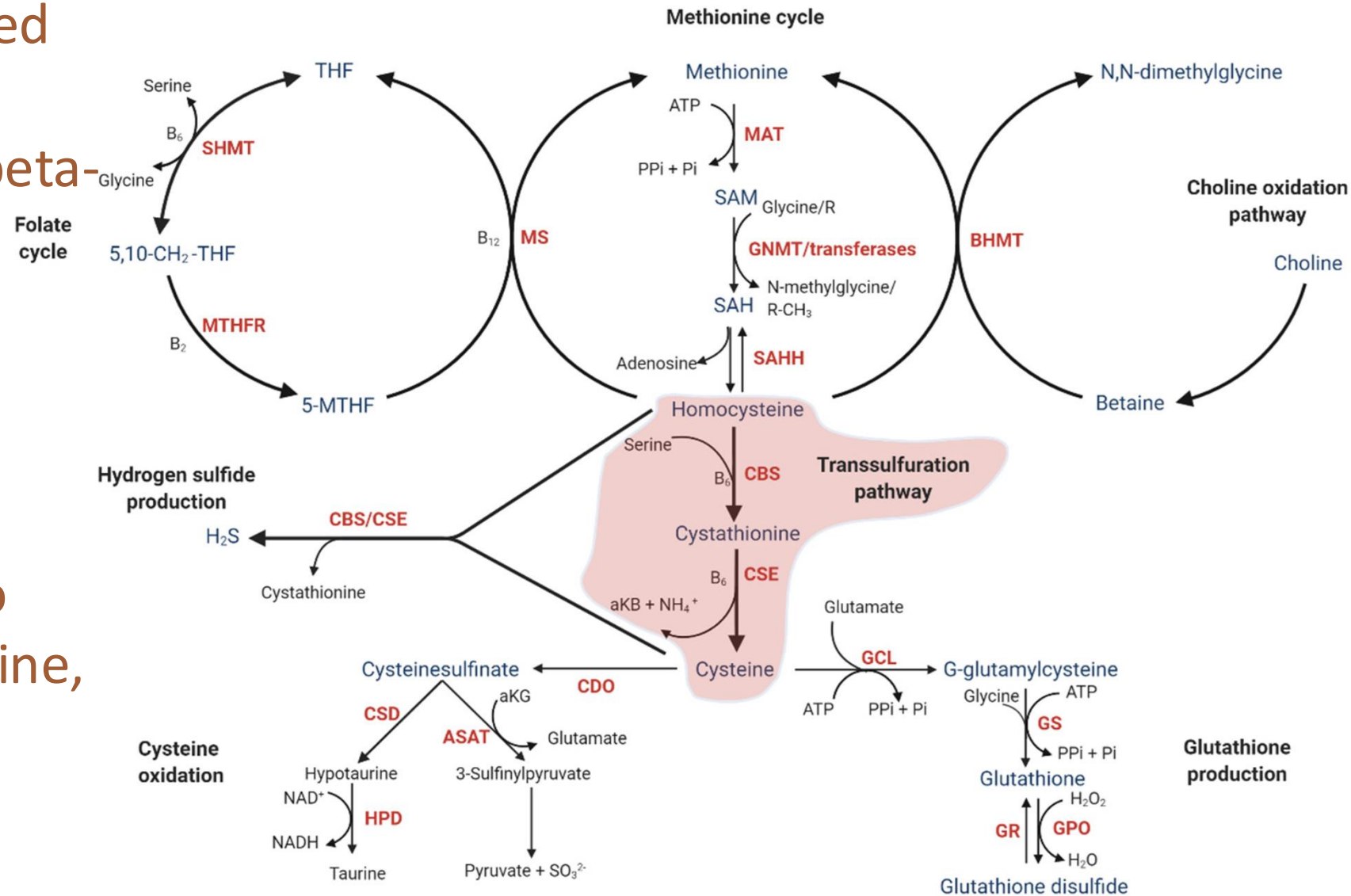


OAT: Organic Acid Test:



The CBS pathway (named after the enzyme cystathionine beta-synthase) is part of the transsulfuration pathway

which connects the methionine cycle to the production of cysteine, a key building block of glutathione (GSH)



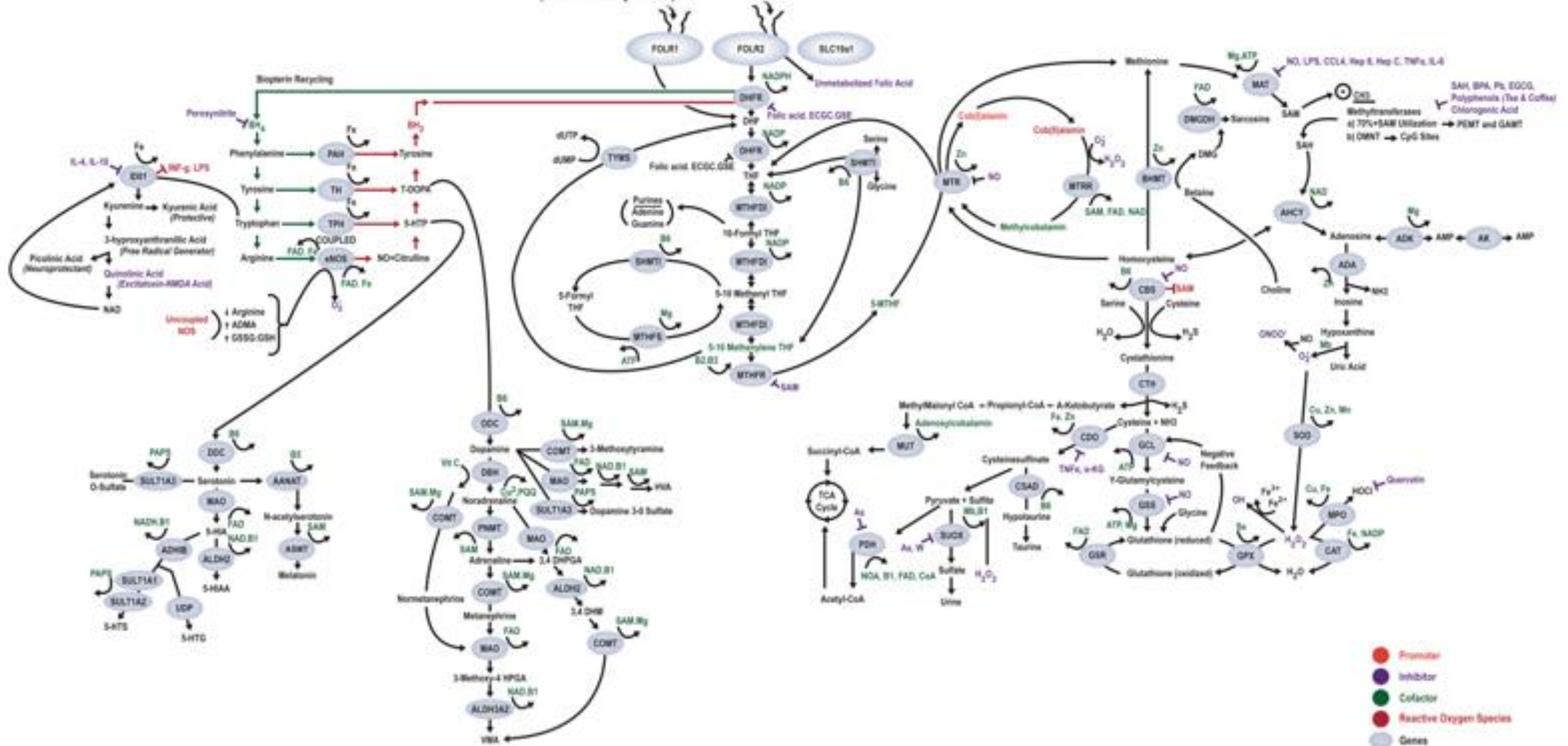
<https://www.mdpi.com/2077-0383/10/5/1081>

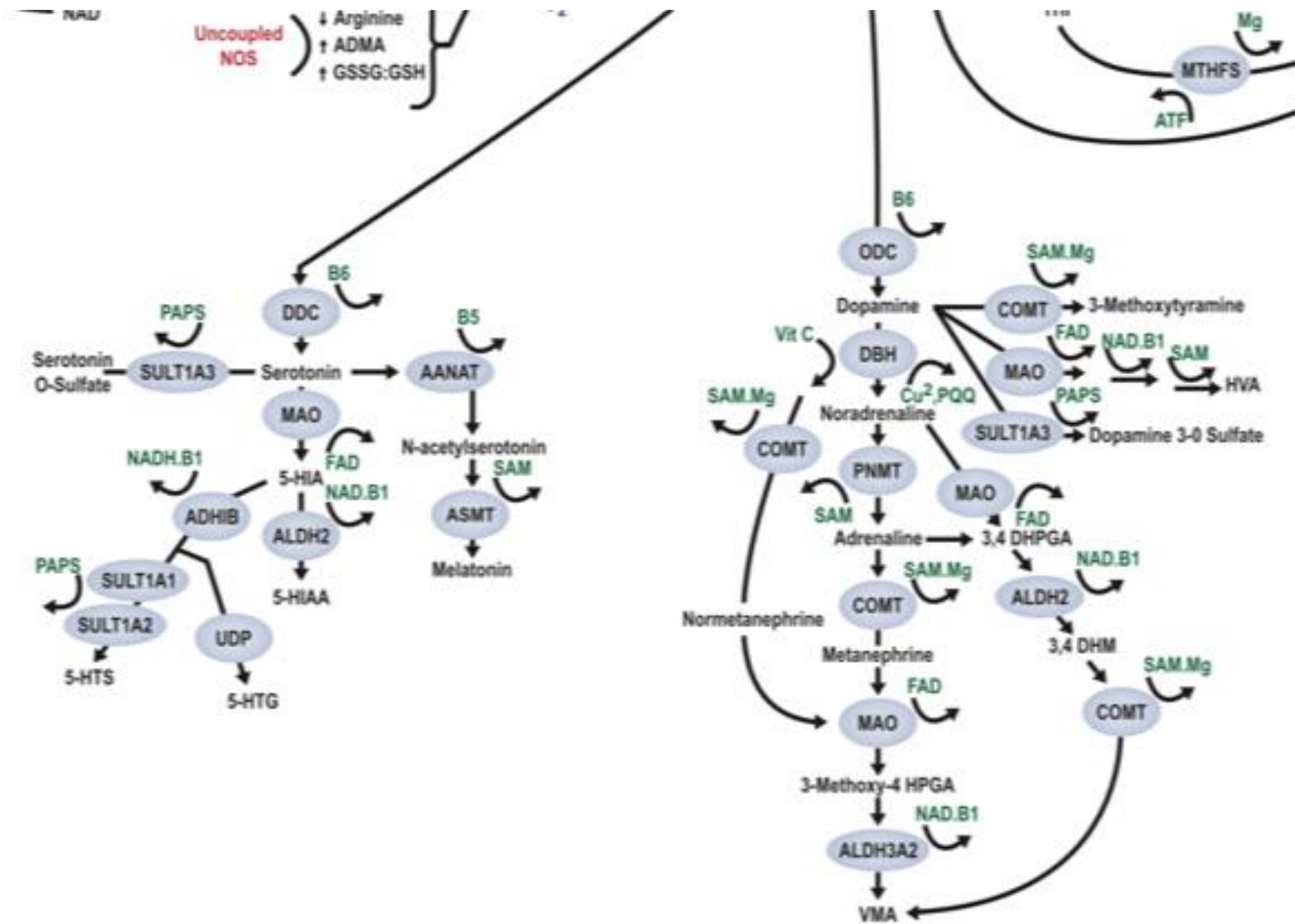
OAT: Organic Acid Test:



Reduced Folates (Uncooked Leafy Greens)

Folic Acid





Case 1: 41 year old woman (MM)

At age 36, after 2 healthy children, sudden onset anaphalaxis to erythromycin. History of ear infections as a child. And consistent reactions to medications since age 12 cumulating in the anaphalaxis at age 36 yoa. Chronic and unexplained iron deficiency. Severe fecal loading found via bowel x-ray assessed for fecal loading. Patient was on paleo coming into the visit. Had an anaphylactic reaction to fish oil.

Panic attacks, PEM, cold urticaria, psychosis with St. John's wort, migraines from chemical, hives w perfume

Case 1: 41 year old woman (cont'd)

Supplements

- **Magnesium oxide (1600mg) per tsp [Manufactured]** 1 teaspoon once a day
- Comments : A typical reaction is loose stool after 1 hour and 2-5 loose stool done after 6 hours.
- **B12 15mg (Methylcobalamin 15,000mcg) or 15mg** 1 tablet , once a day.
- **B100 100mg** 3 capsule(s) , Once a day , Comments : B1 100-300mg, B6 200-400mg.

Case 1: 41 year old woman (cont'd)

Home tests:

1. Heart rate, oxygen blood pressure. Check HR in each position. Should be 55-65.

Lying down

Standing

HR should increase 10-15 points when stand. Should go back to resting heart rate in 2-3 minutes. HR should go back to normal standing at 2-3 minutes.

What is your heart rate lying in bed in the morning? This is a true resting heart rate.

Heart rate

Seated: note most stable number after 1-2 minutes, where it settles

Lying down: note the most stable number after 1-2 minutes, where it settles

Stand: note the highest number you see.

Case 1: 41 year old woman (cont'd)

Home tests (cont'd):

2. Burp test. $\frac{1}{4}$ tsp of baking soda in one shot/ounce of water. Drink. Immediate burp is a pass. No burp means stomach acid is too basic.
3. Transit time test. Eat beets (2 pickled beets, or regular beets) and then 3 days later eat $\frac{1}{4}$ cup corn. Transit time is last time see food. Should be 8-18 hours.

Case 1: 41 year old woman (cont'd)

Home tests: Results

1. HR resting 70 bpm

lying down HR 62 bpm

stand of HR 120 bpm

2. Burp test: fail

3. Transit time test: no beets, no corn seen

Case 1: 41 year old woman (cont'd)

Supplements

- **Magnesium oxide (1600mg) per tsp [Manufactured]** 1 teaspoon once a day
- Comments : A typical reaction is loose stool after 1 hour and 2-5 loose stool done after 6 hours.
- **B12 15mg (Methylcobalamin 15,000mcg) or 15mg** 1 tablet , once a day.
- **B100 100mg** 3 capsule(s) , Once a day , , Comments : B1 100-300mg, B6 200-400mg.
- Quercetin 500mg 2/day
- Vitamin C 1000mg 1/day Liposomal or regular

Case 1: 41 year old woman (cont'd)

- Just saw this patient after not seeing her for 5 years
- No hives in years
- No reactivity to chemical
- No migraines
- Iron still an issue
- No cold urticaria
- Still has to use magnesium to manage constipation. ...been doing a variation of the previous protocol for 5 years.

Key Takeaways

- Histamine needs a methyl unit to break it up
- B6 can reduce most histamine cases
- Vitamin C stabilizes mast cells and stops degranulation.
- The digestive system is usually where the root of the case lies
- Think about chronic infection, mold, chemicals, toxicants, metals as agents that trigger histamine

Questions?