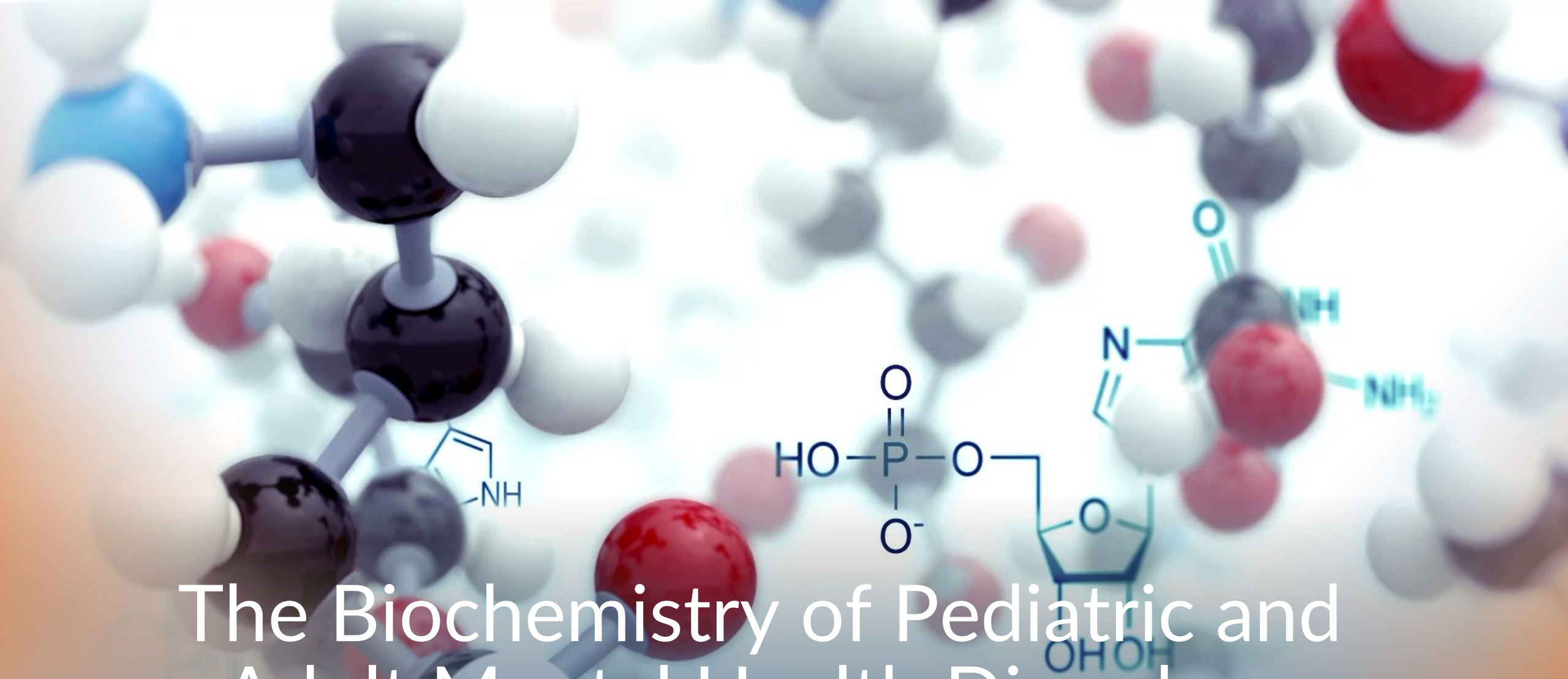


The Biochemistry of Pediatric and Adult Mental Health Disorders

Dr. Sonya Doherty, ND and Dr. Carissa Doherty, BSc., ND

Conflict of Interest

- Dr. Carissa Doherty, BSc, ND, is a clinical advisor for NFH
- Drs. Carissa and Sonya have an educational platform called Exceptional ND

LENSES

- Why use a lens?
- Step by step process – where is your patient now, where are they headed?
  - river, mountain visuals
- Explaining symptoms – give whole body overview
- Predicting outcomes
- Outcome measures – testing!

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.

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

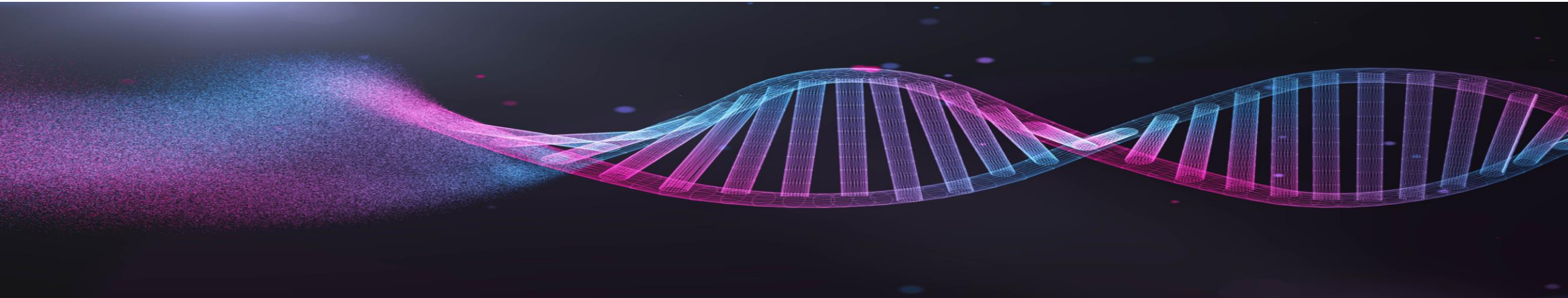
NATUROPATHIC ROLE

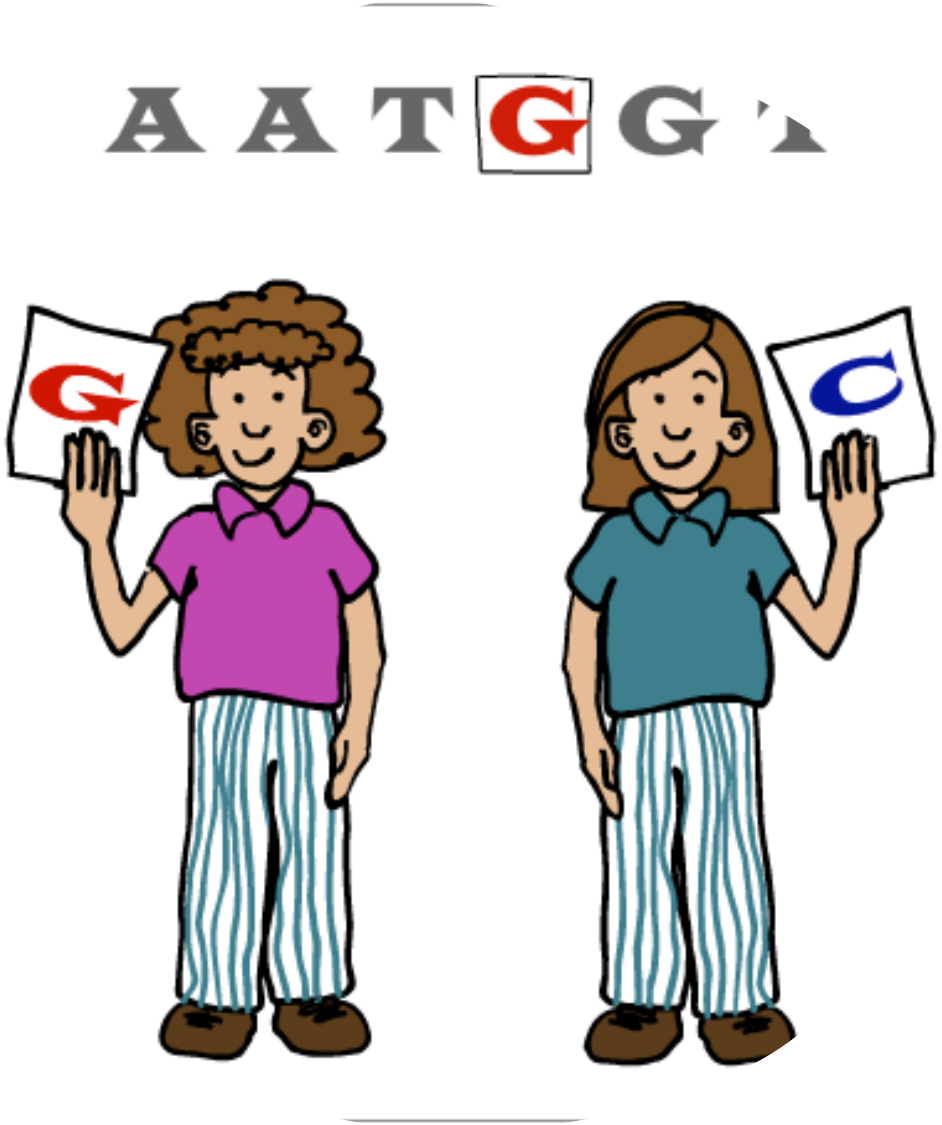
The Human Genome Project

- Completed in April 2003, the HGP gave us the ability to read nature's complete genetic blueprint for building a human being
- DNA contains all of our genes, and is made of 4 chemical bases, that pair up and make the “rungs” of the DNA molecule

DNA Methylation

- DNA methylation is an epigenetic mechanism used by cells to control gene expression.
- Low methylation = more RNA bases incorporated into **DNA**
- This triggers repair mechanisms that increases frequency of **DNA** being read/repaired resulting in **impaired function**





Single Nucelotide Polymorphisms - SNPs

- Human genome = 10, 000 SNPS
- Accounting for differences such as:
  - appearance
  - response to drugs
  - pathology
- Many show no change at all

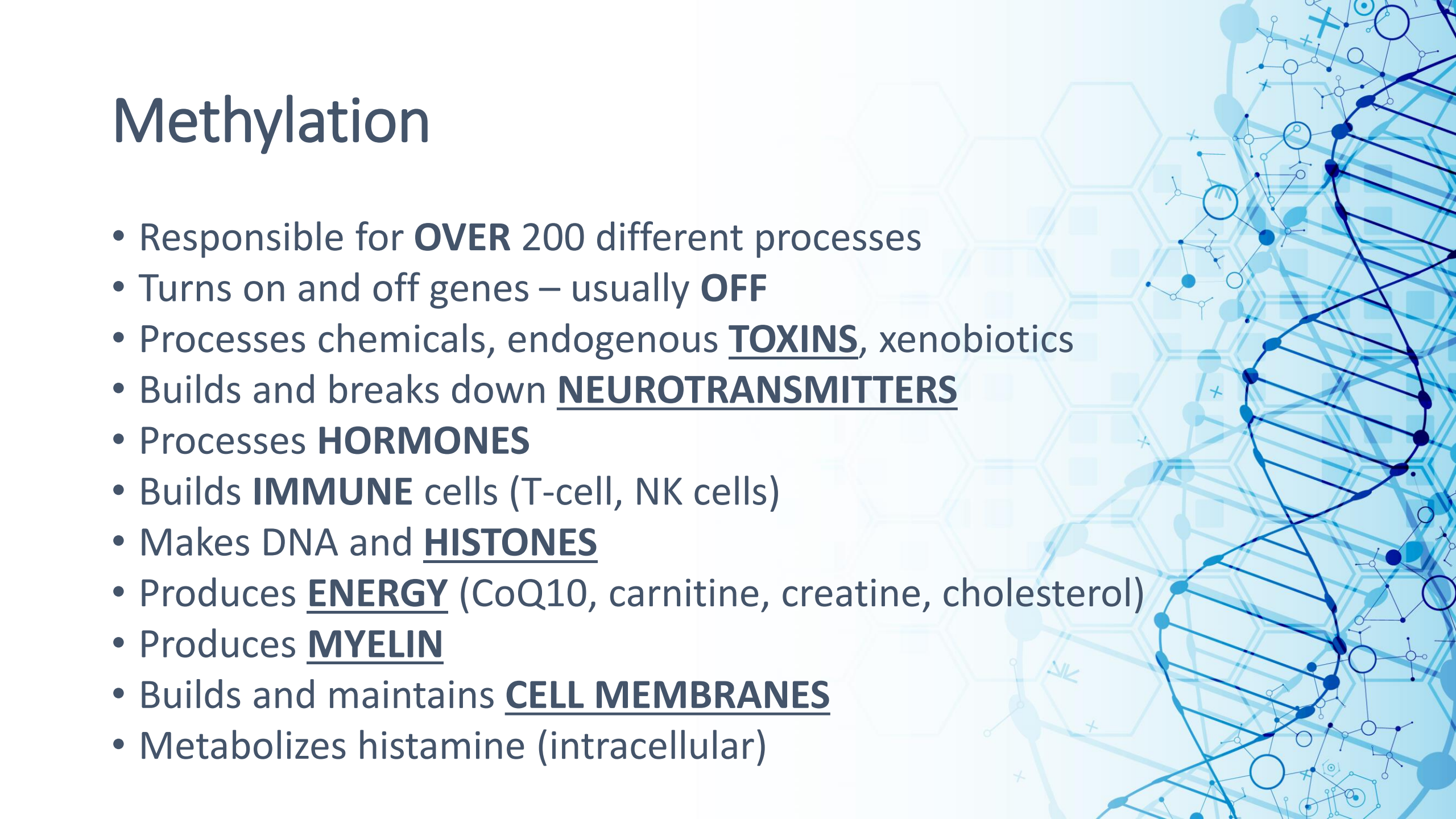
The Methyl Cycle

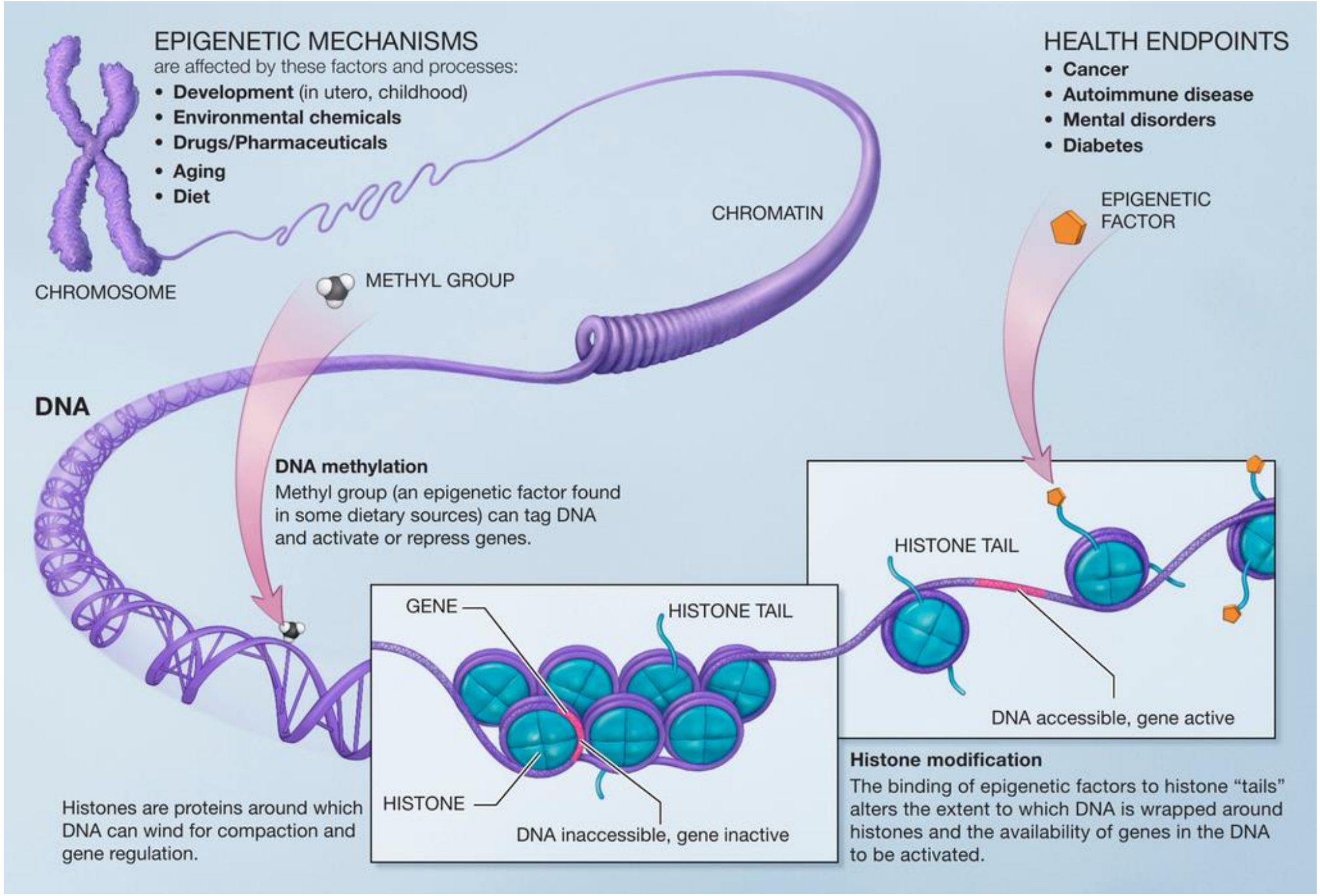
- Back bone of our physiology
- Its functional status determines our resistance to **environmental toxins and microbes**

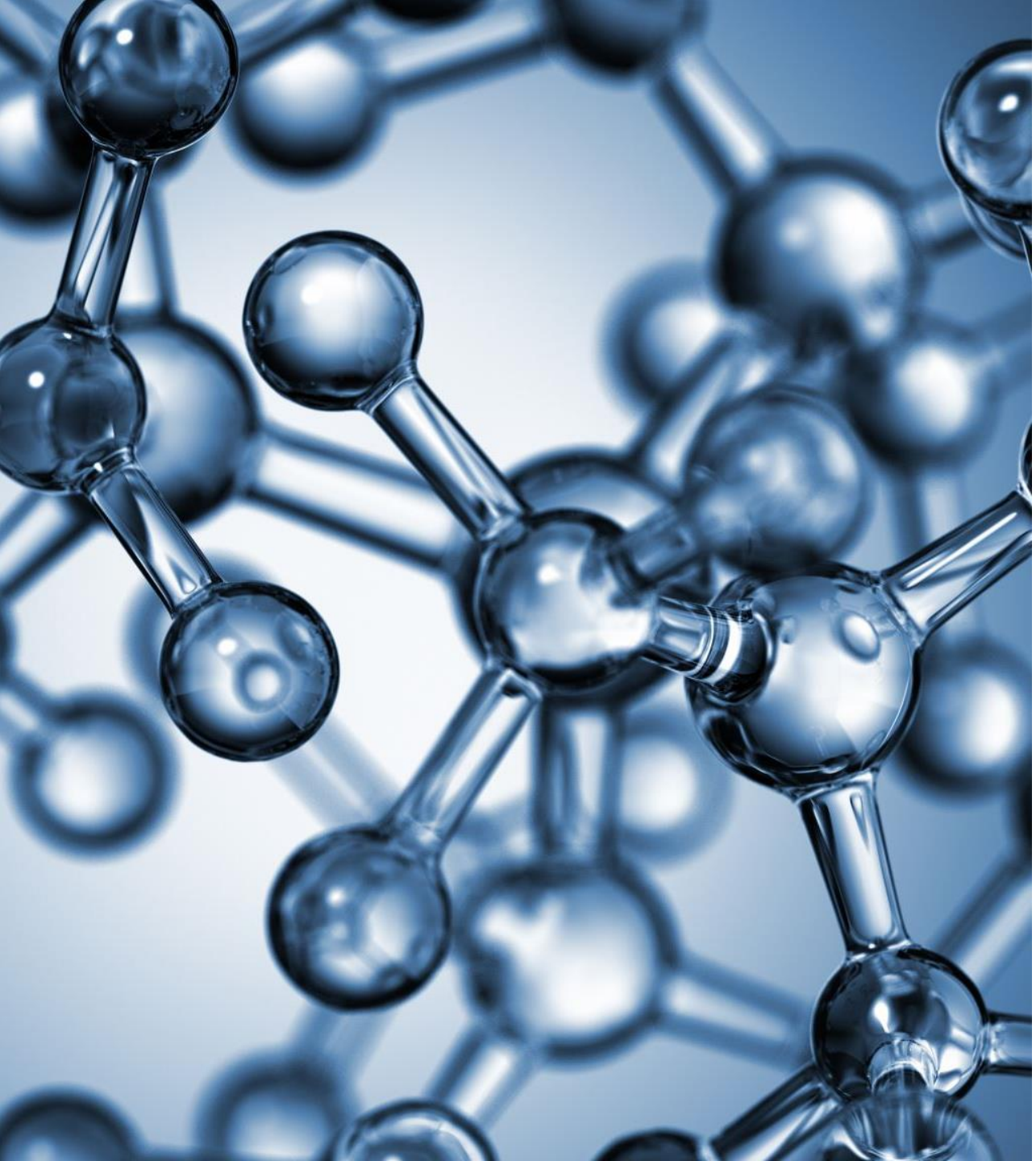
- We can't CHANGE our DNA, but if we know your weak links, we can create **"nutritional workarounds"**

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**
- Produces **ENERGY** (CoQ10, carnitine, creatine, cholesterol)
- Produces **MYELIN**
- Builds and maintains **CELL MEMBRANES**
- Metabolizes histamine (intracellular)




EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

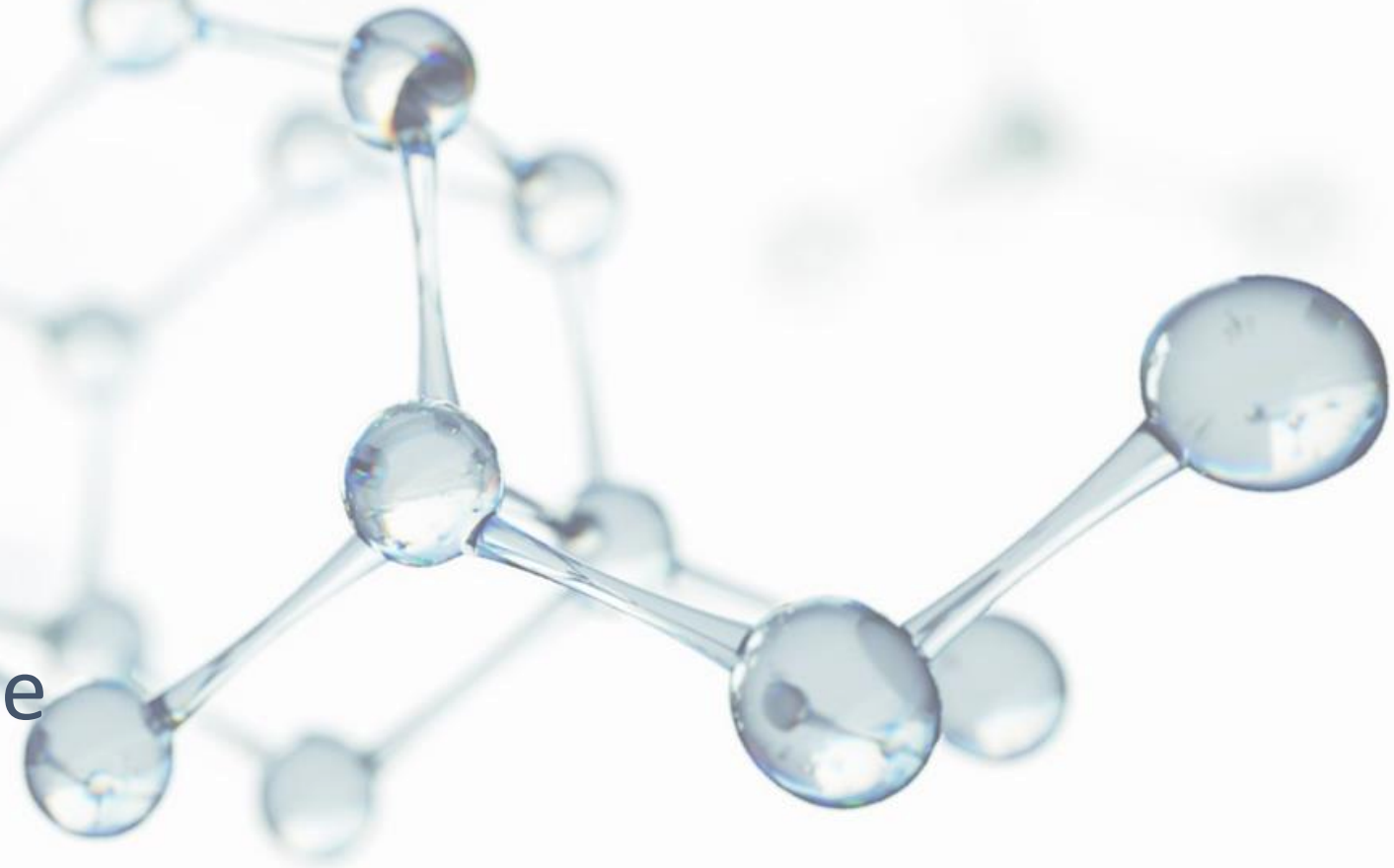


Methylation and SNPs

- Low methylation = more RNA bases incorporated into **DNA**
- This triggers repair mechanisms that increases frequency of **DNA** being read/repaired resulting in **impaired function**

Methyl Cycle Products

- Glutathione
- Metallothioneins
- Cell membranes
- Carnitine
- Creatine
- Phosphatidylcholine
- Neurotransmitters



Methyl Cycle Products

- **Glutathione**
  - Removes toxicants
  - Regulates glutamate
- **Cell membranes**
  - Lipid peroxidation
  - Impaired mitochondrial function
- **Carnitine**
  - Shuttles fats into mitochondria to make energy
  - Damaged by toxicants, harmful microbes, oxidative stress

Epigenetics

- Environment
  - Toxins
  - Food
  - Stress
  - 'Bugs'
  - Medications
  - Illness

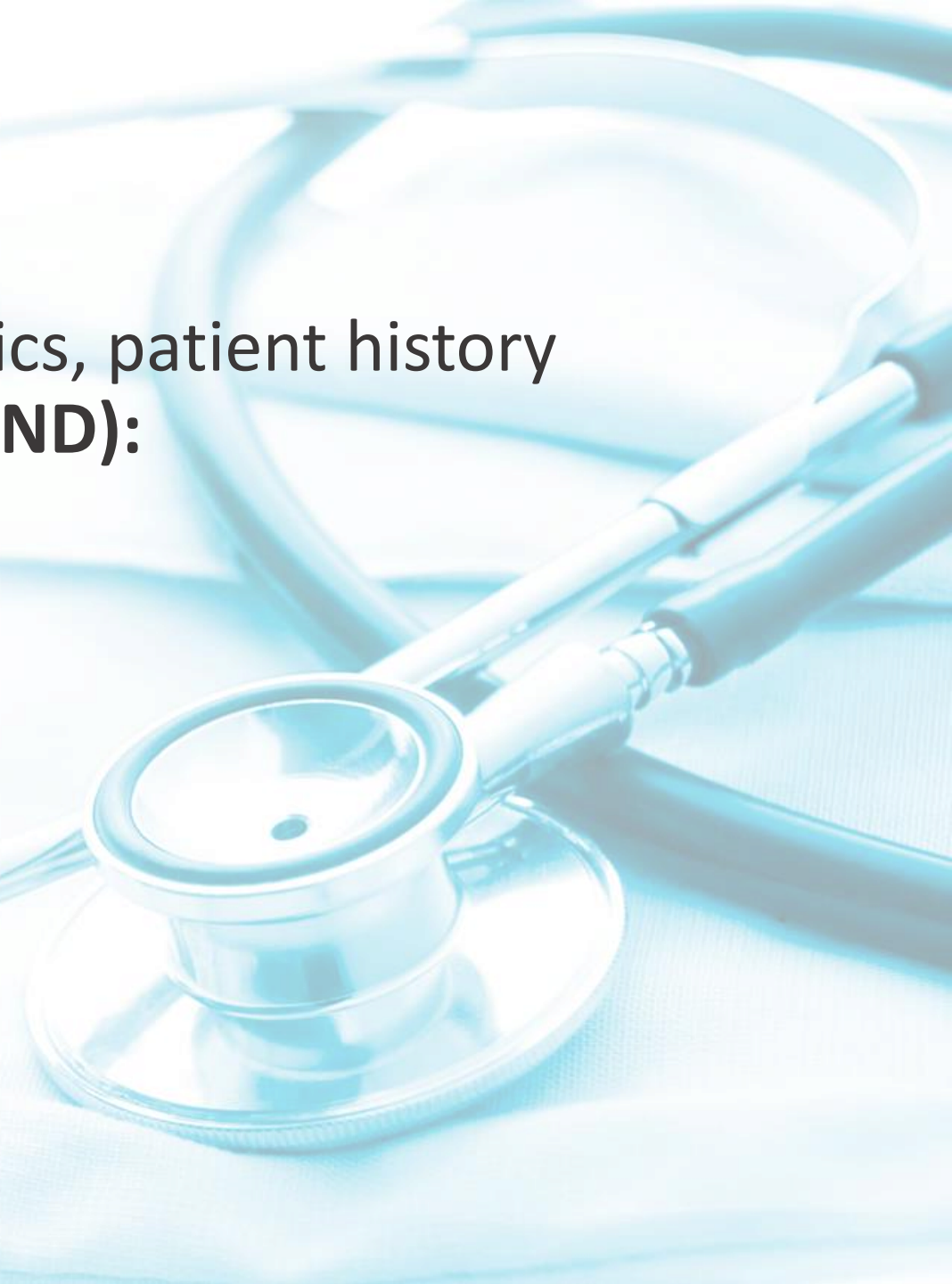
"ON/OFF"

- We will have the same SNPs through life, but whether you're expressing it depends on **Epigenetics – shows phenotype plasticity**

Gene & Variation	rsID	Alleles	Result
COMT V158M	rs4680	GG	-/-
COMT H62H	rs4633	CC	-/-
COMT P199P	rs769224	GG	-/-
VDR Bsm	rs1544410	CT	+/-
VDR Taq	rs731236	AG	+/-
MAO A R297R	rs6323	TT	+/+
ACAT1-02	rs3741049	GG	-/-
MTHFR C677T	rs1801133	AA	+/+
MTHFR 03 P39P	rs2066470	GG	-/-
MTHFR A1298C	rs1801131	TT	-/-
MTR A2756G	rs1805087	AG	+/-
MTRR A66G	rs1801394	AG	+/-

Epigenetic Testing

- There is **NO** test for epigenetics, patient history is **BEST (Dr. Walter Crinnion, ND):**
  - Toxic exposures**
  - Drug exposure – meds, illegal
  - Stress
  - Diet – organic/dense
  - Family history – also life span
  - Emotional stability
  - Stress
  - Where they've lived, hobbies



Integr Med (Encinitas). 2019 Apr; 18(2): 8–10.

PMCID: PMC6601440

PMID: 31341436

Walter Crinnion, ND—Pioneer in Environmental Medicine. 1953-2019

Joseph Pizzorno, ND, Editor in Chief*

Introduction

Go to:

This is one of the hardest editorials I have had to write. Walter's death was personally devastating: he was a dynamic student in my very first class at the then named John Bastyr College of Naturopathic Medicine (1982 graduate), a good friend for decades, co-author of several IMCJ editorials, and coauthor with me of *Clinical Environmental Medicine*, published by Elsevier in 2018. With his booming voice, expansive gesticulations, wicked humor and colorful patient stories, Walter was bigger than life and his loss is felt deeply by many.

As the environment has become progressively more contaminated, a handful of courageous clinicians have been relentlessly pushing the boundaries of our understanding. Unfortunately, many of them paid a serious personal price for exploring and developing our understanding of the huge contribution of the growing load of environmental metals, chemicals, particulate matter, etc. on everyday ill health and disease burden.

Integr Med (Encinitas)

Toxic Exposure (Rabbit Hole)

In 2005 the EWG investigated chemicals in umbilical cord blood. Of the 287 chemicals detected in the cord blood, we know that 180 cause cancer in humans, 217 are toxic to the brain and nervous system , and 208 cause birth defects or abnormal development in animal tests.

Body Burden: The Pollution in Newborns

The Pollution in Newborns

A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood

Neurobehavioural effects of developmental toxicity

Philippe Grandjean, Philip J Landrigan

- There have been eleven industrial chemicals that have been identified as developmental neurotoxicants:
  - lead, methylmercury, polychlorinated, biophenyls, arsenic, toluene, fluoride*new ,manganese, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT), polybrominated diphenyl ethers (PBDE's) - flame retardants, tetrachloroethylene (organic solvent)

Neurobehavioural effects of developmental toxicity; Dr Philippe Grandjean:Department of Environmental Medicine, University of Southern Denmark, Odense, Denmark, Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA

Methylation cycle and Neurological Health

- **Essential to health in 2016**
  - 90, 000 TOXINS (land, air, water)
- **Methyltransferases**
  - mostly require SAMe to donate methyl. SAMe requires **ATP**
- **Mitochondrial function**
  - need healthy MITO to make ATP
  - Mitochondrial DNA don't have **HISTONES**
  - high rate of mt DNA mutagenesis = oxidative stress and lipid peroxidation of phospholipid bilayer
  - **CELL DANGER RESPONSE slows methylation**
  - Oxidative stress slows MTR enzyme down impairing methylation

Epigenetic Modulation

- Impacts DNA methylation
- Modifies **HISTONES** which protect DNA
- Epigenetic control usually governs fn of SNP
- SNP mutations create gene instability
  - Ex. MTHFR – Riboflavin/FAD)
  - Change in shape decreases co-factor binding
- Ex. Fish oil changes genetic expression towards reducing inflammation

AUTISM: A NEUROEPIGENETIC DISORDER

BY RICHARD C. DETH, PHD,[1] NATHANIEL W. HODGSON,[1] MALAV S. TRIVEDI,[1] CHRISTINA R. MURATORE, PHD,[2] AND MOSTAFA I. WALY, PHD[3]

Affiliations:
1 Department of Pharmaceutical Sciences, Northeastern University, Boston, MA 02115; **2** Center for Neurological Diseases, Harvard Medical School, Boston, MA 02115; and **3** Sultan Qaboos University, Muscat, Oman

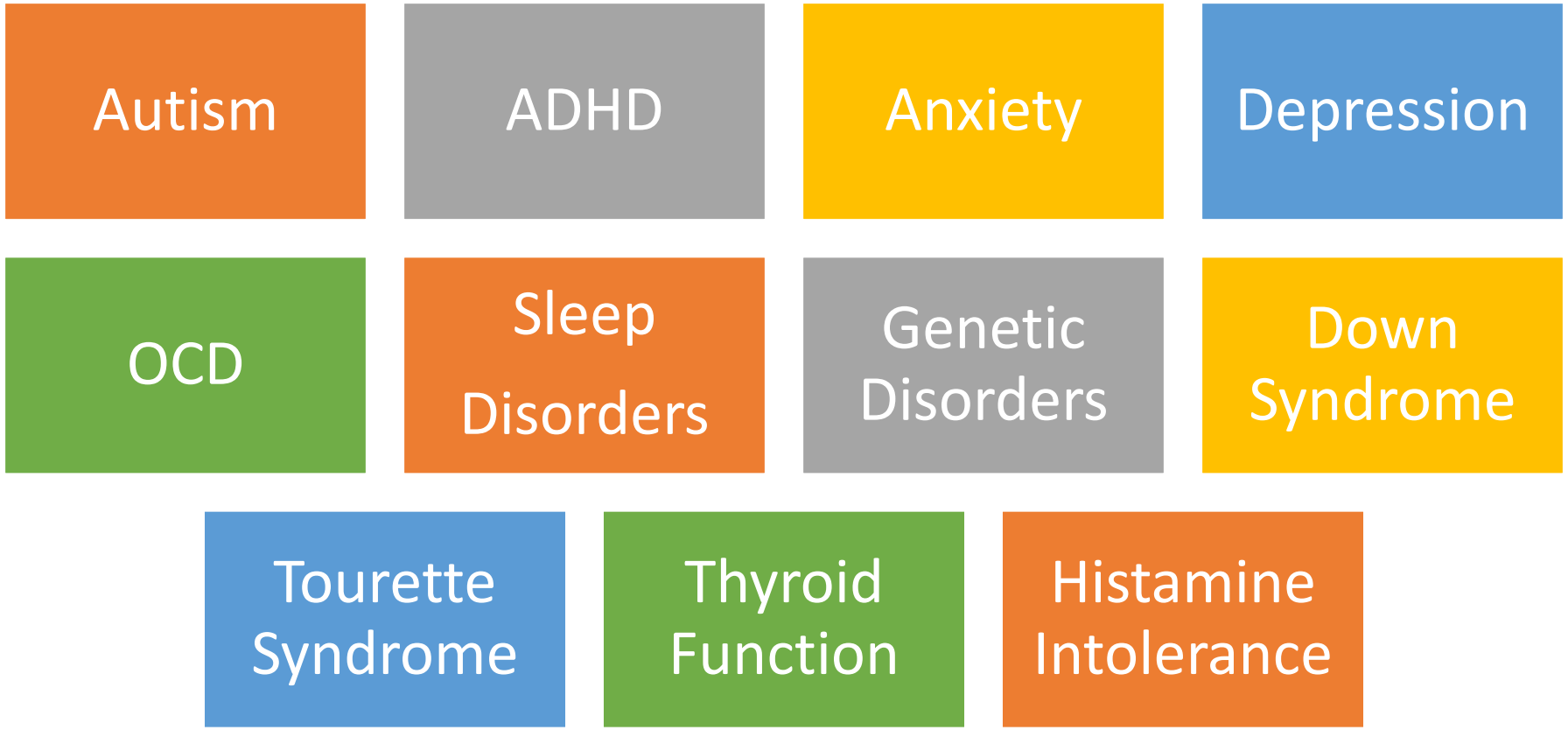
INTRODUCTION

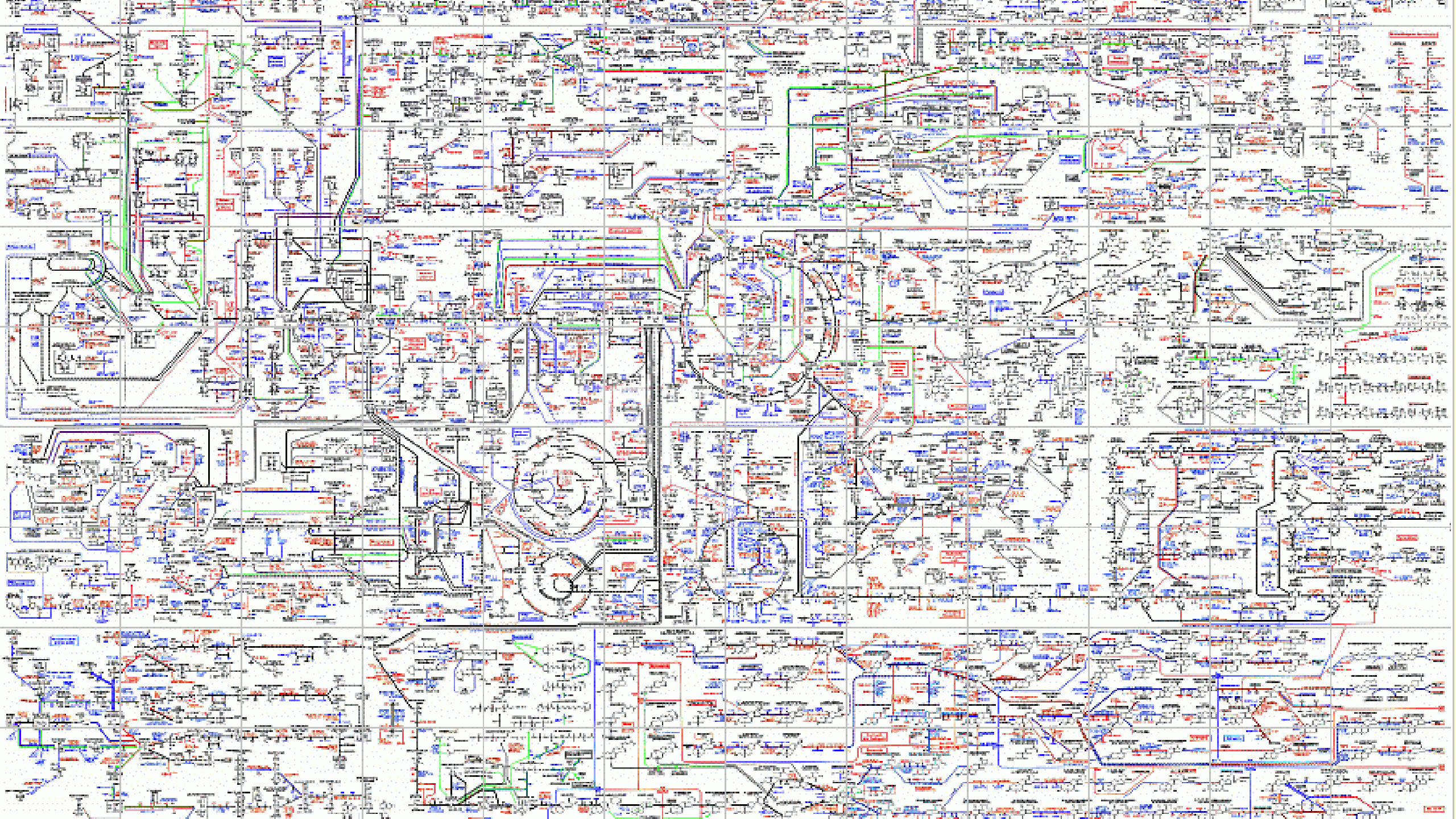
Where to begin in trying to understand autism? Autism is so complex and so variable from child to child. The brain, too, is complex. Is it possible to comprehend the events that cause certain children to stray from the

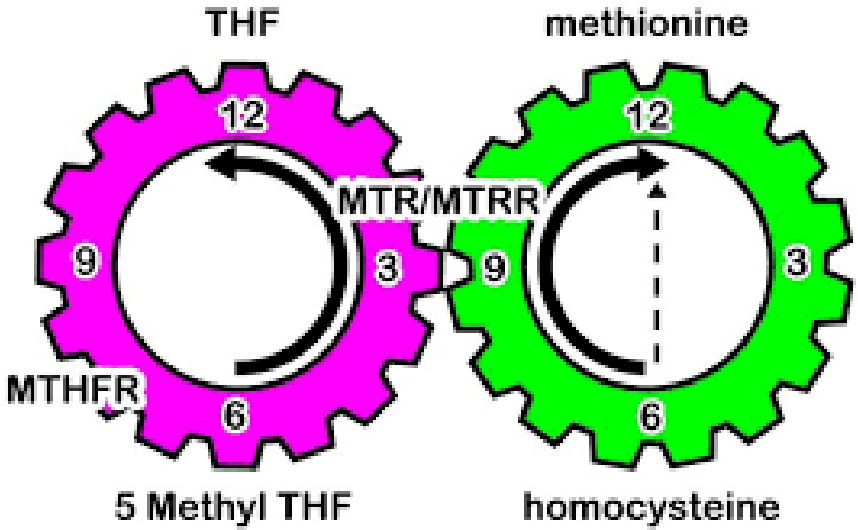
not A or B or C. That said, the most useful perspective is the one that encompasses the largest number of observations and leaves the fewest unaccounted for. It is also obvious that we will learn more from observations made directly on individual autistic children

mental disorder, it is imperative to first understand the factors that guide normal development. It then becomes possible to identify dysfunctional factors that can be linked to autism via studies of autistic individuals. Moreover, it is generally (but

Methylation governs neurological health







These two cycles provide methyl donors to 200 pathways in the body

SAMe delivers methyl to 200 pathways

SAMe requires ATP from mitochondria

Basic Treatment Guidelines - Methylation

- Methyl donor
  - Methyl B12 injections, DMG, TMG, SAMe, Methionine, Beet crystals
- Folate cycle
  - Remove synthetic folic acid
  - Add folate – greens, MTHF, folinic
- Transulfuration – enough B6!!!
- Methylation cycle – zinc, zinc ionophores
- Neurotransmitters are packaged in fat – the brain is 2.5 lbs of FAT!

The FASEB Journal

Nutrition | Free Access

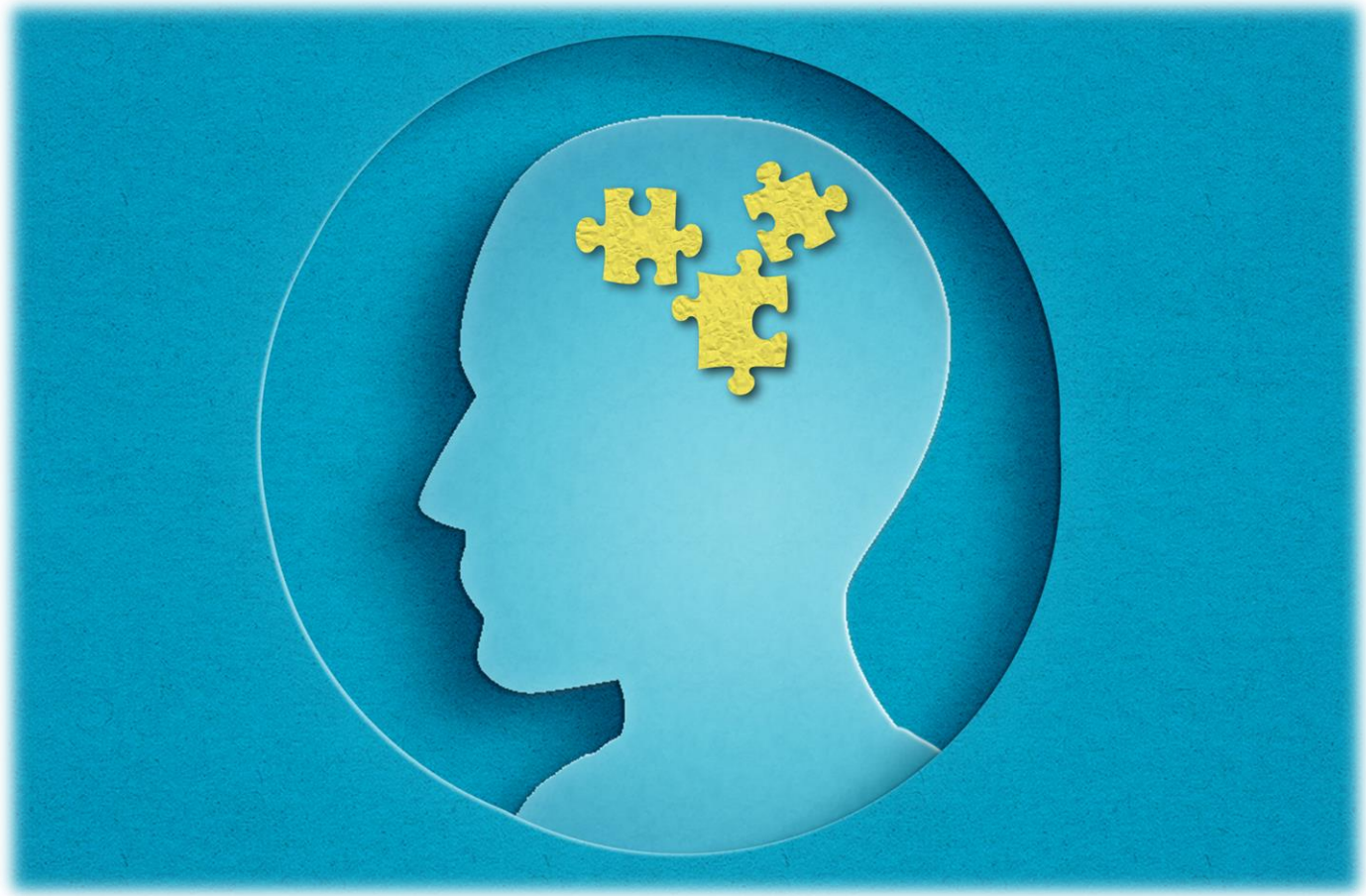
Effect of A1 vs A2 beta-casein containing diet on glutathione antioxidant status: Implications for inflammation and cognitive function via gut-brain axis

Malav Trivedi, Yiting Zhang, Richard Deth

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

Brain Inflammation A Hallmark Of Autism, Large-Scale Analysis Shows

Johns Hopkins study is largest so far of gene expression in autism brains



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 dihydrafolate
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 (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

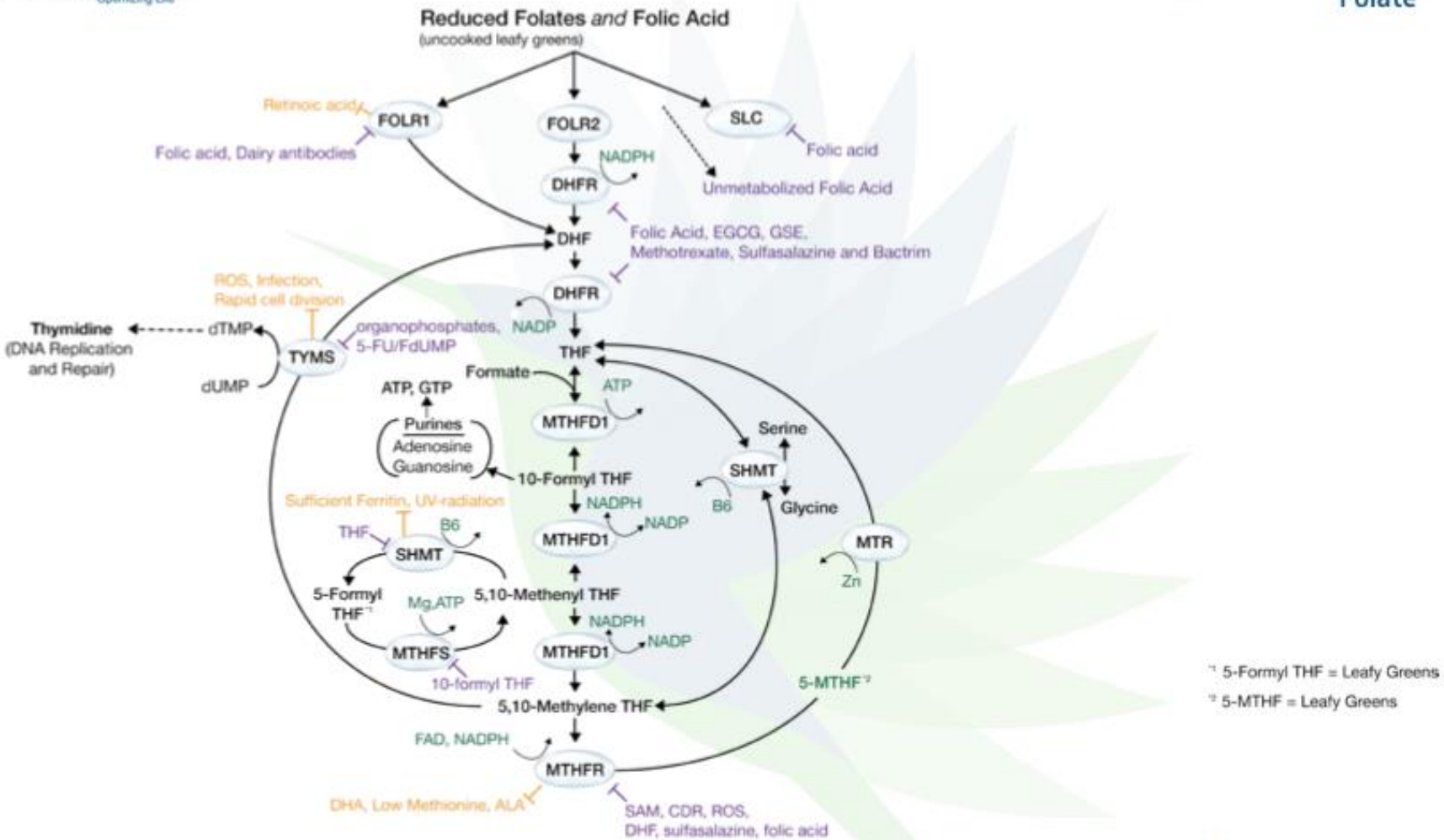
Dietary sources of choline

Dietary sources of choline

SeekingHealth®
Optimizing Life

Pathway Planner

Folate



[1] 5-Formyl THF = Leafy Greens

[2] 5-MTHF = Leafy Greens

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

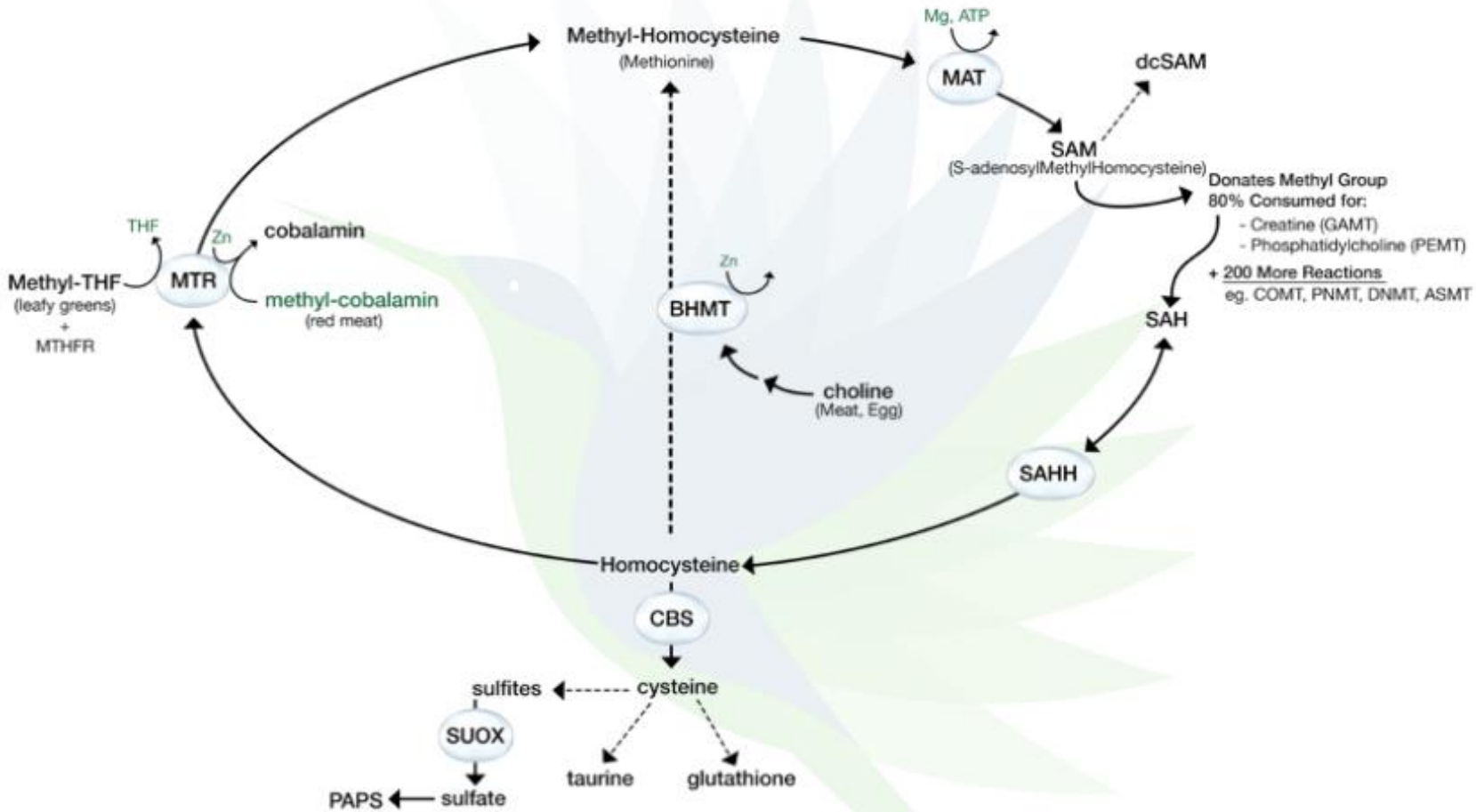
SeekingHealth.com

By Dr. Ben Lynch | 2018

SeekingHealth
Optimizing Life

Pathway Planner

Methyl-Homocysteine



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

SeekingHealth.com

By Dr. Ben Lynch | 2018

Nutritional Workarounds – Ex. MTHFR

Reduce the impact of SNPs

Take the pressure off (remove synthetic folic acid)

Increase concentration of co-factor (B2)

Supplement with end-product (MTHF, Folinic acid)

Methyl Donors and Essential nutrients

- B2/FAD – **MTHFR**
- Methyl folate – donates methyl group to SAMe
- B12 – needed for **MS**
- SAMe – needed to support 200 different pathways – **METHYLTRANSFERASES (MT)**
- **Creatine* – uses up half the methyl in the body**
- Phosphatidylcholine* – consumes a large amounts of SAMe
- Glycine - **SHMT**
- Betaine (needs zinc) – needed for BHMT
- B6 – needed for **CBS, PST, SHMT and many more**
- Magnesium – needed for **COMT**

* **Primary users of SAMe – creatine (GAMT) and phosphatidycholine (PEMT)**

Methylation and Neurotransmission

- B12 acts as a cofactor in synthesis of neurotransmitters such as serotonin and dopamine, thus B12 deficiency affects mood, emotions and sleeping and can lead to psychiatric disorders
- The collective effect of B vitamins are particularly prevalent to numerous aspects of brain function, including energy production, DNA/RNA synthesis/repair, genomic and non-genomic methylation, and the synthesis of numerous neurochemicals and signaling molecules.
- Kreb cycle provides energy to make neurotransmitters.

https://www.ncbi.nlm.nih.gov/pubmed/9622603
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3271502/
https://www.ncbi.nlm.nih.gov/pubmed/22549035

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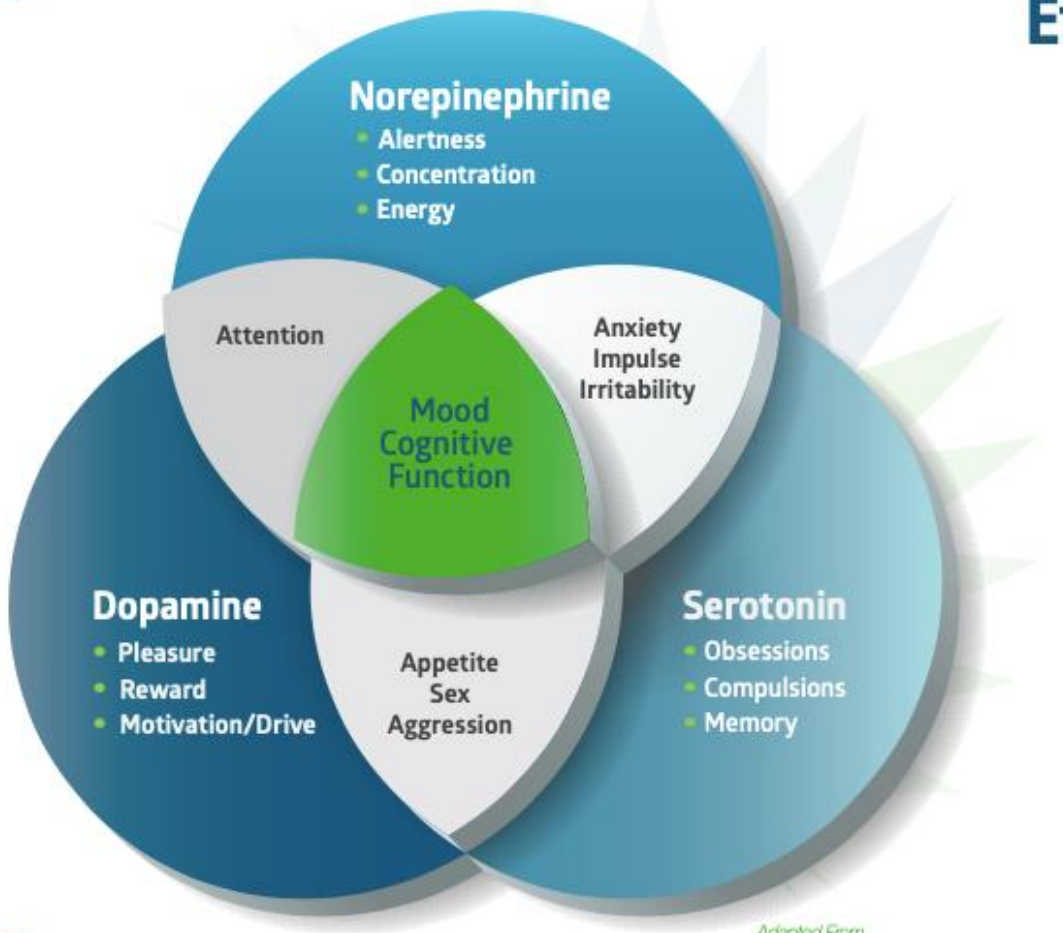
Neurotransmitter Effects



SeekingHealth.com

Adapted From
Deplin *deplin.com/depression/understanding-depression*

By Dr. Ben Lynch | 2018

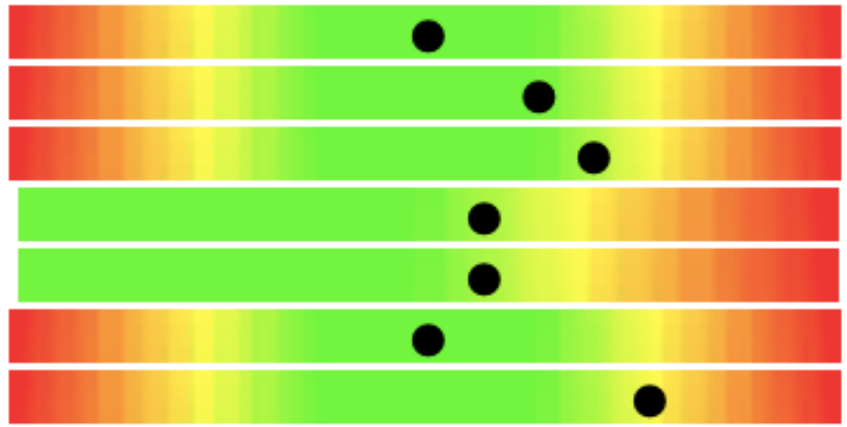
Serotonin	Dopamine
Learning	Brain Function
Sleep	Processing of info
Memory	Sensitivity
Behaviour	Perception of change
Noise sensitivity	Relaying info
Appetite	Emotional Responses

Cell Regulation Markers

NEUROTRANSMITTER METABOLISM

(Tyrosine, Tryptophan, B6, Antioxidants)

25.	Homovanillic Acid (HVA)	5.00		1.40 - 7.60	ug/mgCR
26.	Vanillylmandelic Acid (VMA)	4.60		1.20 - 5.30	ug/mgCR
27.	5-Hydroxyindoleacetic Acid (5HIAA)	9.60		1.60 - 9.80	ug/mgCR
28.	Kynurenic Acid.	1.1		0.0 - 1.5	ug/mgCR
29.	Quinolinic Acid (OA)	4.70		0.00 - 5.80	ug/mgCR
30.	Picolinic Acid	10.0		2.8 - 13.5	ug/mgCR
31.	Cortisol (OA)	*555*	*H	166 - 507	nmol/L



Methodology: Liquid Chromatography with tandem mass spectrometry (LC-MS-MS).

Glutathione is made by the methylation cycle

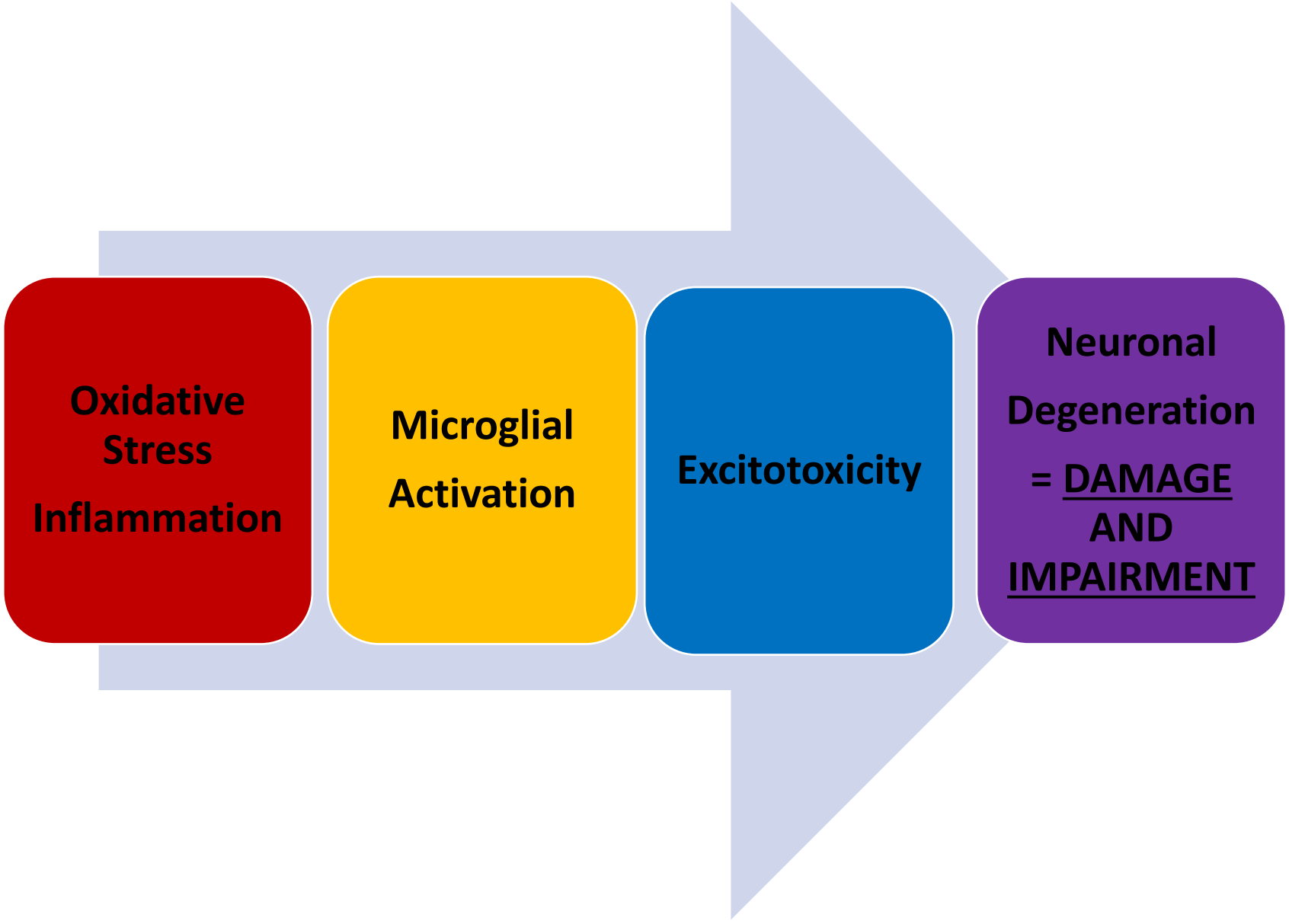
- Regulation of **cell growth** and division
- **DNA** synthesis and repair
- Protein synthesis
- Amino acid transport
- Enzyme catalysis and activation
- **Metabolism of toxins** including carcinogens, heavy metals, xenobiotics, chemicals, endogenous by-products, gliotoxins from yeast and mold
- Regulation of homocysteine
- Enhancement of systemic immune function including **humoral immune function**
- **Composed of CYSTEINE, GLYCINE and GLUTAMATE**

Glutathione

- Governs redox health
- Resistance to UV radiation
- Decreases radiation damage
- Decreases free radical damage & **oxyradical damage**
- Metabolizing of hydrogen peroxide **(H2O2)**
- Recycling of other antioxidants (master antioxidant role) including **vitamin C and E, and lipoic acid**
- Storage and transport of cysteine - metallothioneins

Glutathione Deficiency

- Causes increased glutamate = **IMMUNOEXCITOTOXICITY**
- Causes lipid peroxidation of cell membranes = **CELL DANGER RESPONSE**
- Slows removal of harmful chemicals, heavy metals and microbial toxins = **IMPAIRED DETOXIFICATION**
- Damages mitochondria = **OXIDATIVE STRESS**
- **Causes NEUROINFLAMMATION**



IMMUNOEXCITOTOXICITY

Mitochondrion

Volume 16, May 2014, Pages 7–17

Metabolic features of the cell danger response

- The Cell Danger Response (CDR) is defined in terms of an ancient metabolic response to threat.
- The CDR encompasses inflammation, innate immunity, oxidative stress, and the ER stress response
- The CDR is maintained by extracellular nucleotide (purinergic) signaling
- Abnormal persistence of the CDR lies at the heart of many chronic diseases
- Antipurinergic therapy (APT) has proven effective in many chronic disorders in animal models

Cell Danger Response

- **SLOWS DOWN METHYLATION!**
- Stiffens cell membranes
- Damages carnitine shuttles
- Creates **REACTIVE OXYGEN SPECIES**
- Pathways are immature in newborns and children leading not only to inflammatory and immune changes but also negatively impacting neurodevelopment

Basic Treatment Guidelines - Mitochondria

- Omega 3 and omega 6 fatty acids
- B6 – key to producing DGLA
- Fat soluble vitamins – vitamin E stops the lipid peroxidation of the cell membrane
- CoQ10
- Acetyl-L-carnitine
- Phosphatidylcholine

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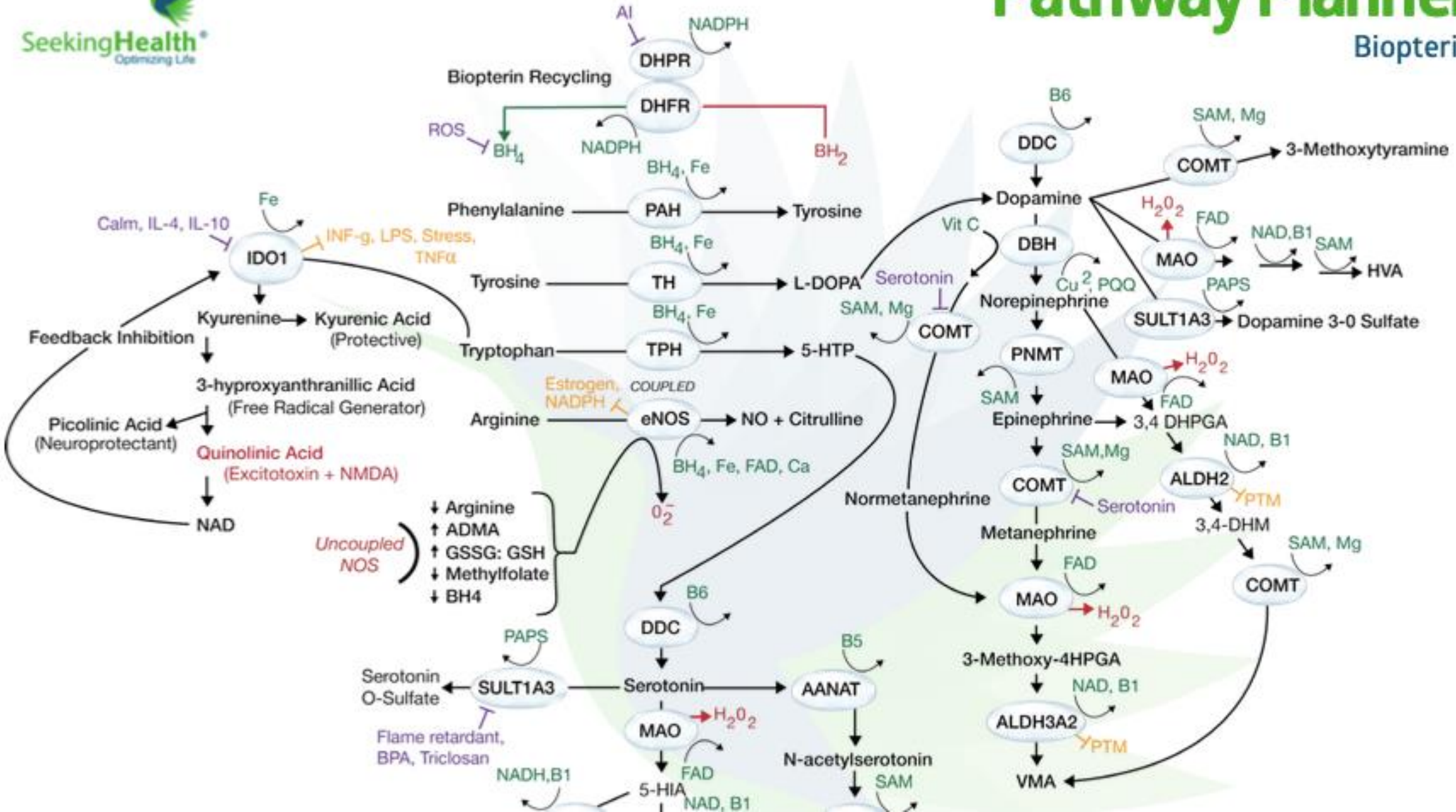
Pathway Planner

Biopterin



Methylation impairment leads to upregulation of the IDO pathway

- IDO1 (indoleamine 2, 3 dioxygenase)
- Leads to inflammation
- oxidative stress
- Peroxynitrate
- Oxidative stress
- Interferes with biopterin recycling
- eNOS uncoupling

Basic Treatment Guidelines - Oxidative stress, IDO, Immunoexcitotoxicity

- Modified ketogenic – 90% of tryptophan evaporates with IDO upregulation
- B6
- B3
- Curcumin, ECGC, Pycnogenol
- NAC is the rate limiting step to making glutathione
- Glutathione – zinc, zinc ionophores
- Glutathione if there are mold toxins
- Methylation, mitochondria, microbiome

BMC Complement Altern Med. 2017 May 10;17(1):259. doi: 10.1186/s12906-017-1763-7.

Postnatal treatment using curcumin supplements to amend the damage in VPA-induced rodent models of autism.

Al-Askar M[1], Bhat RS[1], Selim M[2], Al-Ayadhi L[3,4,5], El-Ansary A[6,7,8].

Author information

Abstract

BACKGROUND: Valproic acid (VPA) is used as a first-line antiepileptic agent and is undergoing clinical trials for use as a treatment for many disorders. Mothers undergoing VPA treatment during early pregnancy reportedly show increased rates of autism among their offspring. The benefits of curcumin supplementation were investigated using an animal model of VPA-induced autism.

METHODS: The study was performe the 12.5th day of gestation. At 7 days fr ty neonatal male Western Albino rats v he, rats in group II were the prenatal VPA expo ith postnatal curcumin, and rats in grou

RESULTS: VPA rats exhibited delay ty, such as depletion of IFN-γ, serotonin, glu ease in CYP450, IL-6, glutamate, and oxidiz nd was especially noticeable in improving delayed maturation and abnormal weight.

CONCLUSIONS: Curcumin plays a significant therapeutic role in attenuating brain damage that has been induced by prenatal VPA exposure in rats; however, its therapeutic role as a dietary supplement still must be certified for use in humans.

Curcumin plays a significant therapeutic role in attenuating brain damage that has been induced by prenatal VPA exposure in rats.

J Trace Elem Med Biol. 2017 Dec;44:88-92. doi: 10.1016/j.jtemb.2017.06.004. Epub 2017 Jun 15.

Effects of sulforaphane and vitamin E on cognitive disorder and oxidative damage in lead-exposed mice hippocampus at lactation.

Sun B[1], Zhang X[1], Yin Y[1], Sun H[1], Ge H[1], Li W[2].

Author information

Abstract

OBJECT: To investigate the effects of sulforaphane (SFN) and vitamin E (VE) on spatial learning and memory ability and oxidative damage of hippocampus in lead-exposed mice at lactation.

METHODS: A total of 18 adult Kunming mice, all 12 female mice were divided into two groups by body weight randomly, 10 mice drank water containing 0.2% lead acetate at lactation, the other 2 mice drank lead free deionized water named as the normal group. Then, they were mated at a 1:2 ratio of male to female. After weaning, the pups were divided into 5 groups by weight randomly (10 each group): normal saline (NS) group, corn oil (CO) group, SFN group, VE group and SFN+VE group. They were subject to gavage daily for four weeks. Gavage doses of SFN and VE were 25mg/kg and 30 IU/kg respectively. Meanwhile, 10 pups of the normal gr
spatial learning and r
determined by polaro
measured by the kits.

RESULTS: Compared
decrease. In water m

Sulforaphane and vitamin E could ameliorate cognitive decline and oxidative damage in pups with lead exposure at lactation from maternal milk.

N-Acetyl-Cysteine

- Rate limiting step to making glutathione
- Improves pediatric OCD
- Improving hormone regulation
- Mucolytic
- Glutamate modulator - Reduces glutamate, reduces neuroinflammation

http://www.cpn.or.kr
Clinical Psychopharmacology and Neuroscience
This article | Aims and Scope | Information for Authors | E-Submission

Clin Psychopharmacol Neurosci. 2015 Apr; 13(1): 12–24.
Published online 2015 Apr 30. doi: 10.9758/cpn.2015.13.1.12
PMCID: PMC4423164
PMID: 25912534

N-Acetyl Cysteine in the Treatment of Obsessive Compulsive and Related Disorders: A Systematic Review

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Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Sometimes it's the right supplement but the wrong dose

Clin Psychopharmacol Neur

Results

Four clinical trials and five case reports/series were identified. Study durations were commonly 12-weeks, using 2,400–3,000 mg/day of NAC. Overall, NAC demonstrates activity in reducing the severity of symptoms, with a good tolerability profile and minimal adverse effects. Currently there are three ongoing randomized controlled trials using NAC for OCD (two adults and one pediatric), and one for excoriation.

Besides ASD, NAC is shown to be effective for the symptoms of ADHD, OCD, and impulse control disorders such as nail biting, skin picking, and TTM [13–15,22]. NAC reported to be an effective agent as an add-on therapy to SSRIs in the treatment refractory OCD [23] and a treatment option in adults with TTM [14].

Taylor & Francis Online
https://www.tandfonline.com › ... › Volume 27, Issue 2

N-acetylcysteine may reduce repetitive behaviors in children ...

Conclusion: NAC adjunction to risperidone treatment may be helpful to reduce repetitive behaviors in children with ASD with limited adverse effects and good tolerability.

POTS….The Missing Piece to Your Case

75%

of POTS patients have encountered a doctor who has never heard of POTS.

DYSAUTONOMIA AWARENESS MONTH

CUREDYS.ORG/AWARENESS

DYSAUTONOMIA INTERNATIONAL

Percentage of POTS patients who are told some version of "it's all in your head" prior to finding out they have POTS.

Source: Journal of Internal Medicine

DYSAUTONOMIA
AWARENESS MONTH

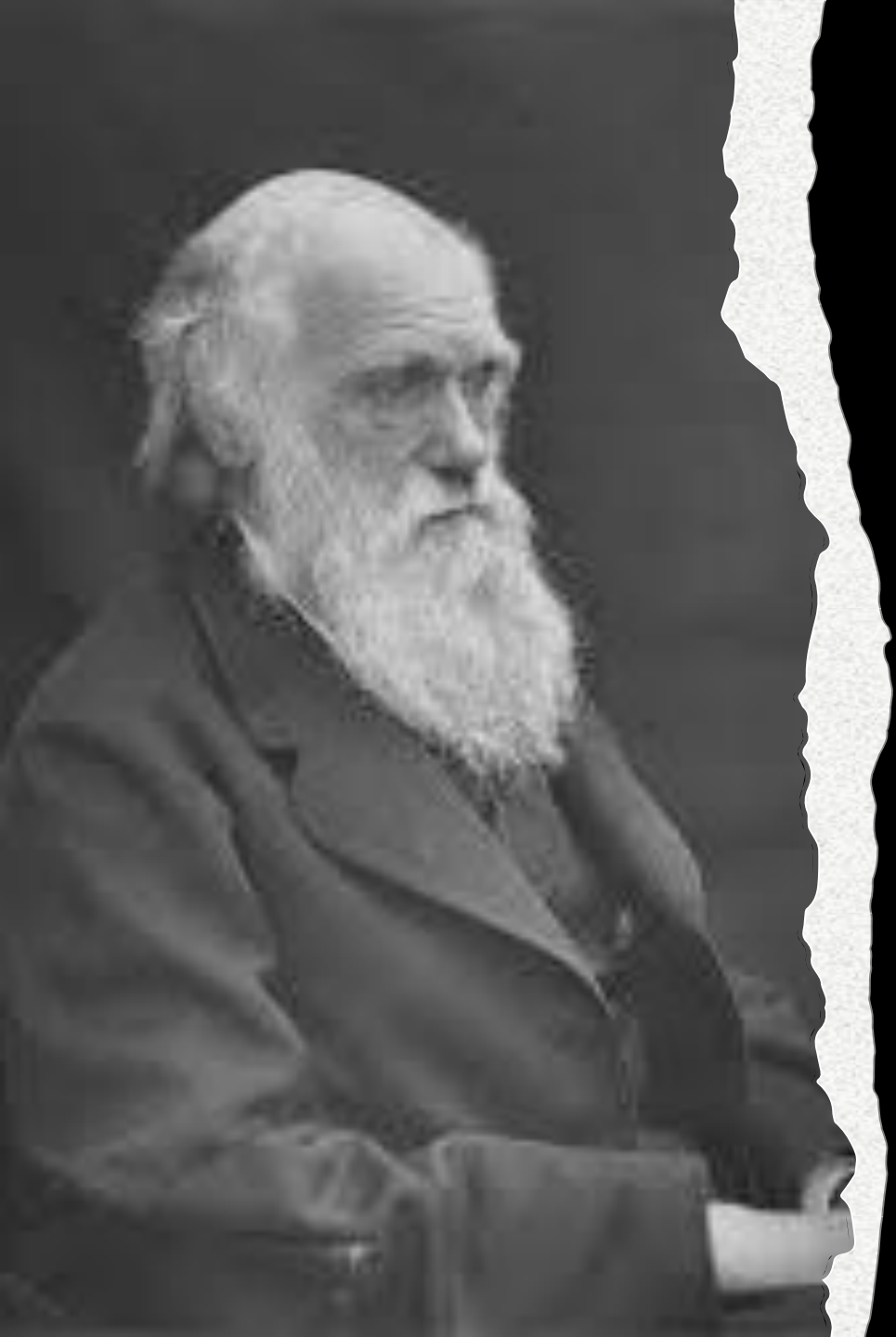
POTS: THE ROAD TO DIAGNOSIS

OVER 75%

OF POTS PATIENTS ARE MISDIAGNOSED PRIOR TO BEING DIAGNOSED WITH POTS.

DysautonomiaInternational.org

7 DOCTORS BEFORE RECEIVING A POTS DIAGNOSIS.



Famous person with POTS

For over forty years…….. suffered intermittently from various combinations of symptoms such as:

- Fatigue, malaise, vertigo, dizziness, muscle cramps, tremors, vomiting, bloating, headaches, vision issues, fatigue, nervous exhaustion, dysnpea, scalp blisters, anxiety, sense of impending death, loss of consciousness, tachycardia, insomnia, tinnitus or depression.

What is POTS?

- Postural orthostatic tachycardia syndrome (POTS) is a heterogeneous multifactorial disorder characterized by orthostatic tachycardia and intolerance, which significantly impairs quality of life.
- POTS symptoms may be induced by physical deconditioning, immunological factors, hypovolemia, autonomic dysfunction, elevated sympathetic tone, and venous pooling

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455430/

Clinical Definition of POTS

- A sustained HR increment of no less than 30 beats/minute within 10 min of standing or head-up tilt. For individuals who are 12 to 19 years old, the required HR increment is at least 40 beats/minute; and
- An absence of orthostatic hypotension (i.e. no sustained systolic blood pressure [BP] drop of 20 mmHg or more); and
- Frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position. Symptoms may include lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, and fatigue; and
- Duration of symptoms for at least 3 months; and

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

What if its not POTS?

Sinus tachycardia causes that are not POTS:

- anorexia nervosa
- primary anxiety disorders
- Hyperventilation
- Anemia
- Fever
- Pain
- Infection
- Dehydration
- Hyperthyroidism
- pheochromocytoma,
- use of cardioactive drugs (e.g. sympathomimetics, anticholinergics) or
- severe deconditioning caused by prolonged bed rest.

POTS

- Experts have estimated that 500,000 to 3,000,000 Americans could be affected, and potentially 70 million world-wide.
- One study in China reported 6.8% of adolescents met clinical criteria for POTS
- POTS is a common neurocardiovascular disease, representing approximately 32.2% of all corresponding syncope cases
- POTS is one of the most common forms of autonomic dysfunction.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455430/
https://pubmed.ncbi.nlm.nih.gov/25474569/
https://pubmed.ncbi.nlm.nih.gov/28286247/

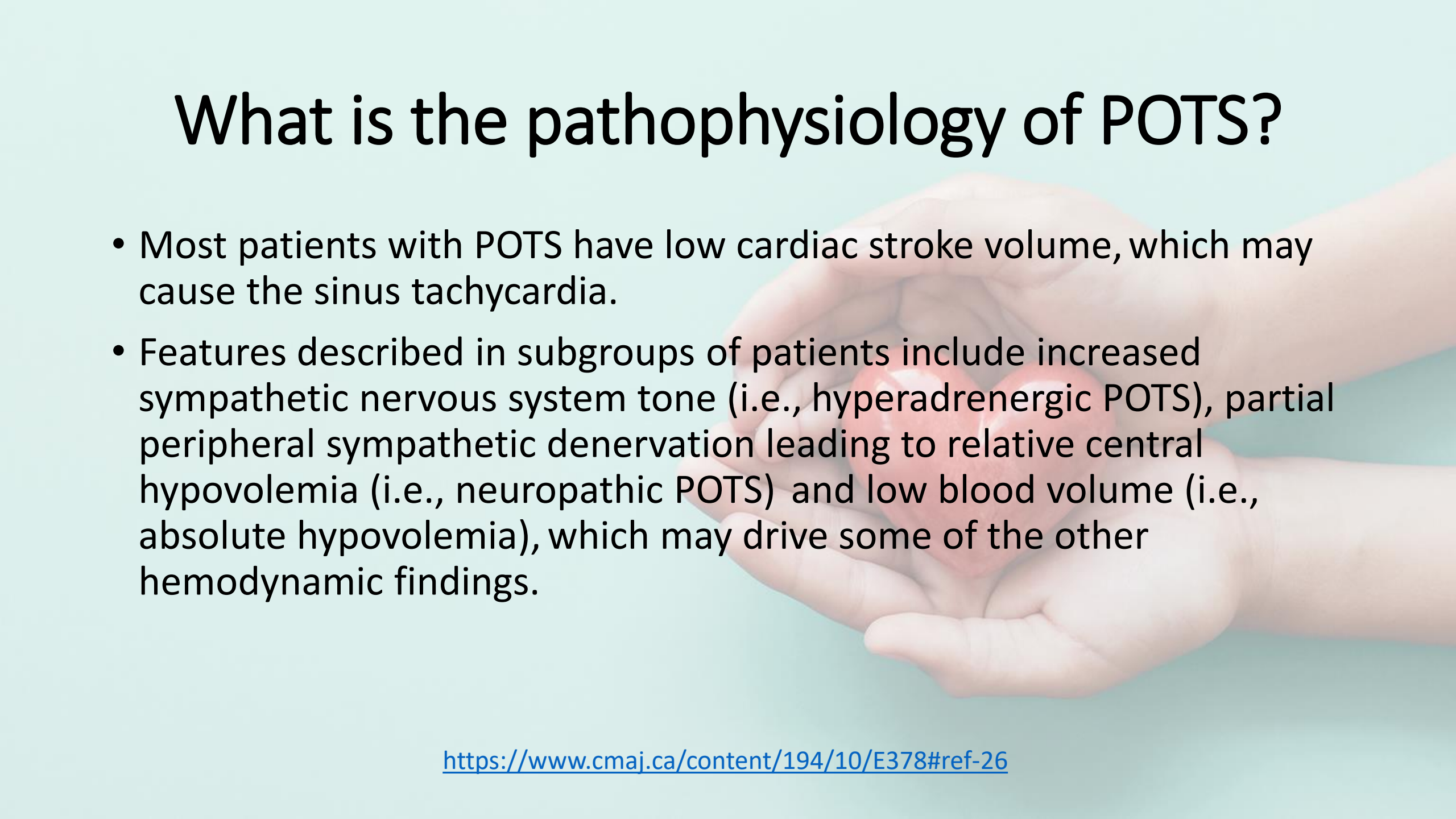
It’s not anxiety….It’s POTS

- On initial presentation, patients with POTS are frequently misdiagnosed as having an anxiety disorder. In a large survey of patients with POTS, 75-77% of respondents reported being told that they had a psychiatric or psychological disorder before their diagnosis of POTS, but this decreased to 37% after their diagnosis.
- These misdiagnoses likely occur because anxiety may be associated with tachycardia, palpitations and lightheadedness, insomnia
- I can’t sleep because I wake up with heart palpitation, when I get up to use the washroom, my heart palpitations stop me from going back to sleep

https://www.cmaj.ca/content/194/10/E378
https://pubmed.ncbi.nlm.nih.gov/http:/www.n?dopt=Abstract

What is the pathophysiology of POTS?

- Most patients with POTS have low cardiac stroke volume, which may cause the sinus tachycardia.
- Features described in subgroups of patients include increased sympathetic nervous system tone (i.e., hyperadrenergic POTS), partial peripheral sympathetic denervation leading to relative central hypovolemia (i.e., neuropathic POTS) and low blood volume (i.e., absolute hypovolemia), which may drive some of the other hemodynamic findings.



https://www.cmaj.ca/content/194/10/E378#ref-26

What is the pathophysiology of POTS?

- Postural orthostatic tachycardia syndrome may have an immunological cause.
- Many patients describe a postviral onset, **and** 15%–20% of patients with POTS report a history of an autoimmune disorder such as Hashimoto thyroiditis, rheumatoid arthritis or Sjögren syndrome

https://www.heartrhythmcasereports.com/article/S2214-0271(21)00223-2/fulltext
https://www.sciencedirect.com/science/article/pii/S0002934321004721

5 Types of POTS

There are 5 subtypes of POTS based on its pathophysiology: 3 are known and 2 are anecdotal

- Hypovolemic
- Hyperadrenergic
- Immune-related (MCAS)
- Joint hypermobility–related
- Neuropathic

What kinds of POTS are there?

1. Low blood volume or hypovolemic….SALT
2. Inflammation in the blood vessels. Immunophore (zinc and quercetin), antihistamines…like raynauds in the blood vessels
3. Adrenaline or hyper adrenergic…inositol combo, valarian, B12, magnesium, melatonin
4. Microcirculation….vitamin E and coenzyme Q10, herbs such as ginko, grape fruit seed extract, hawthorn, carnitine
5. Neurogenic ...B1, sulfate, salt, B12, CoQ10, carnitine

Hyper-adrenergic POTS

- Hyperadrenergic features can include tremulousness, anxiety, migraine and angina-like chest pain.
- Some perturbations of the autonomic nervous system, particularly the sympathetic nervous system, may be primary (i.e., central hyperadrenergic POTS) or secondary to another physiologic abnormality (e.g, hypovolemia).

Why do I care now? POTS is famous

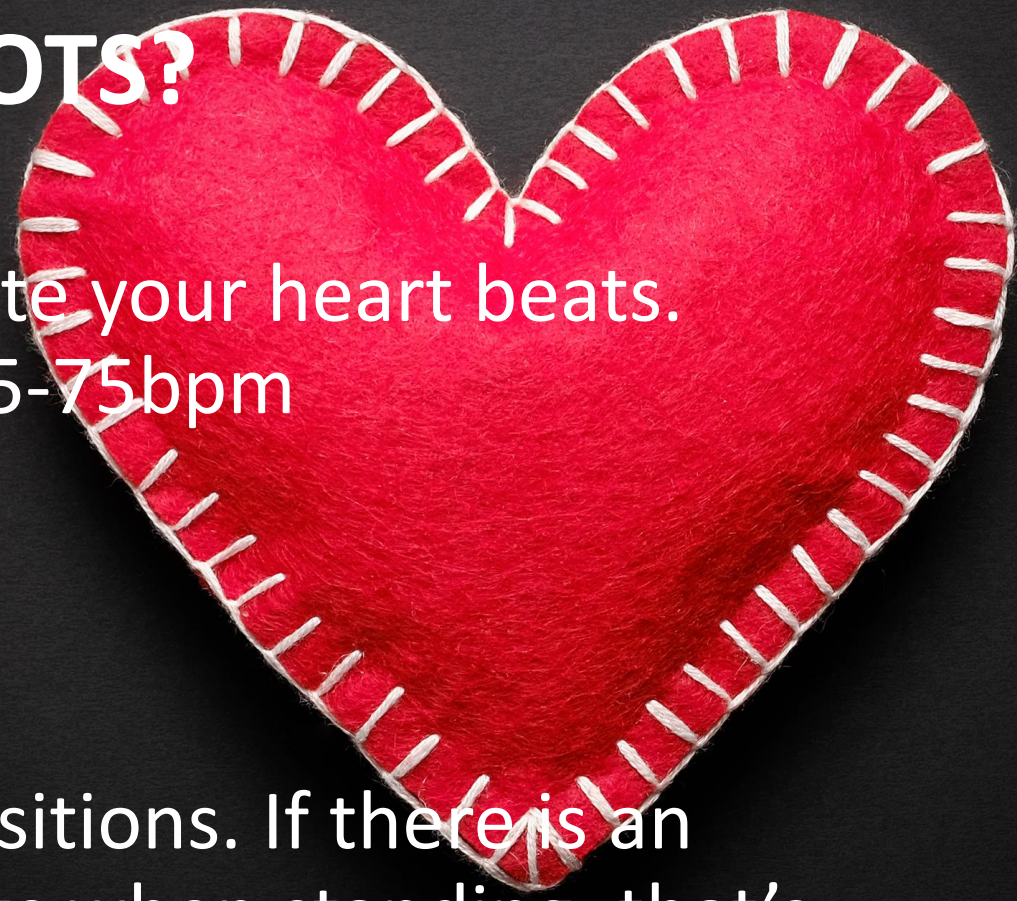
- Recent reports indicate that 2%-14% of coronavirus disease 2019 (COVID-19) survivors develop POTS and 9%-61% experience POTS-like symptoms, such as tachycardia, orthostatic intolerance, fatigue, and cognitive impairment within 6-8 months of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
- Post–acute sequelae of SARS-CoV-2 syndrome," "post–coronavirus disease 2019 (COVID-19) syndrome," "long-haul COVID," or "long COVID" and are usually defined as symptoms that persist for >4 weeks from acute illness.

Possible Mechanism for Long COVID

- Although the symptoms of Long COVID are multifarious, some researchers argue that Long COVID causes fibrin amyloid micro-clots (fibrinaloids) to block up capillaries, and thus to limit the passage of red blood cells and hence O_2 exchange, can actually underpin the majority of these symptoms of Long COVID.

https://portlandpress.com/biochemj/article/479/4/537/230829/A-central-role-for-amyloid-fibrin-microclots-in
https://pubmed.ncbi.nlm.nih.gov/34425843/
https://pubmed.ncbi.nlm.nih.gov/34896917/

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

- 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.

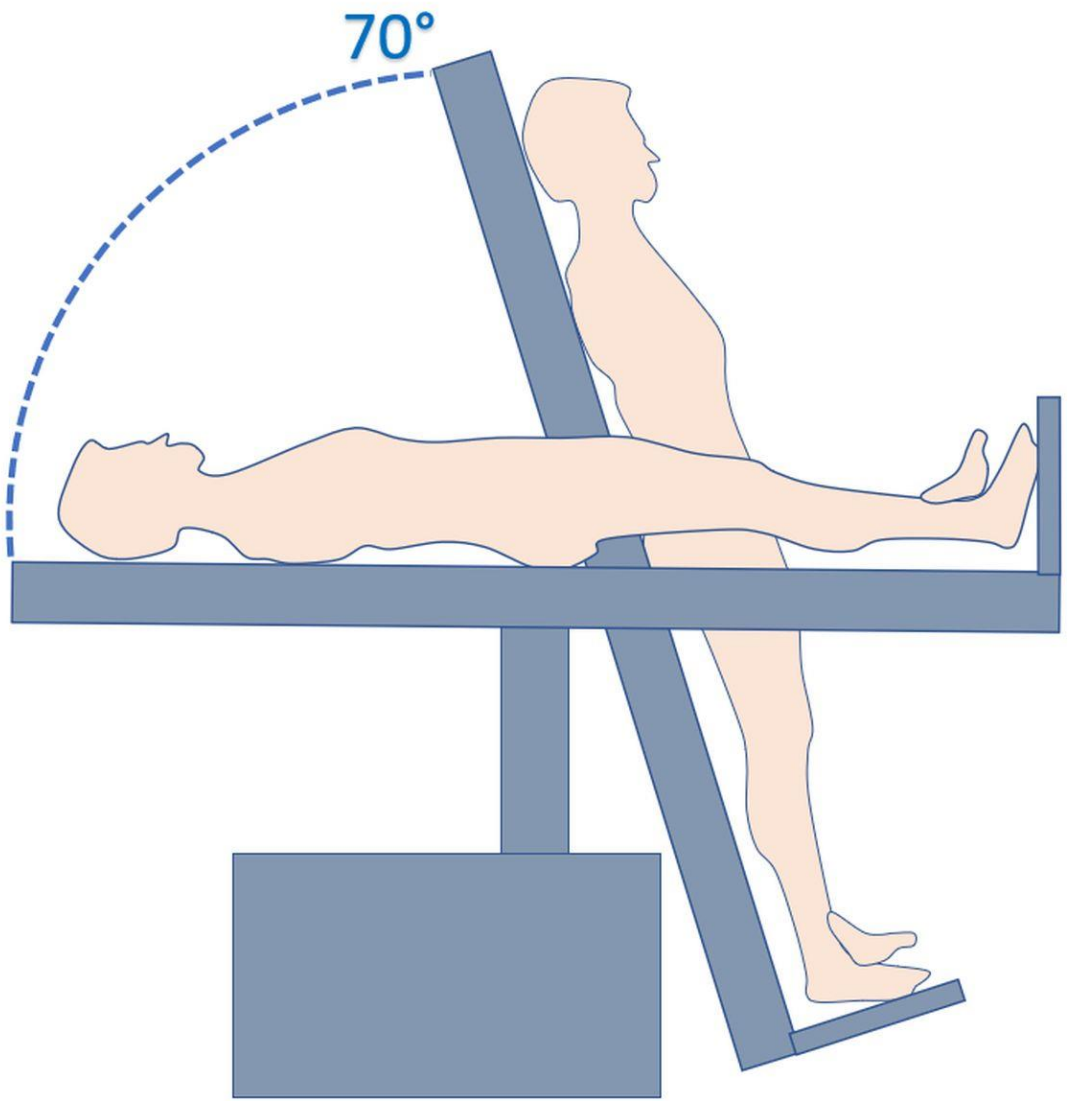
How to assess for POTS

Heart rate and blood pressure must be measured when the patient has been supine for 5–10 minutes to allow fluid equilibration, and then after standing for 1 minute, 3 minutes, 5 minutes, 8 minutes and 10 minutes.

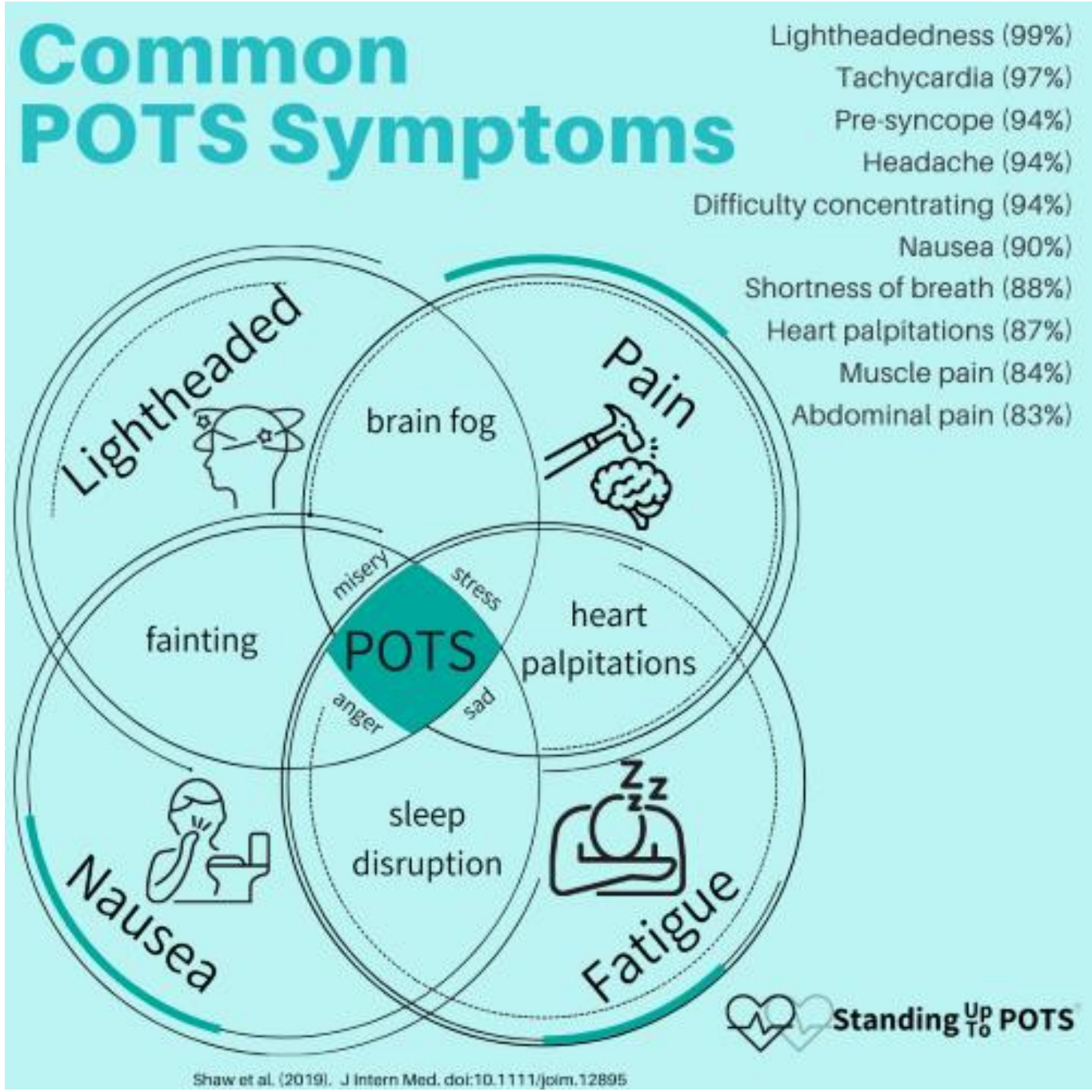
To diagnose excessive orthostatic tachycardia (required for POTS), patients should have a sustained heart rate increase of at least 30 beats/min (for adults) or at least 40 beats/min (for patients aged 12–19 yr) on at least 2 of the readings taken when standing. The systolic blood pressure should not fall by more than 20 mm Hg.

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

How to assess for POTS

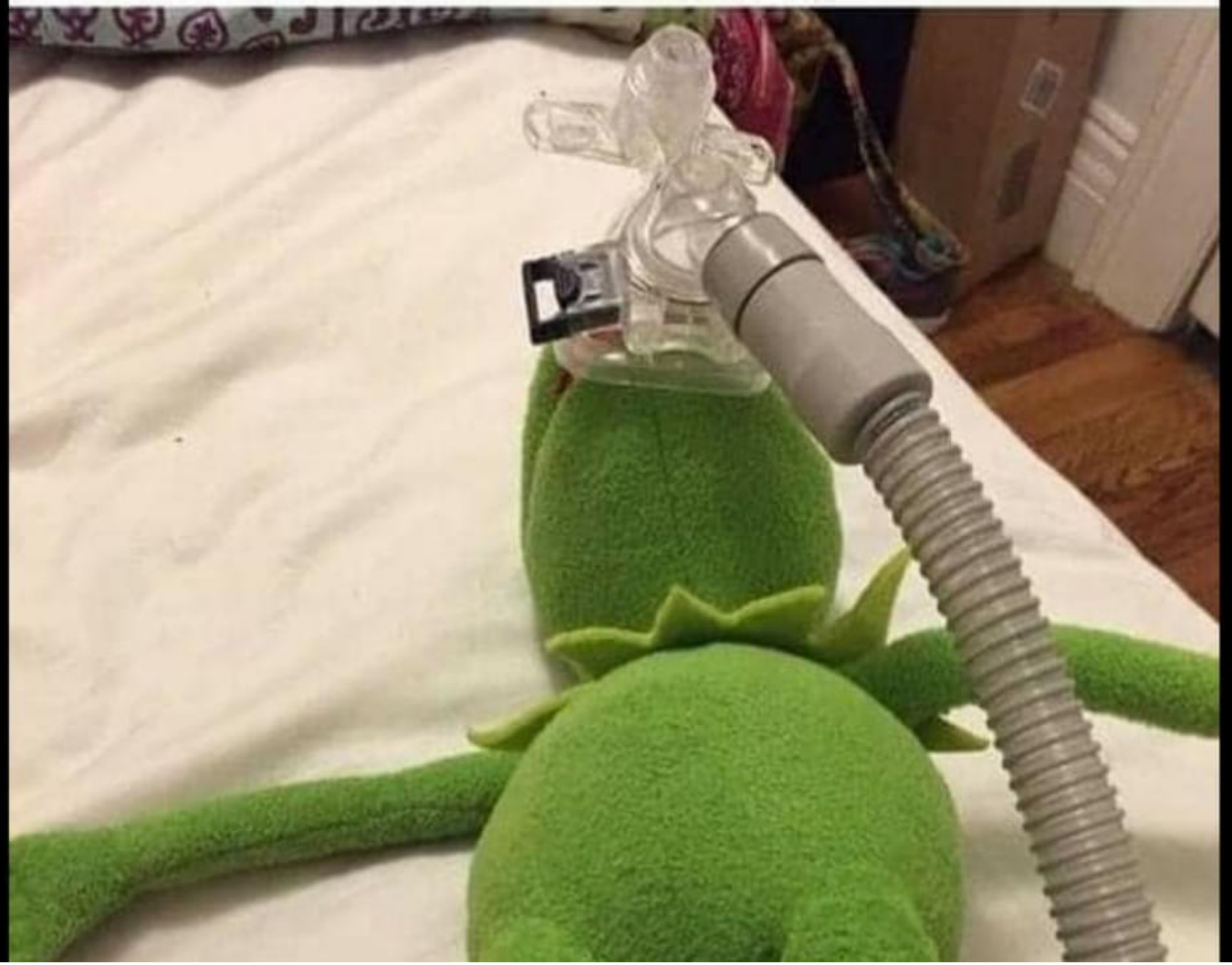


- A tilt table test, sometimes known as a passive head-up tilt test (HUTT).
- This procedure is used to record both blood pressure and heart rate each minute, while the patient is tilted on a table at varying levels.
- IV takes blood to measure adrenaline.
- Blood pressure cuff on both arms and electrical activity of the heart are taken.



https://www.standinguptopots.org/livingwithpots/pots-symptoms

Me after I put the fitted sheet on the bed by myself



POTS Definition, Assessment, and Naturopathic Treatment by Dr Carissa Doherty, ND

What is POTS?

Symptoms of POTS are as follows (2):

Cardiovascular symptoms:

Lightheadedness (99%)

Tachycardia (97%)

Pre-syncope (94%)

Shortness of breath (88%)

Palpitations (87%)

Chest pain (79%)

Low blood pressure (71%)

Syncope (36%)

Gastrointestinal symptoms:

Nausea (90%)

Stomach pain (83%)

Bloating (79%)

Constipation (71%)

Diarrhea (69%)

Neurological symptoms (head and brain):

Headache (94%)

Difficulty concentrating (94%)

Memory problems (87%)

Tremulousness (78%)

Neurological symptoms (eyes and ears):

Blurred vison (75%)

Dry mouth (66%)

Dry eyes (60%)

Neurological symptoms (extremities):

Muscle pains (84%)

Cold feet (94%)

Muscle weakness (83%)

Hand coldness (82%)

Hand tingling (76%)

Foot tingling (67%)

Hand numbness (65%)

Foot numbness (58%)

Skin symptoms:

Skin flushing (69%)

Bladder symptoms:

Frequent urination (68%) (2)

POTS IS MORE COMMON THAN WELL-KNOWN MEDICAL CONDITIONS LIKE MULTIPLE SCLEROSIS.

DYSAUTONOMIA INTERNATIONAL

Where does POTS fit in a case?

- POTS has an impact on the circulatory system in both blood volume and inflammation.
- If a patient has POTS and say, any other condition, the POTS mechanically impacts the successful treatment of any thing else.
- You need blood to deliver your protocol and this condition stops effective blood flow

- **<u>Fix the POTS first in a case</u>**

Laboratory Values in POTS

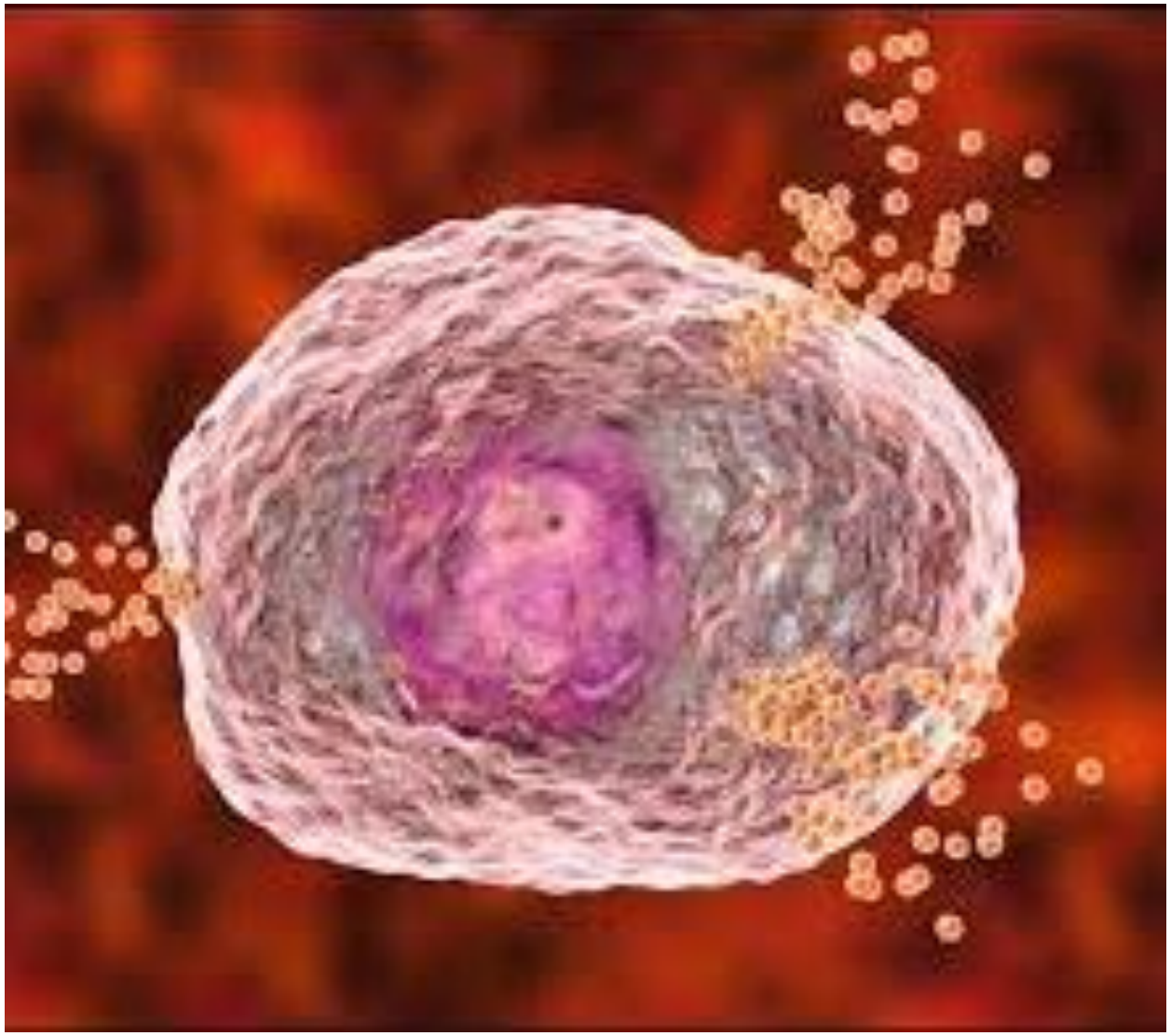
- There is also a growing body of evidence reporting the presence of antinuclear antibodies, antiphospholipid antibodies, α_1, β_1, and β_2 adrenergic receptors antibodies, angiotensin 2 type 1 receptor antibodies, ganglionic N-type and P/Q-type acetylcholine receptor antibodies, opioid-like 1 receptor antibodies, and muscarinic M2 and M4 antibodies in patients with POTS.
- and Mayo Clinic's serum autoimmune dysautonomia panel including ganglionic acetylcholine receptors (G-AChRs) antibody, autoantibodies to cardiovascular G-protein.

https://www.heartrhythmjournal.com/article/S1547-5271(22)02185-3/fulltext

More Lab work we have access to

- Blood work, including morning cortisol, renal function, antinuclear antibody (ANA), ferritin level, complete blood count (CBC), thyroid-stimulating hormone (TSH), urine metanephrine

https://testcatalog.org/show/DYS2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455420/



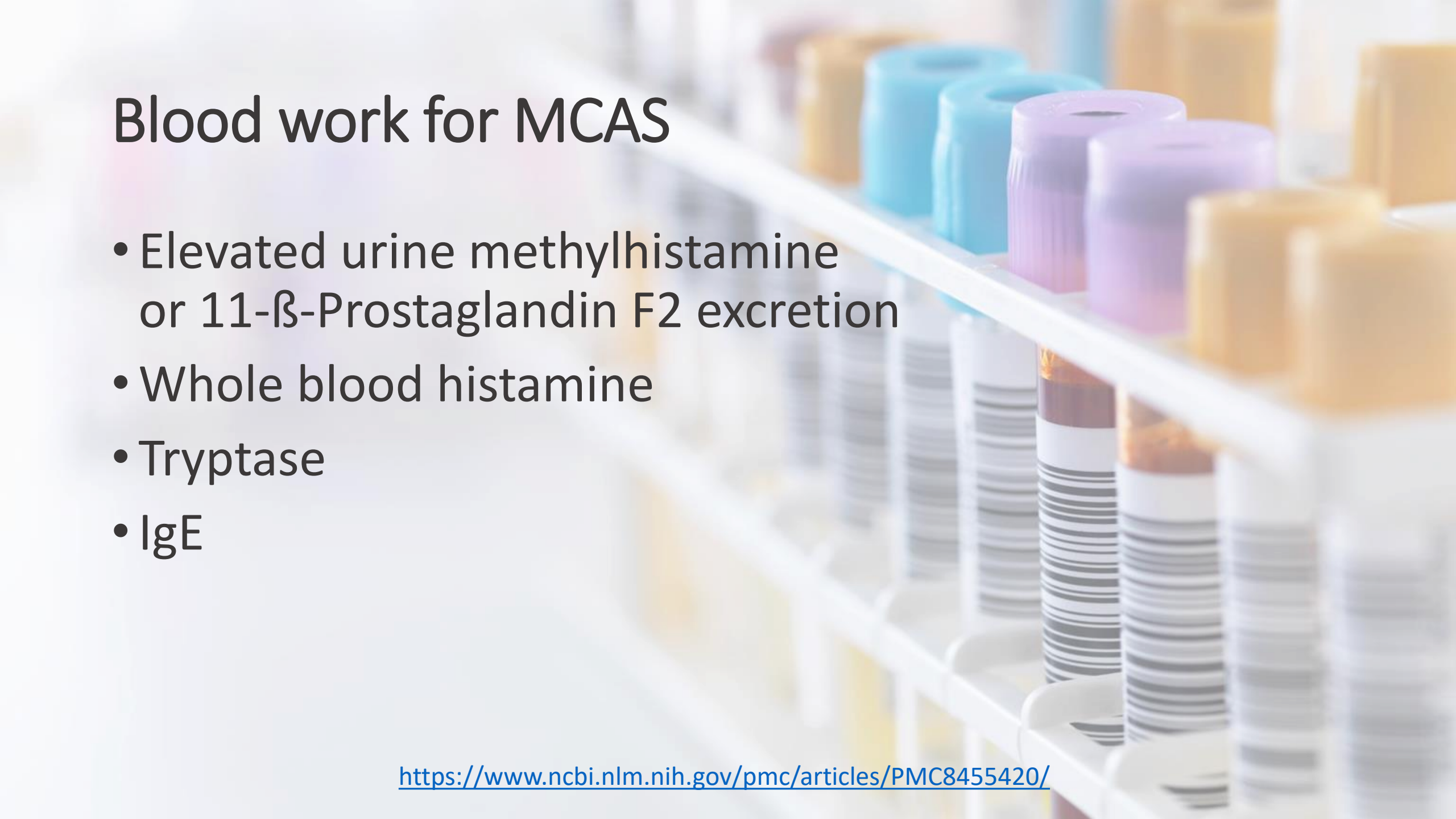
Mast Cell Activation Syndrome

- Mast Cell Activation Syndrome (MCAS) is defined by the combination of 1) typical symptoms, 2) laboratory abnormalities and 3) response to treatment.
- These three factors form a working diagnosis for MCAS and can be applied to patients with recurrent flushing, anaphylaxis, recurrent crampy abdominal pain, diarrhea, and itching.

https://www.autonomicneuroscience.com/article/S1566-0702(17)30338-7/fulltext

Blood work for MCAS

- Elevated urine methylhistamine or 11-ß-Prostaglandin F2 excretion
- Whole blood histamine
- Tryptase
- IgE

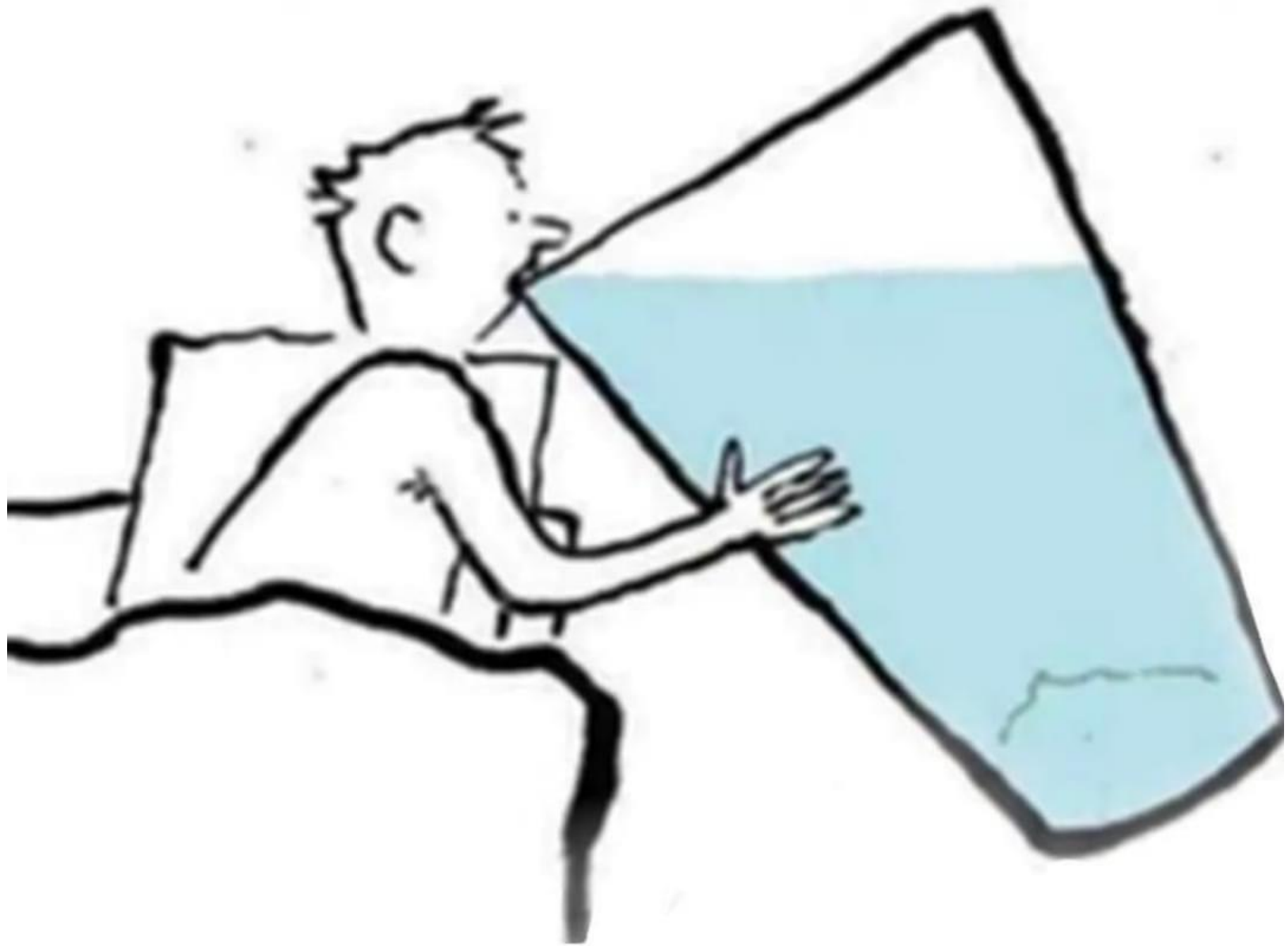


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455420/

Initial POTS Treatments

- Nonpharmacological treatments
    - Water 3 L/d
    - Salt 5 mL/d (2 tsp/d)
    - Waist-high compression garments
- Pharmacological treatments
    - If standing heart rate very high: propranolol
    - 10–20 mg, 4 times per day
    - If standing heart rate very high and β-blocker is contraindicated: ivabradine 5 mg 2 times per day
    - If standing heart rate is not too high and blood pressure is low: midodrine 5 mg orally every 4 hours, 3 times per day (8 am, noon, 4 pm)

https://www.jacc.org/doi/abs/10.1016/j.jacc.2021.03.005
https://www.cmaj.ca/content/194/10/E378#ref-41



How low can you go…Blood Volume

- The imposition of an orthostatic stress, such as standing, causes a rapid gravitational displacement of approximately 500-700 mL of central blood volume into the splanchnic and lower extremity vascular beds.
- This venous pooling decreases the return of blood to the heart, producing a thoracic blood volume drop of approximately 30%, which decreases stroke volume and cardiac output
- Although the mechanisms of POTS are heterogenous, its effects resemble well-known forms of hypovolemia, with reduced systemic venous return and reduced cardiac output (CO)
- Therefore, **treatment has included attempts at repletion of blood volume**

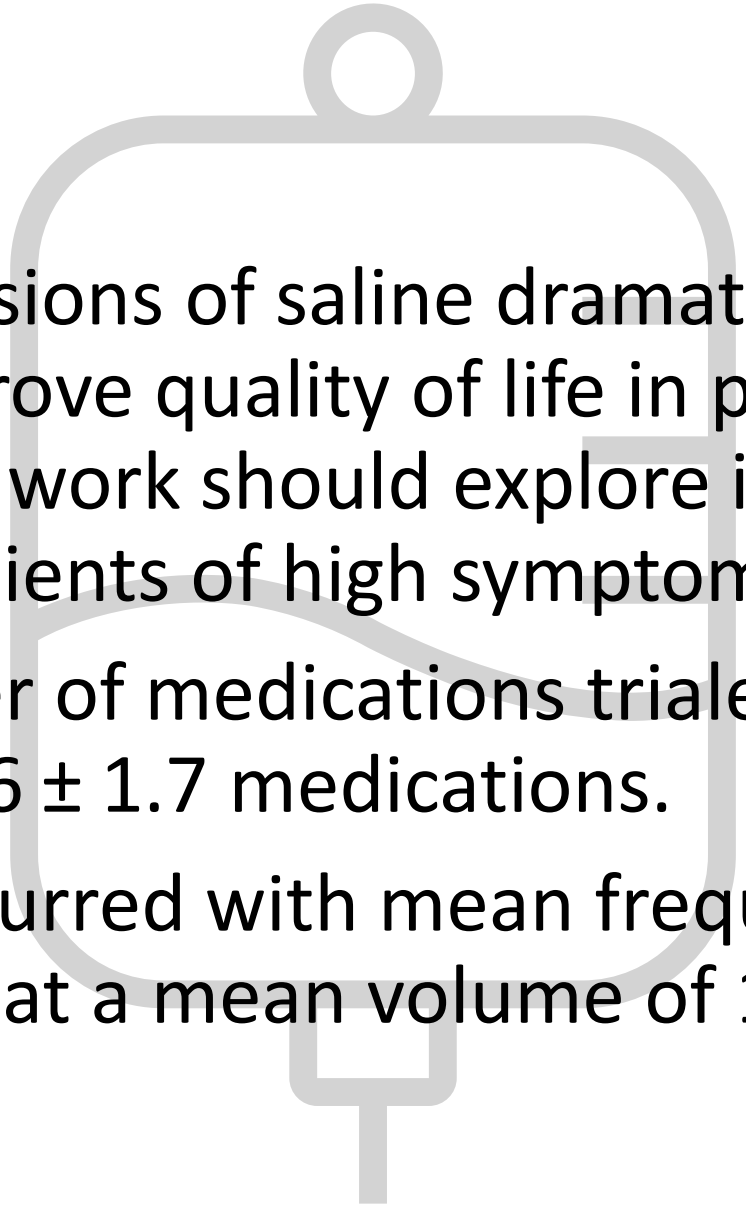
https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltexthttps://www.sciencedirect.com/science/article/pii/S1566070222000108

Salt, Salt and more Salt by IV

- More direct methods have been used to mitigate the effects of orthostasis, including the administration of intravenous (IV) saline solution, which can improve all forms of orthostatic intolerance by increasing central blood volume and venous return.
- Thus, saline may prevent syncope and improve orthostatic intolerance and HR changes in patients with POTS

https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltext

Saline IV



- Intermittent IV infusions of saline dramatically reduce symptoms and improve quality of life in patients suffering from POTS. Further work should explore its efficacy as a bridge study for patients of high symptomatic severity.
- The average number of medications trialed before referral for IV hydration was 3.6 ± 1.7 medications.
- Saline infusions occurred with mean frequency of 11.3 ± 8.5 days and at a mean volume of 1.5 ± 0.6 litre per infusion

https://pubmed.ncbi.nlm.nih.gov/28185102/

But what is better? IV or oral?

- IV saline is expensive, there is a repeated need for infusions, and unacceptable risks (eg, bruising, infection) of chronic central venous catheterization.
- Alternatives to IV saline, such as oral salt and water, have been recommended to reduce orthostatic intolerance symptoms
- One study at 2000mg salt found that oral rehydration solution (salt with water and glucose or ORS) is a convenient, safe, and effective therapy for short- term relief of orthostatic intolerance.

https://www.jpeds.com/article/S0022-3476(19)30893-5/fulltext
https://www.sciencedirect.com/science/article/pii/S1566070222000108

Salt? But how much? ALOT!

- Patients are encouraged to consume electrolyte beverages to increase osmotic pressure and keep the fluids in the intravascular space.
- The rationale is expansion of intravascular volume to compensate for intravascular hypovolemia and orthostatic pooling.
- Consensus-based guidelines have recommended, in addition to drinking 2 to 3 L of water daily, sodium chloride, 8 g/d to 12 g/d (350–520 mmol/d sodium)

https://www.sciencedirect.com/science/article/pii/S1566070222000108

Medications for POTS

- Most medications that are used in POTS target:
  - Reduction of upright sinus tachycardia or sympathetic tone
  - Enhanced vasoconstriction or augmented blood volume

https://pubmed.ncbi.nlm.nih.gov/34127505/

https://www.cmaj.ca/content/194/10/E378#ref-41

Drug	Dosing	Quality of evidence	Adverse effects	Other considerations
Heart rate inhibitors				
Propranolol	10–20 mg orally up to 4 times daily	Moderate	Hypotension, bradycardia, bronchospasm	Can worsen asthma
Ivabradine	2.5–7.5 mg orally twice daily	Moderate	Visual disturbances, bradycardia	Expensive
Pyridostigmine	30–60 mg orally up to 3 times daily	Low	Increased gastric motility and cramping	
Vasoconstrictors				
Midodrine	2.5–15 mg orally 3 times daily	Moderate	Headache, scalp tingling, supine hypertension	Avoid within 4 hr of bedtime to avoid supine hypertension
Sympatholytic drugs				
Methyldopa	125–250 mg orally twice daily	Low	Hypotension, fatigue, brain fog	Start with a low dose
Clonidine	0.1–0.2 mg orally 2–3 times daily or long-acting patch	Low	Hypotension, fatigue, brain fog	Start with a low dose; withdrawal can lead to rebound tachycardia and hypertension
Blood volume expanders				
Fludrocortisone	0.1 to 0.2 mg orally per day	Low	Hypokalemia, edema, headache	Serum potassium should be monitored
Desmopressin	0.1 to 0.2 mg orally per day, as needed	Low	Hyponatremia, edema	Serum sodium should be monitored if used chronically

https://www.cmaj.ca/content/194/10/E378#ref-41

Medications for POTS

- Propranolol blocks both β_1- and β_2-adrenergic receptors. A 2009 randomized crossover study found that low-dose oral propranolol improved tachycardia and symptoms on standing
- Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel (I_f) blocker that lowers sinus node rate without β-blocker effects.
- Pyridostigmine is a peripheral acetylcholinesterase inhibitor that increases synaptic acetylcholine and can acutely decrease upright heart rate in patients with POTS

https://pubmed.ncbi.nlm.nih.gov/http:/www.n?dopt=Abstract

Medications for POTS

- Midodrine is a peripheral α_1-adrenergic receptor agonist prodrug that enhances venous return, cardiac preload and stroke volume. It may be most beneficial in patients with POTS accompanied by low blood pressure
- Central sympatholytic drugs can be useful in patients with increased sympathetic activity or hyperadrenergic features. Clonidine and methyldopa are both antihypertensive medications that can decrease central sympathetic nerve traffic and norepinephrine release from peripheral sympathetic neurons. Both medications have narrow therapeutic ranges, and it is important to start with lower doses.

Medications for POTS

- Drugs that expand blood volume can be useful if nonpharmacologic approaches to blood volume expansion are not successful, or if low blood volume is objectively documented by an assessment of blood volume using nuclear medicine
- Fludrocortisone (0.1–0.2 mg daily) is a synthetic version of aldosterone that promotes renal sodium absorption and secondary blood volume expansion; hypokalemia is a potential adverse effect.

https://www.cmaj.ca/content/194/10/E378#ref-47
https://pubmed.ncbi.nlm.nih.gov/17630589/?dopt=Abstract

Procedural treatments

- Radiofrequency ablation of the sinus node has been reported as a treatment for POTS.
- Both the Heart Rhythm Society and the Canadian Cardiovascular Society currently recommend against this approach, and any other procedural treatment for POTS, based on a lack of evidence for benefit and potential risks of serious harm.

https://www.cmaj.ca/content/194/10/E378#ref-51

Low-Dose Naltrexone (LDN) and POTS

- (1 mg every night as opposed to dose escalation to ideal dose of 4.5 mg)
- Ultra-low-dose naltrexone (1mg) for 6 weeks improved body pain, mood, memory, sleep, flushing, food and odour sensitivities and paraesthesia: 7% decrease in POTS and 17% decrease in MCAS severity scores.
- LDN is inexpensive, safe and appeared to provide effective, adjunctive therapy in both MCAS and POTS.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778345/

Intravenous immunoglobulin (IVIg) and POTS

- IVIg 1.5 g/kg (Privigen) and 125 mg methylprednisolone were administered monthly.
- When co-administered with LDN, six days after the first IVIg infusion, syncope, tinnitus, anal outlet disorder and vascular spasm ceased.
- Capillary refill time was >1 min before IVIg and reduced to <2 s. The next two infusions further improved body pain, weakness, vertigo, ability to eat and facial changes. Subsequent infusions maintained symptomatic improvement but the efficacy did not improve further
- The platelet counts normalized when measured after the sixth infusion.
- IVIg appeared to be effective for multiple manifestations of POTS but this treatment is expensive and has potential significant side effects.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778345/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5778345/

POTS and B12

- Vitamin B12 is involved in the production of adrenaline from noradrenaline and it is also involved in catecholamine degradation
- B12 is involved in myelin synthesis
- The current study aimed to investigate the association between vitamin B12 levels and postural orthostatic tachycardia syndrome (POTS) during adolescence when accelerated myelin synthesis increases the vitamin B12 need.
- A low vitamin B12 level was defined as ,300 pg/mL

https://tahomaclinic.com/Private/Articles4/PosturalTachycardia/Oner%202014%20-%20Postural%20orthostatic%20tachycardia%20syndrome%20(POTS)%20and%20vitamin%20B12%20deficiency%20in%20adolescents.pdf

POTS and B12

- Some studies have shown that the functions of sympathetic postganglionic nerves require vitamin B12
- Additionally, autonomic dysfunction, POTS, and syncope have been shown to be common in diseases related to myelinization deficits
- Both peripheral and autonomic neuropathy develop in vitamin B12 deficiency, and treatment improves autonomic nervous system functions more rapidly.

Methylcobalamin

<u>James Neubrander Protocol</u>:

- 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

Suggested syringe

- Insulin syringe ultra fine (6mm or 8 mm)
- 3/10 ml
- 15/64”
- 31 Gauge

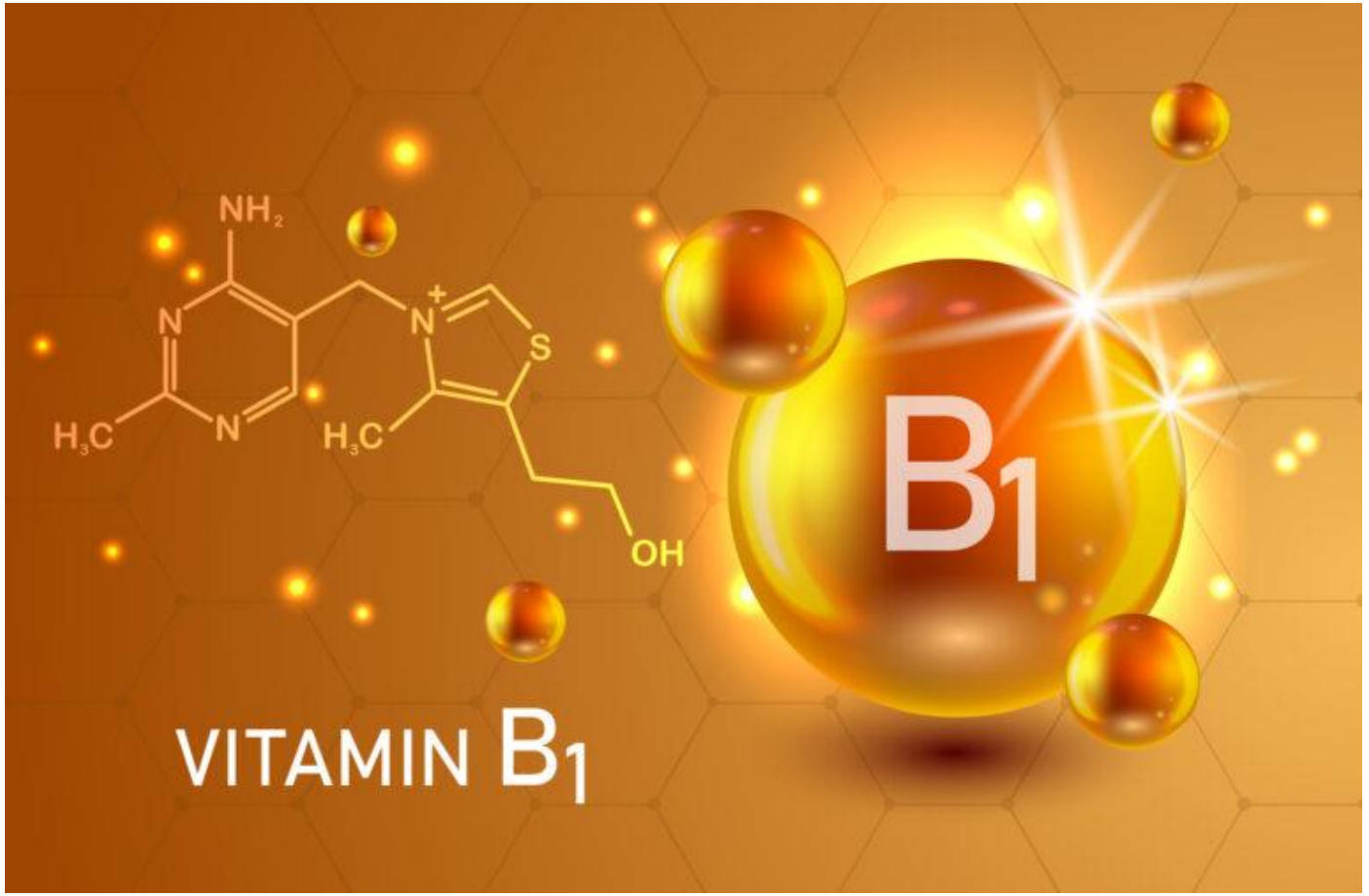
POTS and Melatonin

- Melatonin produced varying effects on HR and blood pressure (BP) in healthy adults
- Significantly decreased standing plasma norepinephrine levels in healthy women
- Melatonin did not improve VOSS score compared to placebo
- Vanderbilt Orthostatic Symptom Score (VOSS), the VOSS consists of 9 orthostatic symptoms rated on a scale of **0 (no symptom) to 10 (worst the participant has experienced)** at the end of each HUT.
- These symptoms are mental clouding, blurred vision, shortness of breath, rapid heartbeat, tremulousness, chest discomfort, headache, lightheadedness, and nausea.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999238/
https://pubmed.ncbi.nlm.nih.gov/9486289/

POTS and B1

- A small subset of patients with POTS may have vitamin B1 deficiency. Testing for vitamin B1 deficiency and correcting the deficiency is recommended.



https://pubmed.ncbi.nlm.nih.gov/28531358/

Vitamin E

- Vitamin E, comprising eight vitamers (four tocopherols (TFs) and four tocotrienols (TTs)), is the most abundant liposoluble antioxidant compound in the human body, and its modulatory effects regarding signal transduction, cellular pathways (e.g., NF-κB signaling), and gene expression (e.g., pro-inflammatory
cytokines) have recently gained notoriety

- Vitamin E has to be methylated to be active in the body

- Vitamin E has known anti-clotting properties, elastin degradation, immunomodulation, and managing vascular health.

https://pubmed.ncbi.nlm.nih.gov/19623831/
https://cardiab.biomedcentral.com/articles/10.1186/s12933-021-01359-7
file:///Users/carissadoherty/Downloads/immuno-01-00003%20(1).pdf

17 Arfors, K.-E., Cockburn, J., and Gross, J., *Microvasc. Res.* (in t
18 Born, G. V. R., and Cross, M. J., *J. Physiol., Lond.*, 168, 178–195
19 Braasch, D., and Rogausch, H., *Pflügers Arch. ges. Physiol.*, 32
20 Kwant, W. O., and Seeman, P., *Biochim. biophys. Acta*, 193, 338–
21 Brown, C. H., Leverett, L. B., Lewis, C. W., Alfrey, C. P., and
J. lab. clin. Med., 86, 462–471 (1975).
22 Richardson, P. D., *Bull. N.Y. Acad. Med.*, 48, 379–382 (1972).
23 Packham, M. A., and Mustard, J. F., in *Platelets: Produc
Transfusion and Storage* (Gruner and Stratton, New York, 197

Inhibition of plasmin-mediated fibrinolysis by vitamin E

BIOLOGICAL effects attributed to vitamin E i
maintenance of cell membrane integrity, inh
enzyme-dependent lipid peroxidation, partici
oxidative phosphorylation, and a general, non
antioxidant effect[1]. In spite of these observa
physiological function of the vitamin remains
Natural deficiency in man has been invoked in
genesis of several disorders, with convincing evider
to a specific type of haemolytic anaemia[2]. Thera
vitamin E has its advocates in treatment of
vascular and thromboembolic disease, although d
tion for its efficacy is meagre[3]. Although it is
non-toxic[4], little is known about adverse effects of
dietary vitamin E.

Plasminogen is the plasma proenzyme which,
version to its active form, plasmin, is considered re

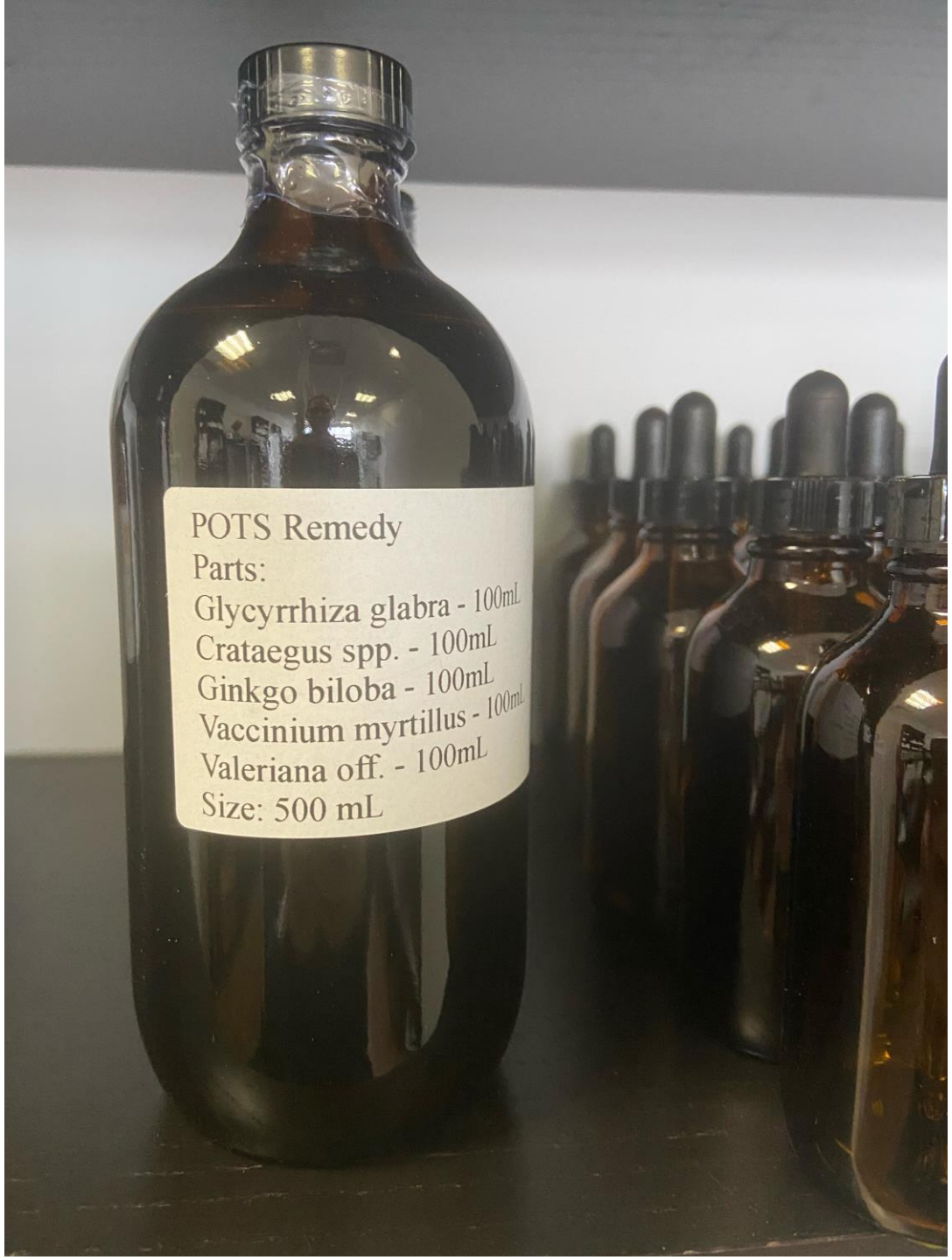
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC41118/?page=1

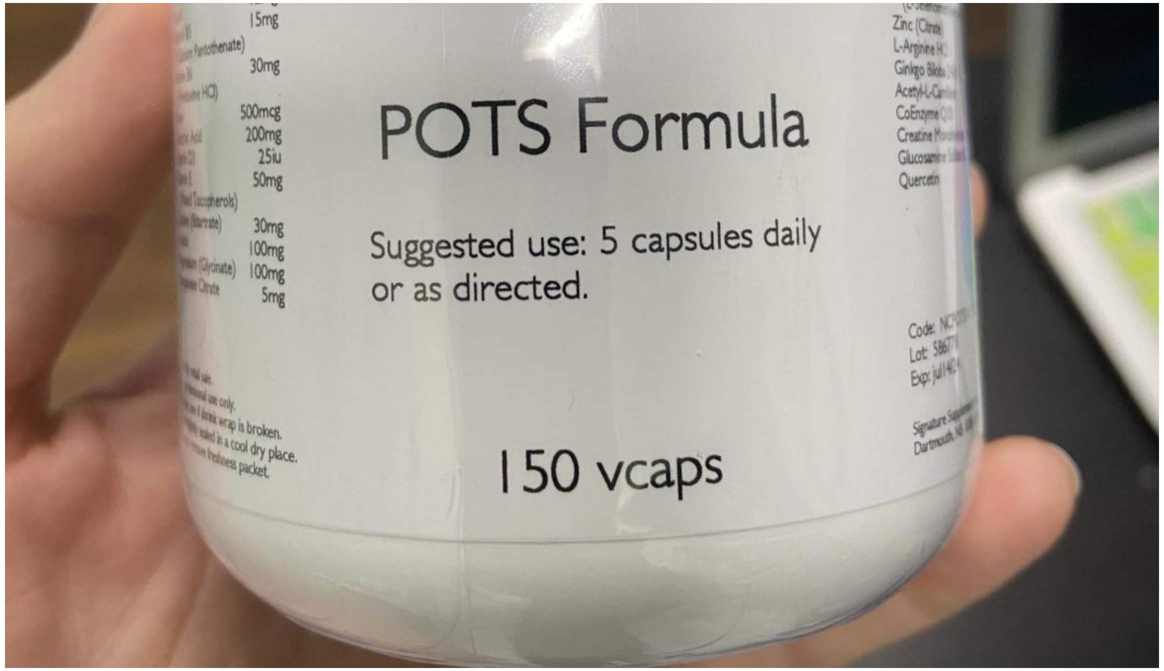
Vitamin E high dosing needs vitamin K

- As vitamin E is a fat soluble vitamin, there is a safe upper limit of 100-300mg/kg
- Vitamin E has slight blood thinning properties and may cause easy bruising and bleeding.
- Once a formula with the proper vitamin E/vitamin K ratio is used, there may be nose bleeds or telangiectasia if there is carnitine deficiency or a fat absorption issue. That may have to be addressed first.

POTS Botanical

Dose - 2 TBSP BID




POTS Formula
Suggested use: 5 capsules daily or as directed.
150 vcaps
Quercetin

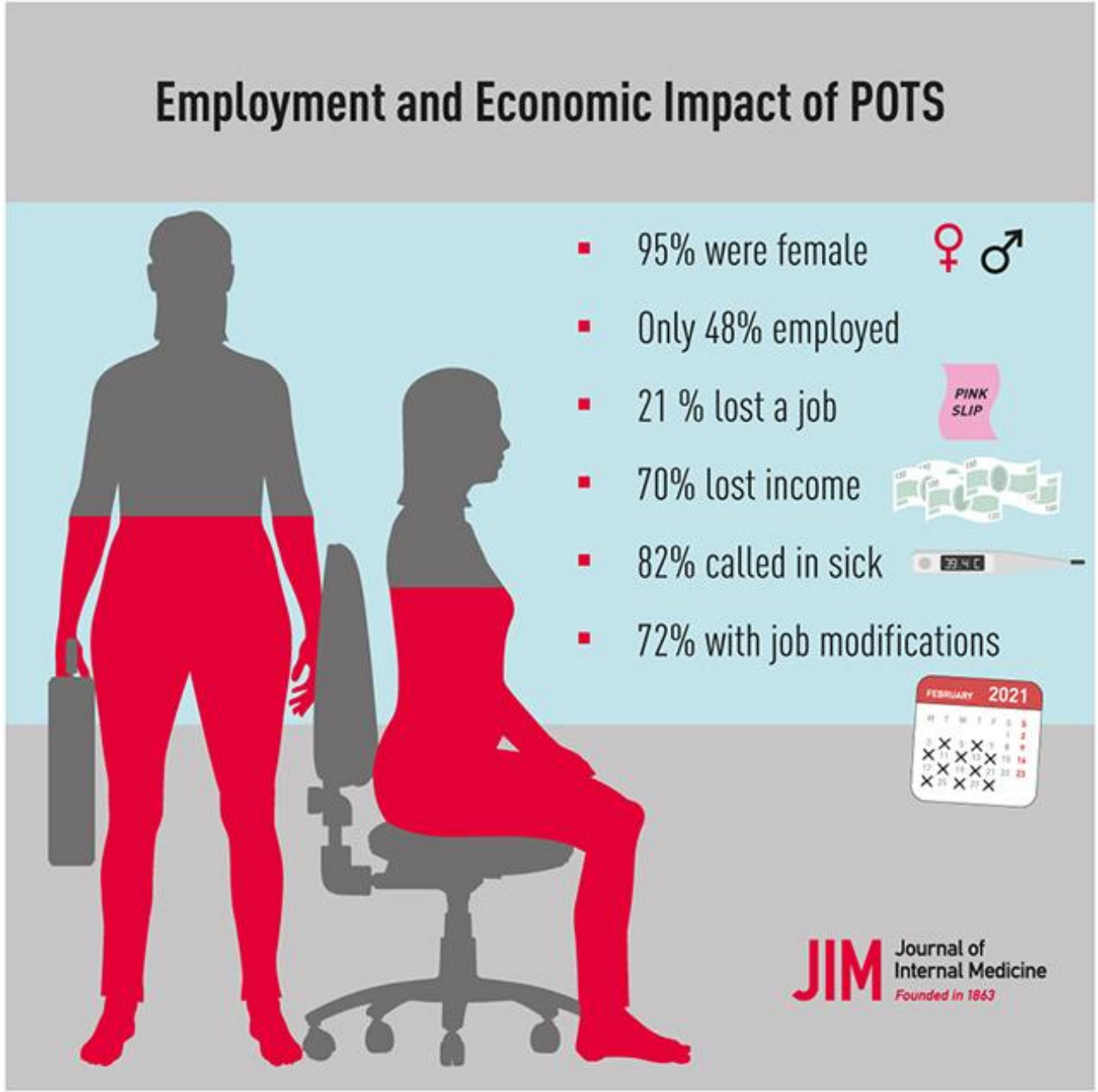
POTS supplement

- Arginine (L-arginine): 500mg
- Biotin (Vitamin B7) 500mcg
- Carnitine (acetylene-L-carnitine 250mg
- Choline 30mg
- Coenzyme Q10 (ubiquinone)125mg
- Creatine 300mg
- Inositol (Myo-inositol) 100mg
- Magnesium glycinate 100mg
- Manganese 50mcg
- Molybdenum 50mcg
- Niacin (Vitamin B3) 12 mg
- Pantothenic Acid (Vitamin B5) 15mg
- Potassium 100mg
- Pyridoxine (Vitamin B6) 30mg
- Riboflavin (Vitamin B2) 30mg
- Selenium 30mcg
- Benfotamine (Vitamin B1) 100mg
- Vitamin C 200mg
- Vitamin D 10 mcg
- Vitamin E 50mg Mixed or Total vitamin E
- Zinc 15mg
- Quercetin 250mg
- Ginko 30mg
- Glucosamine sulfate 15mg

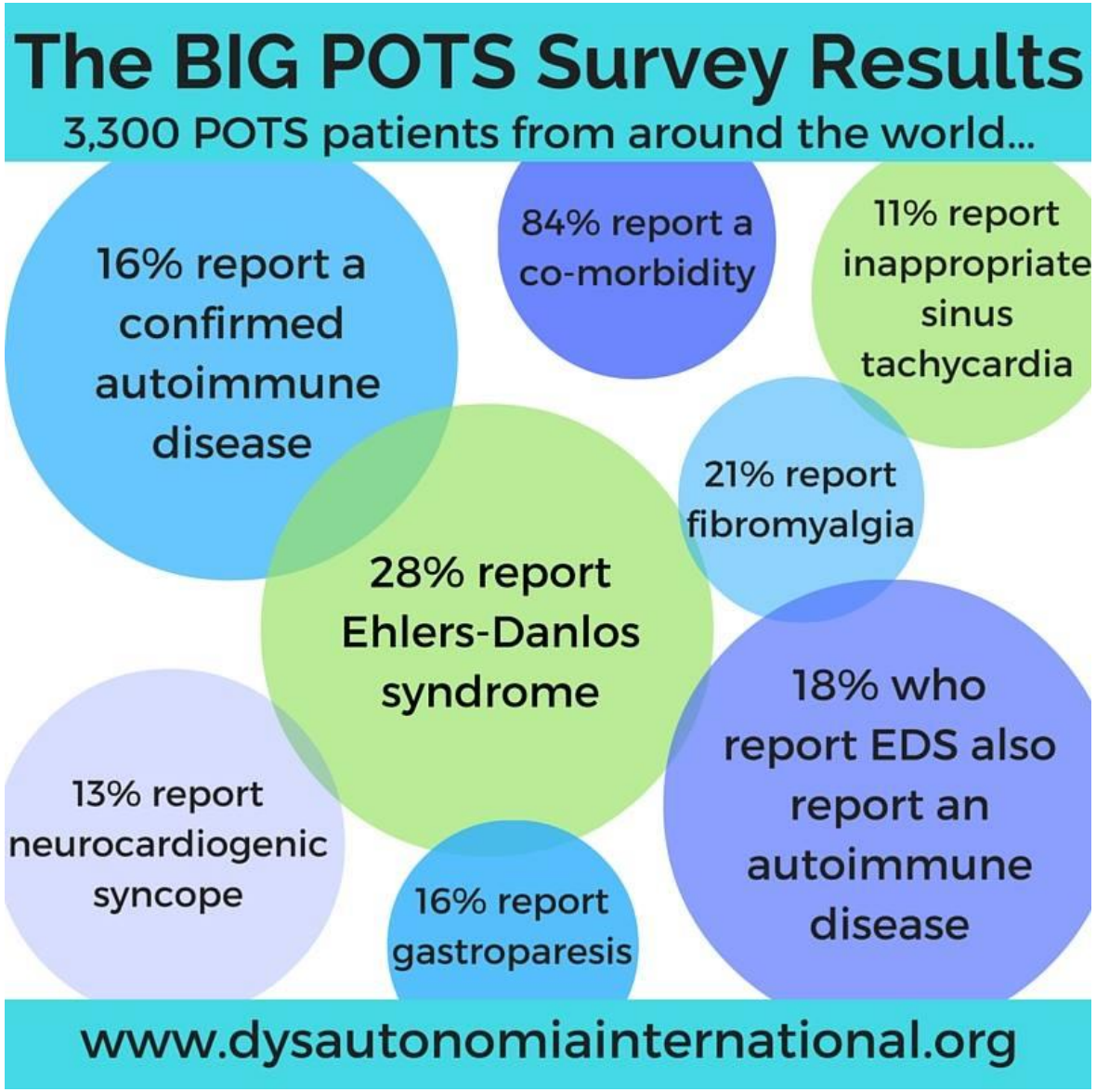
Economic cost of POTS

- 5,556 adult (age ≥ 18 years) participants with a physician-confirmed diagnosis of POTS. The majority of participants were female (95%). Forty-eight percent of participants reported employment during the three months prior to the survey, and of these participants, 66.8% would work greater hours if not for illness limitations.
- Over two-thirds (70.5%) of participants have lost income due to POTS symptoms, with 36.0% of the total cohort losing more than $10,000 USD in the 12 months prior to the survey
- Almost all (95%) participants reported POTS-related out-of-pocket medical expenses since diagnosis, with 51.1% of participants spending $10,000 USD or more.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9156448/



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9156448/


The BIG POTS Survey Results
3,300 POTS patients from around the world...
16% report a confirmed autoimmune disease
84% report a co-morbidity
11% report inappropriate sinus tachycardia
21% report fibromyalgia
28% report Ehlers-Danlos syndrome
18% who report EDS also report an autoimmune disease
13% report neurocardiogenic syncope
16% report gastroparesis
www.dysautonomiainternational.org

What other conditions commonly occur in patients with POTS?

Patients with POTS may have other coexisting symptoms and diagnoses, and it is not clear if these define pathophysiological subsets of POTS.

Headache and sleep disturbances are almost universal. Patients with POTS often have exercise intolerance, more than 90% have chronic fatigue and at least half meet criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

A particularly disabling symptom is “brain fog” or perceived cognitive impairment,which is often worse with upright posture.

Nausea, bloating and functional bowel symptoms are common.

Another common sign is peripheral acrocyanosis in the lower extremities when upright. Common comorbid conditions seen with POTS include hypermobile Ehlers–Danlos syndrome, mast cell activation syndrome, migraine and ME/CFS

https://www.cmaj.ca/content/194/10/E378

Conditions that could explain sinus tachycardia

- ***Other conditions that could explain sinus tachycardia on standing***[5]
- Acute hypovolemia (from dehydration or blood loss)
- Anemia
- Orthostatic hypotension
- Endocrinopathy
  - Adrenal insufficiency
  - Carcinoid tumour
  - Hyperthyroidism
  - Pheochromocytoma
- Adverse effects from medication
- Panic attacks and severe anxiety
- Prolonged or sustained bed rest
- Recreational drug effects
- Finally, patients with POTS have sinus tachycardia, not another supraventricular tachyarrhythmia. Clinicians should consider paroxysmal supraventricular tachycardia, especially if the tachycardia is not always positional, if it has a sudden onset and offset (the heart rate usually increases more gradually in POTS), or if the tachycardia stops with a Valsalva maneuver.

https://www.cmaj.ca/content/194/10/E378

POTS and Genetics

- As many as 14% of POTS patients have a family member with POTS, 31% have a family member with orthostatic intolerance, 20% have a family member with joint hypermobility, and 45% have a family member with autoimmune disease
- In a small study, a single-nucleotide polymorphism of the G-protein β3 subunit C825T was more frequently found in POTS (45.8%) than in controls (20.0%) and was associated with a greater increase in HR on standing

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8455420/
https://pubmed.ncbi.nlm.nih.gov/22882749/

http://www.dysautonomiainternational.org/page.php?ID=205


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Table 3. *Treatment options for POTS patients*

Treatment option	Recommendation	Remarks	Level of evidence*[16]
Lifestyle			
Fluid intake Salt (NaCl) intake	At least 2-3 l, daily Circa 10 grams daily	When hypovolemia suspected (majority of patients)	Expert opinion[1,9,26]
Physical conditioning	Preferably horizontal activity. 20-30 minutes, 3 times a week		Moderate[40-44]
Compression stockings	Waist-high style stockings (pressure 30 to 40 mmHg)		Expert opinion[1,9]
Psychological interventions	Focused on coping mechanisms and somatic hypervigilance		Expert opinion[1,8,26,45]
Pharmacological options			
Propranolol	20 mg daily	Only if blood pressure is sufficient High dose (≥ 80 mg) may worsen symptoms	Moderate[44]
Fludrocortisone	Start 50-62.5 µg/day to max 300 µg daily	When hypovolemia suspected. Caution in patients with migraine. Side effects include hypokalemia, severe headaches and vertigo	Expert opinion[1,9,24]
Desmopressin	0.2 mg	Side effects include hyponatremia. Only for occasional usage	Moderate[43]
Ivabradine	Start 2.5 mg once or twice daily (lower than in case of heart failure)	Potentially beneficial for fatigue; may result in visual abnormalities	Weak[46]
Clonidine Methyldopa	0.1-0.2 mg bid or tid 125-250 mg bid	Hyperadrenergic phenotype; side effects include drowsiness, fatigue and worsening of mental clouding	Weak[34]
Pyridostigmine	30-60 mg tid	Side effects include gastrointestinal symptoms	Moderate[8,33]
Modafinil	100 mg bid	Potentially beneficial for "brain fog"; orthostatic tachycardia may be worsened	Expert opinion[1,2,26]
Midodrine	2.5 mg tid	Neuropathic phenotype; side effects include urinary retention due to prostatic hypertrophy	Moderate[34]

bid = twice a day; tid = three times a day
* Scoring of evidence is as follows: moderate = one randomized controlled trial; weak = only small non-interventional studies; expert opinion = no specific studies in POTS, in most cases based on experience in orthostatic hypotension

The majority of POTS patients have symptoms suggestive of sensory small-fiber neuropathy.

81% of POTS patients experience burning, numbness and/or tingling in their hands.

75% of POTS patients experience burning numbness and/or tingling in their feet.

www.CurePOTS.org

DYSAUTONOMIA INTERNATIONAL

AWARENESS ADVOCACY ADVANCEMENT

Published in Primary Care and 1 other channel
Journal Scan / Research · November 30, 2021

Effect of POTS on Gastrointestinal Transit and Contractility

Digestive Diseases and Sciences

TAKE-HOME MESSAGE

- Postural orthostatic tachycardia syndrome (POTS) patients are known to have severe gastrointestinal problems, such as dysmotility and bloating. This is a retrospective study of the use of wireless motility capsules (WMC) to analyze the transit and contractility patterns of POTS patients, with symptomatic non-POTS patients serving as a control group. Patients were gender- and age-matched to avoid confounding factors. WMC data revealed that 25% of POTS patients had delayed small bowel transit, compared with 0% in the control group (P = .047). The POTS group also showed fewer contractions/minute (2.95 vs 4.22; P = 0.011) and a reduced motility index (101.36 vs 182.11; P = 0.021). Migraine (P = .007, unadjusted analysis; P = .004, adjusted analysis) and anxiety (P = .011, unadjusted analysis) predicted faster small bowel transit time, and the presence of POTS (P = 0.044, adjusted analysis) predicted slower small bowel transit time. About 20% of the POTS patients showed dysmotility in more than one region of the gastrointestinal tract.
- There is a high prevalence of bowel dysmotility and delayed transit in POTS patients. WMC can be used to confirm this and allow specific targeted symptomatic treatment.

– Mukund Venu, MD, FACG

Neurology®

SHARE April 06, 2015; 84 (14 Supplement) APRIL 20, 2015

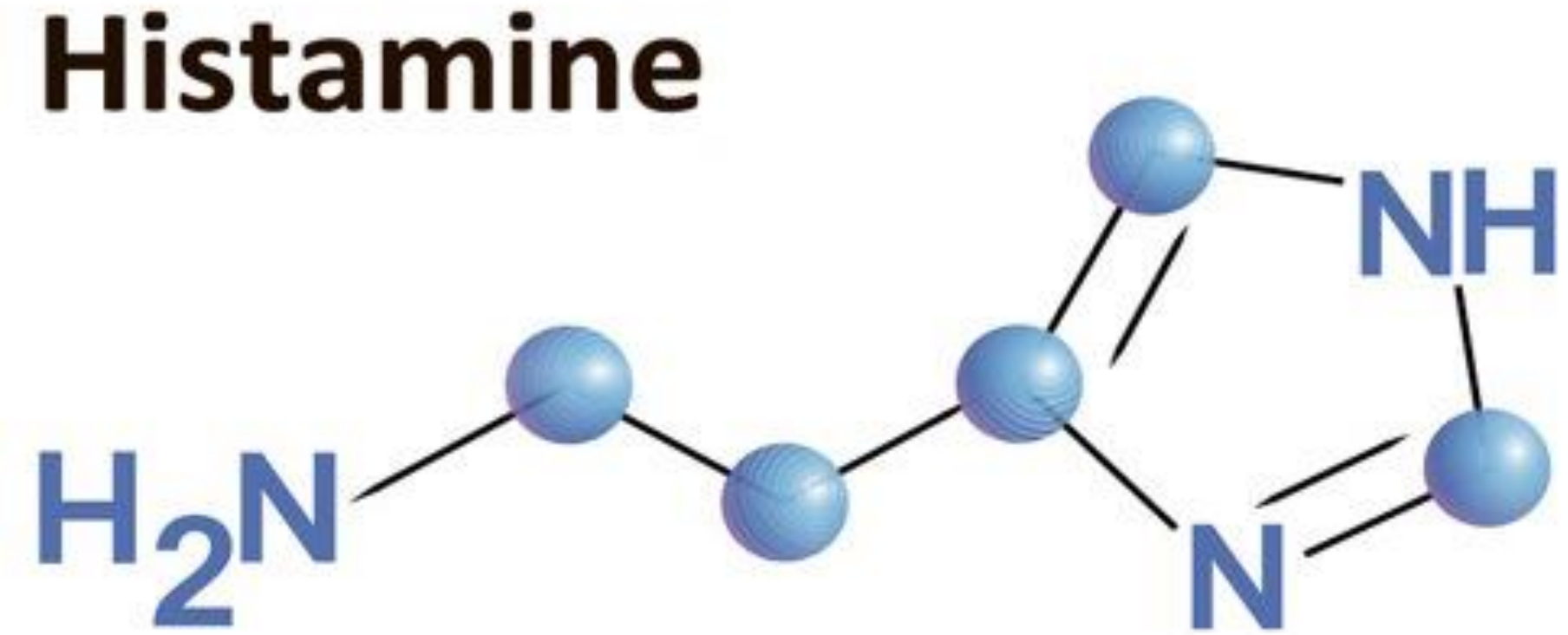
Gastrointestinal manifestations of postural orthostatic tachycardia syndrome (P1.280)

Karen Morgenshtern, Collin Culbertson, Liz Wang, Anindita Deb, Anna Hohler

First published April 8, 2015,

CONCLUSIONS: Subjective GI disturbance is common in patients with POTS, and these symptoms are not necessarily related to primary GI pathology. Symptoms are frequent and prolonged, likely decreasing quality of life. Given the importance of autonomic input to normal GI function, the same autonomic impairment that leads to postural tachycardia may also affect the enteric nervous system, leading to gastroparesis, abnormal gut motility, and esophageal reflux. Further studies correlating subjective symptoms with objective abnormalities of GI autonomics are needed.

Histamine and Mental Health



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 Receptors

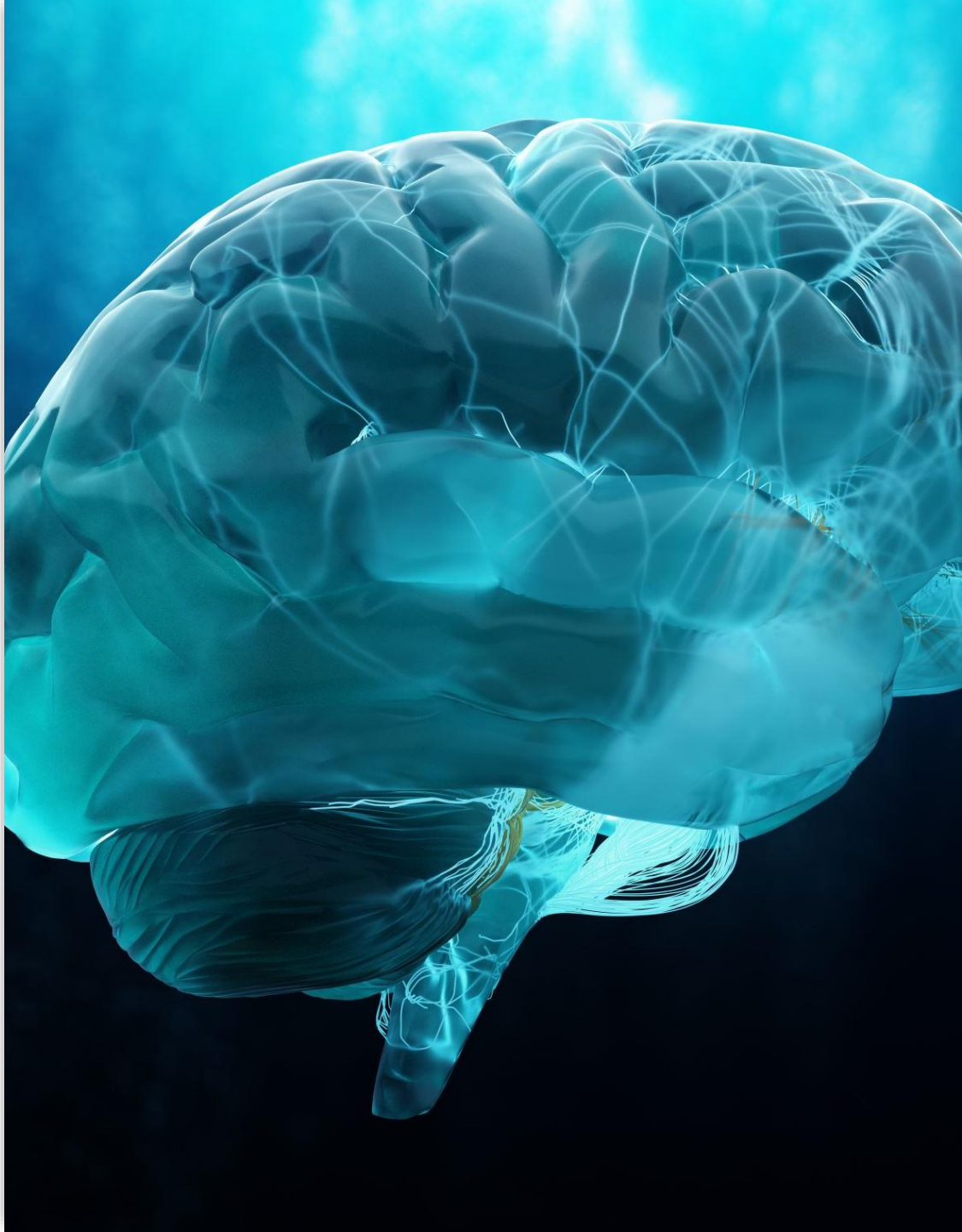
- H1 – mucousal inflammation, pro-inflammatory
- H2 – operates the “proton pump” regulating HCL for digestion
- H1 primarily (but potentially H1 and H2) are associated with respiratory mucousal inflammation and respiratory inflammation
- The GI tract and respiratory tract contain all the elimination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

Histamine

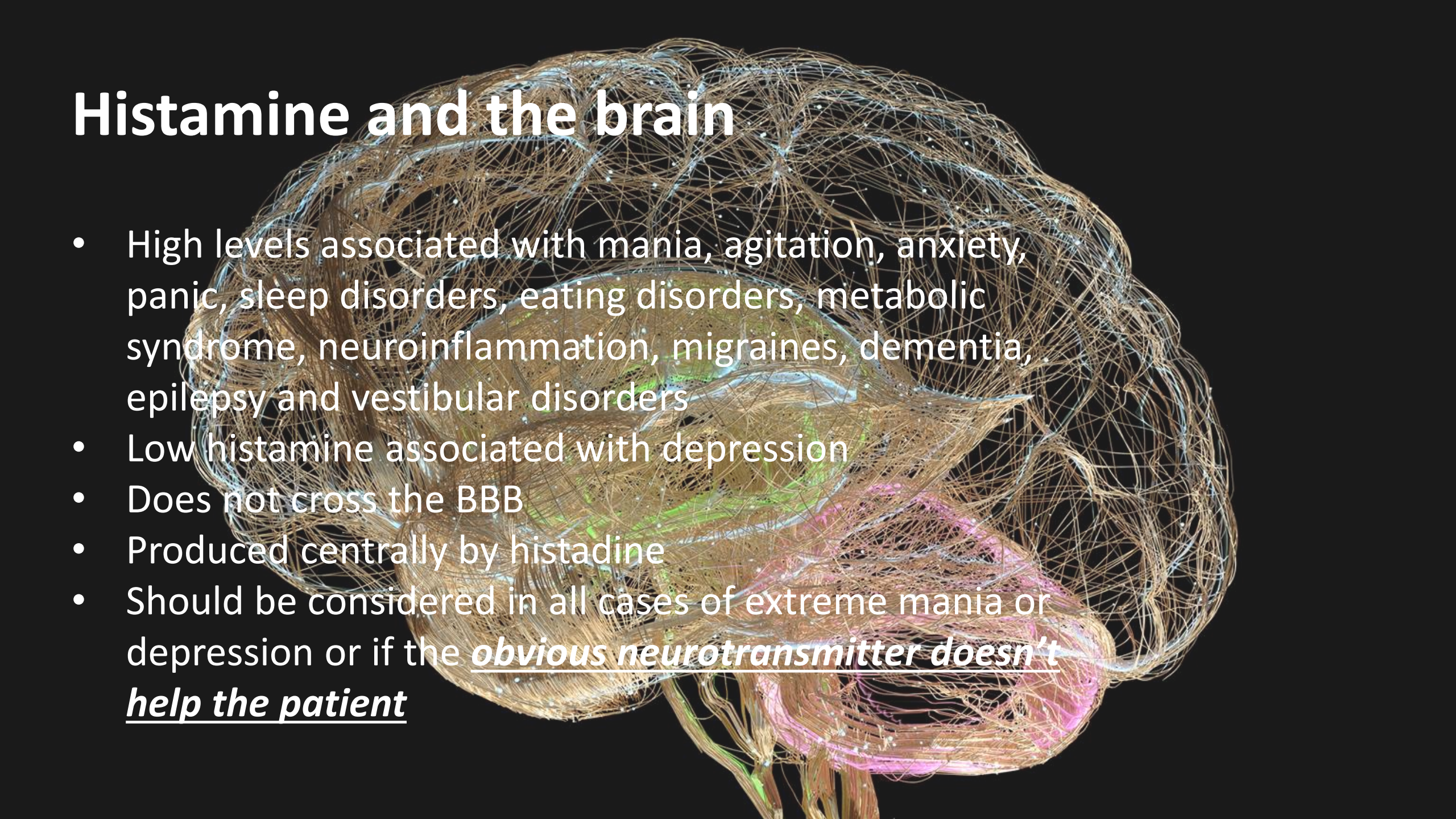
- Histamine is found in nearly all tissues, such as stomach mucosa lining, neurons, mast cells, and basophils
- It plays extensive roles in smooth muscle contraction, brain excitation, widening of blood vessels, and sensory system signaling in the brain
- This role in sensory signaling — specifically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

Histamine 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



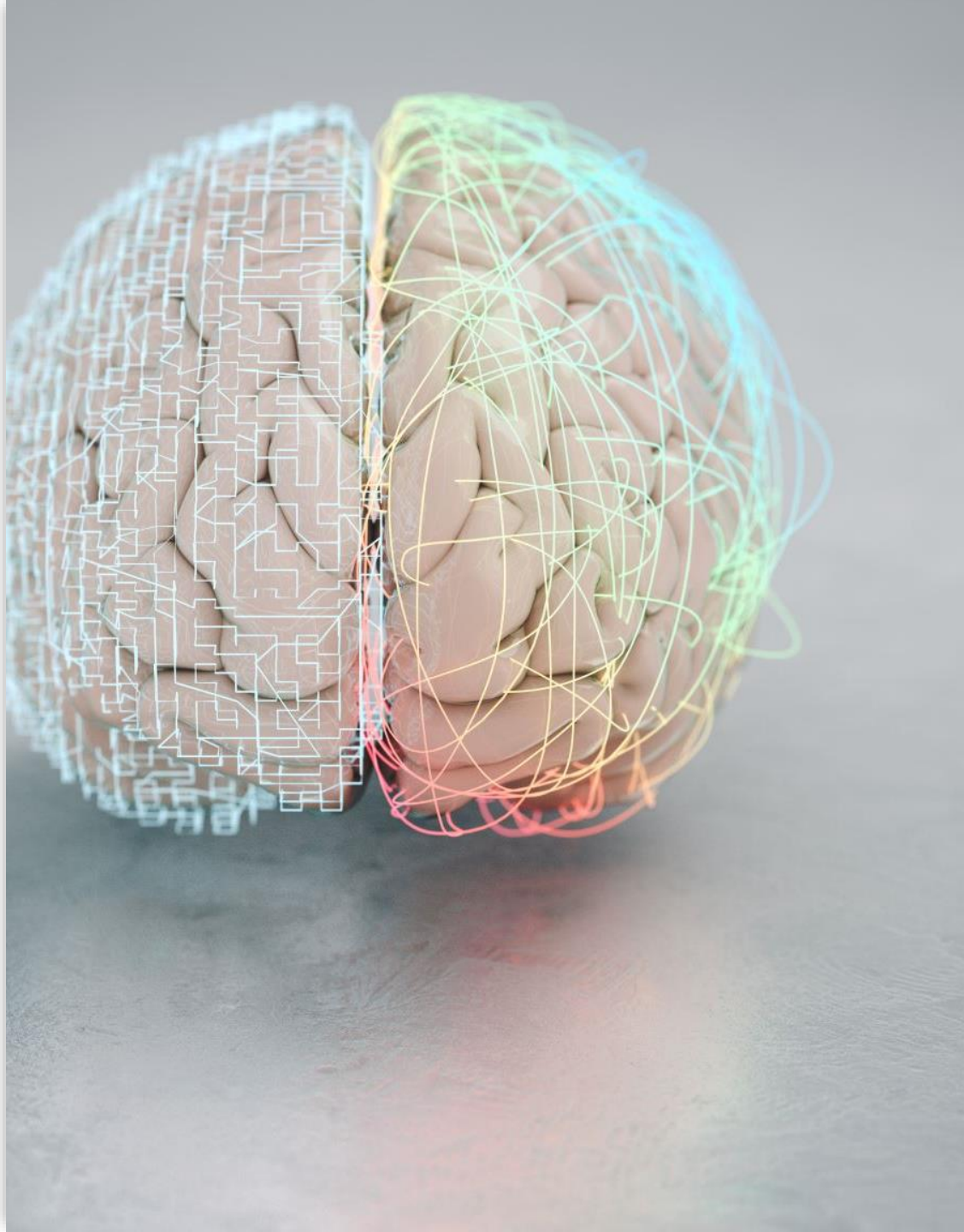
Histamine and the brain



- High levels associated with 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 histadine
- Should be considered in all cases of extreme mania or depression or if the ***obvious neurotransmitter doesn't help the patient***

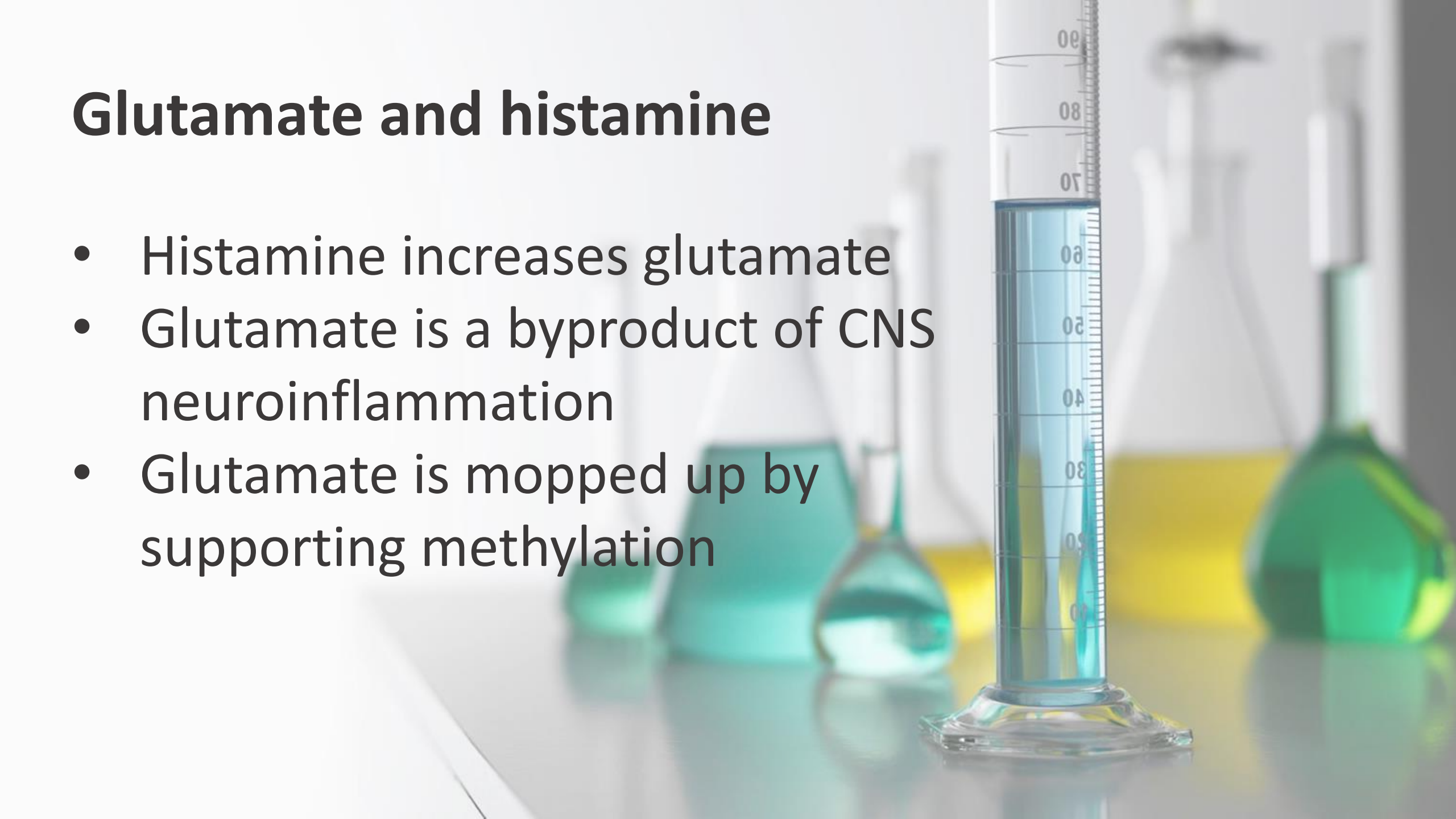
Histamine - gut brain axis

- 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 viscous cycle
- Histamine causes gut inflammation and brain inflammation by inflaming membranes
- Leaky gut = leaky blood brain barrier
- **Healing the gut – diet, healthy fats, manage dysbiosis, curcumin, quercetin, zinc, vitamin A*



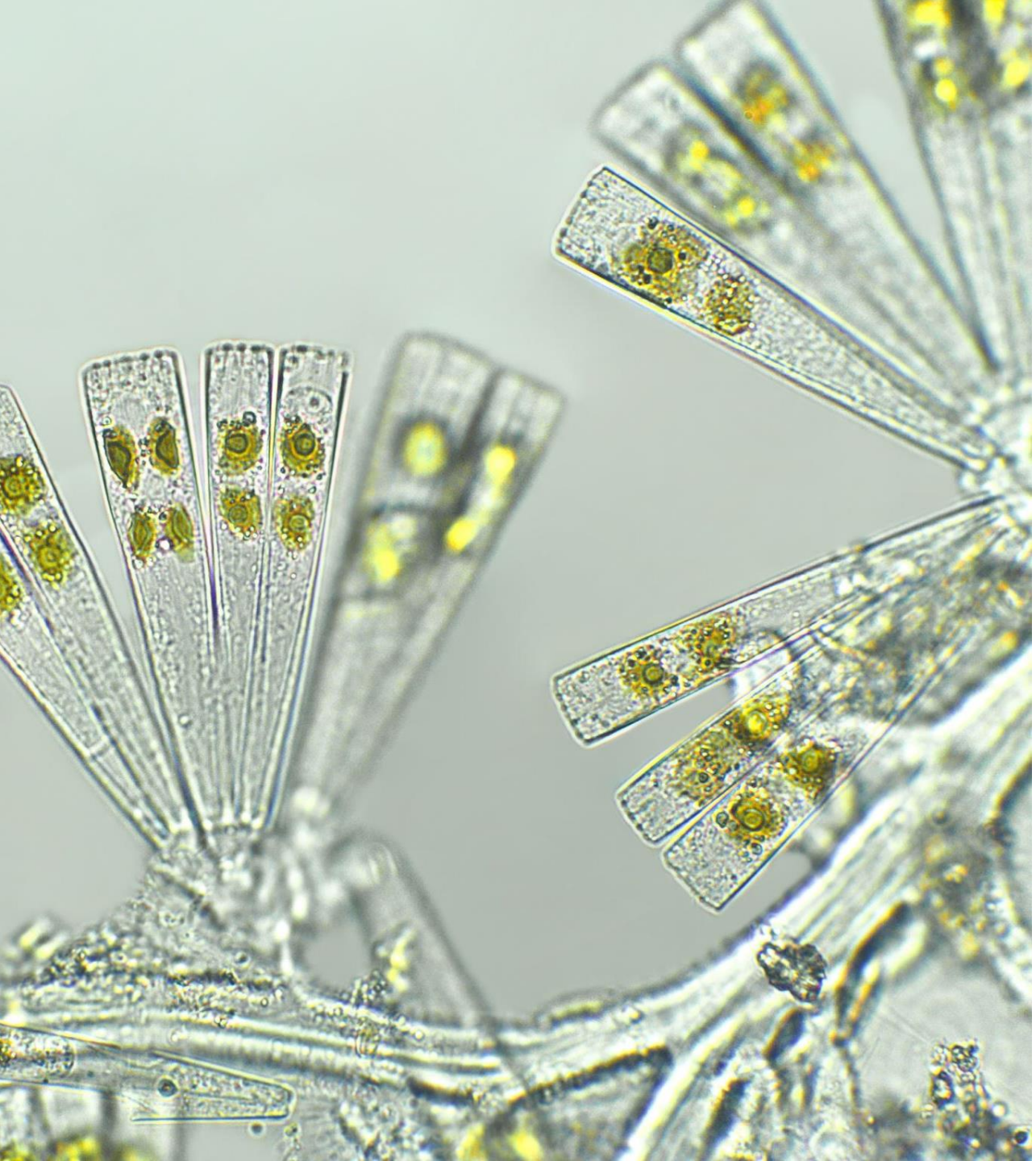
Glutamate and histamine

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



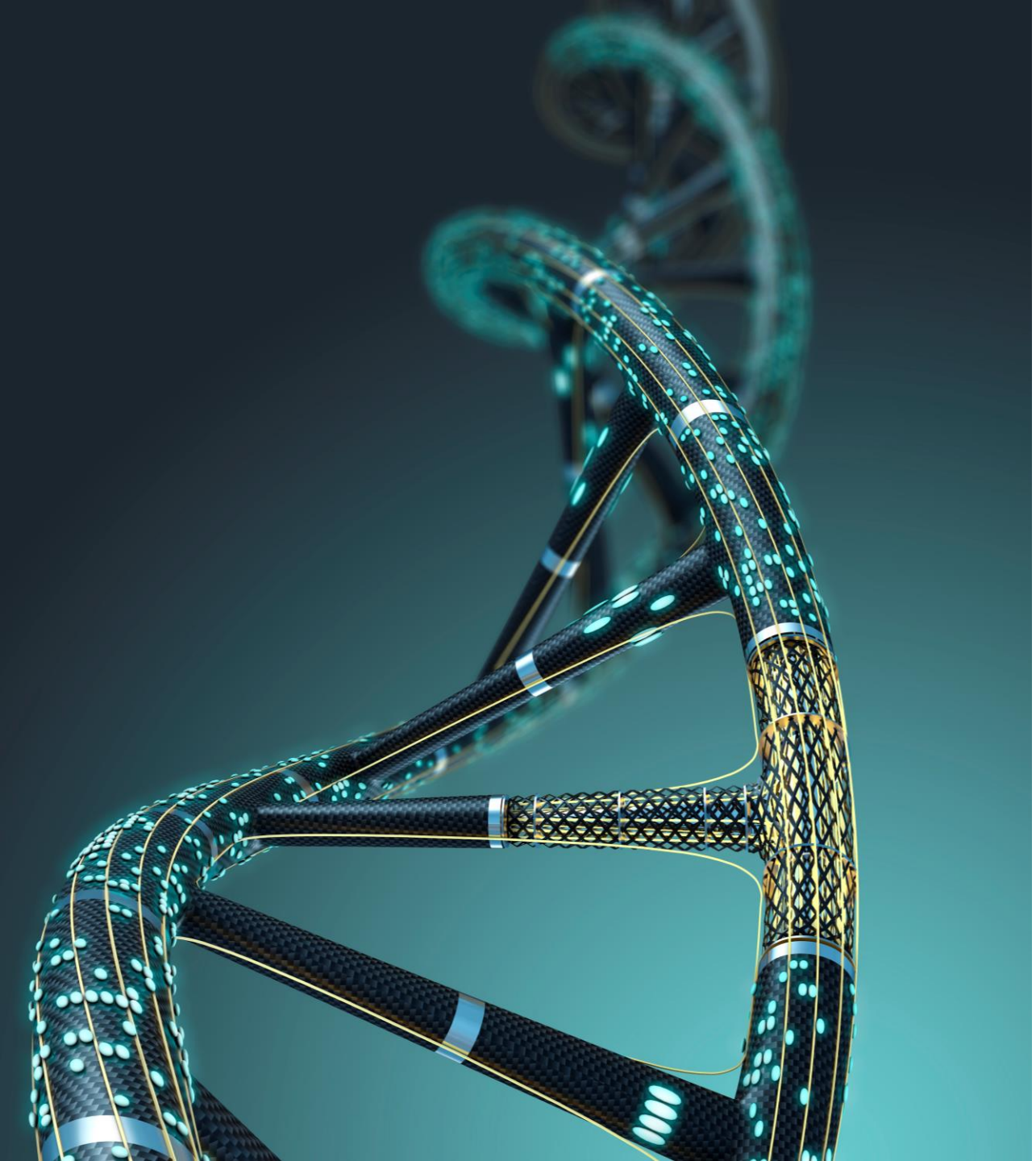
Glutamate & GABA

- Glutamate converts to GABA via GAD
  - Co-factors - B1, B6, NAC
- Glutamine – yes or no?
  - Very few people will have a pro-inflammatory impact from supplementing glutamine
  - The gut will usually absorb most of the glutamine resulting in very little to be converted into glutamate
  - Glutamine provides critical cell support



Histamine Metabolism

- 3 pathways to remove histamine
- There can be blocks in one, two or all three pathways
- Methyltransferase is the primary step
- Followed by MAO and then aldehyde decarboxylase

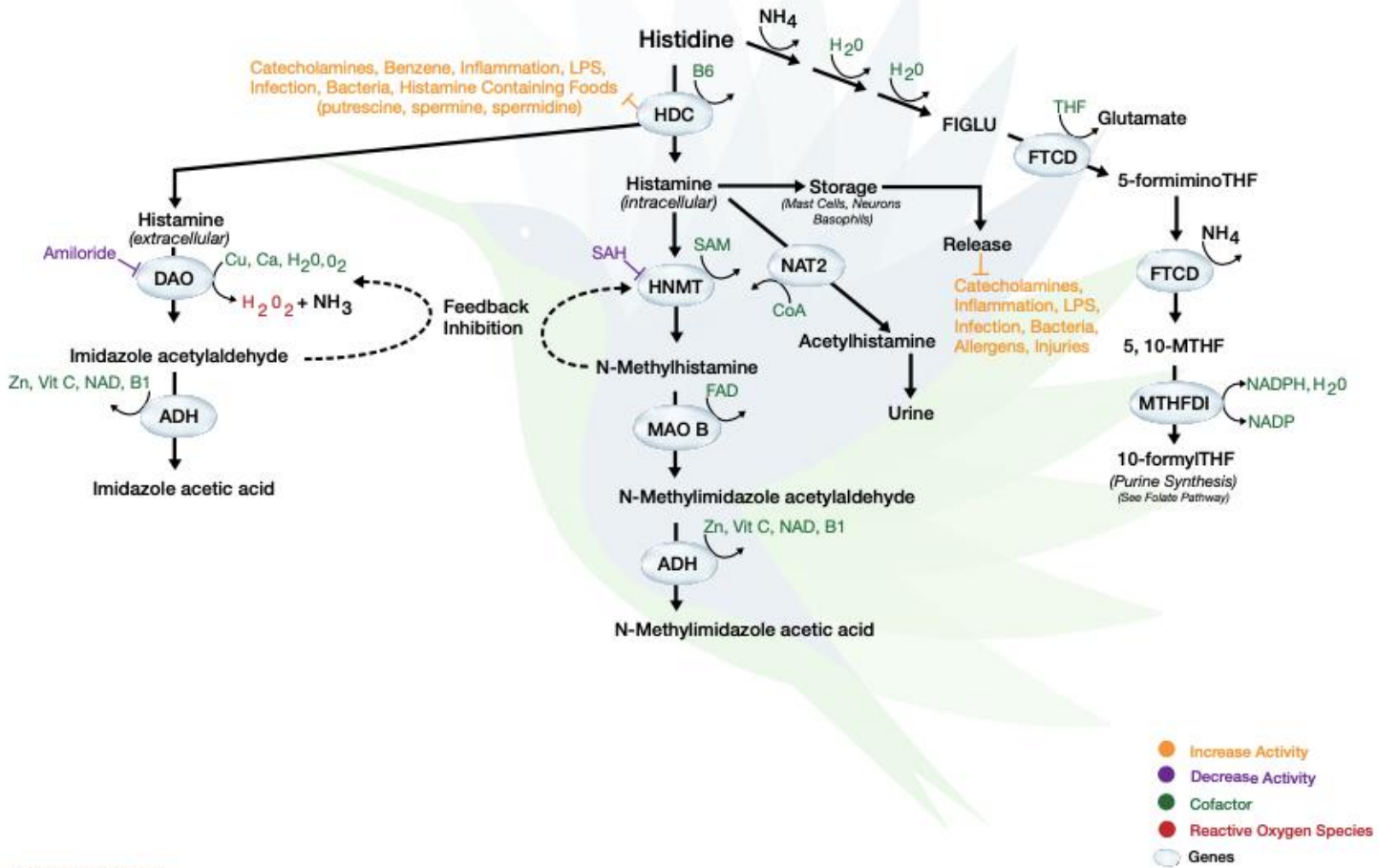


Methylation Supports

- Methyl B12
- Methyl folate
- Folinic
- SAMe – deliver methyl to 200 cycles
- DMG, TMG
- B vitamins
- Phosphatidylcholine and creatine } 50% of methylation is needed to produce

SeekingHealth
Optimizing Life

Pathway Planner
Histamine



SeekingHealth.com

By Dr. Ben Lynch | 2018

Histadine

(B-1)[Histadine Decarboxylase]

Histamine

(B-6,Mg,Cu) Histaminase **[DAO]**

Catabolic Pathway

Acetyl Histamine

[(B5) [**N A T]**

[Histamine **Methyltransferase**]

(B-12, Folate)

Methyl Histamine

(Mg,B-6, VitC) **[MAO]**

Histamine Aldehyde

(B-1) **[Aldehyde Dehydrogenase]**

MIAA

B6

- Magnesium is an important co-factor
- Needed for over 100 biochemical reactions including:
  - Amino acid biosynthesis
  - Fatty acid biosynthesis
  - Antioxidant - quenching ROS
  - Neurotransmitter production and metabolism

B6

- Essential for human health
- Supports:
  - Cardiovascular health
  - Renal health
  - Neurological Health
  - Production of glutathione

B6 and the Microbiome:

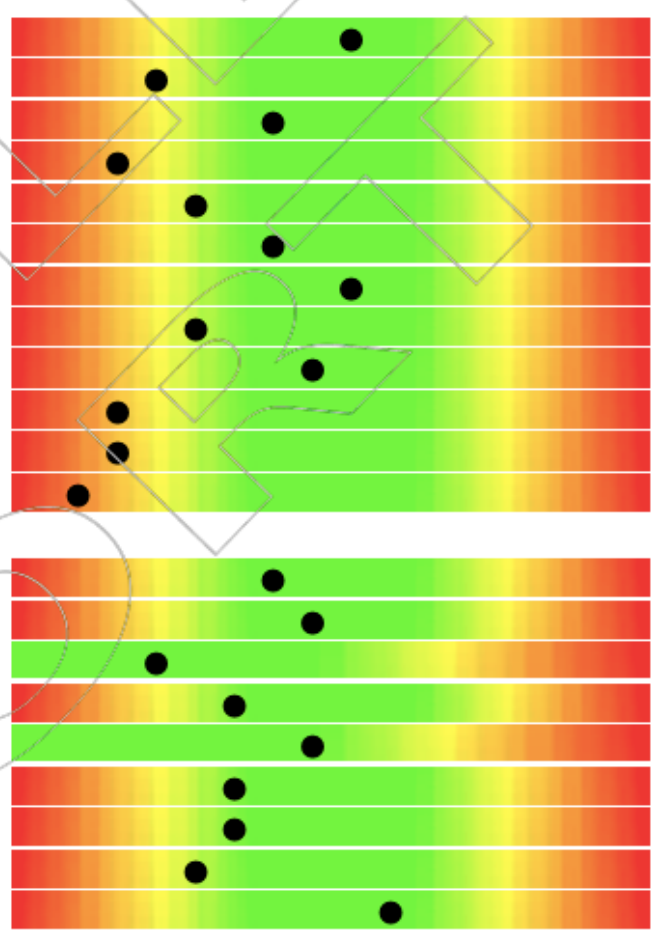
- Clayton, Gandhi, Hellmann, Hossain, Mayengbam, Merrill, Ni, NLM, Sharma, Wan, and Zempleni all discuss both the normal GI metabolism of B6 and the impact that the intestinal microbiome has on B6, and vice versa.
  - B6 adequacy is required for the maintenance of a healthy microbiome.
  - B6 can be synthesized by GI flora.
  - B6, and other B Vitamin deficits can increase microbiome, and systemic oxidative stress.

B6 and the microbiome

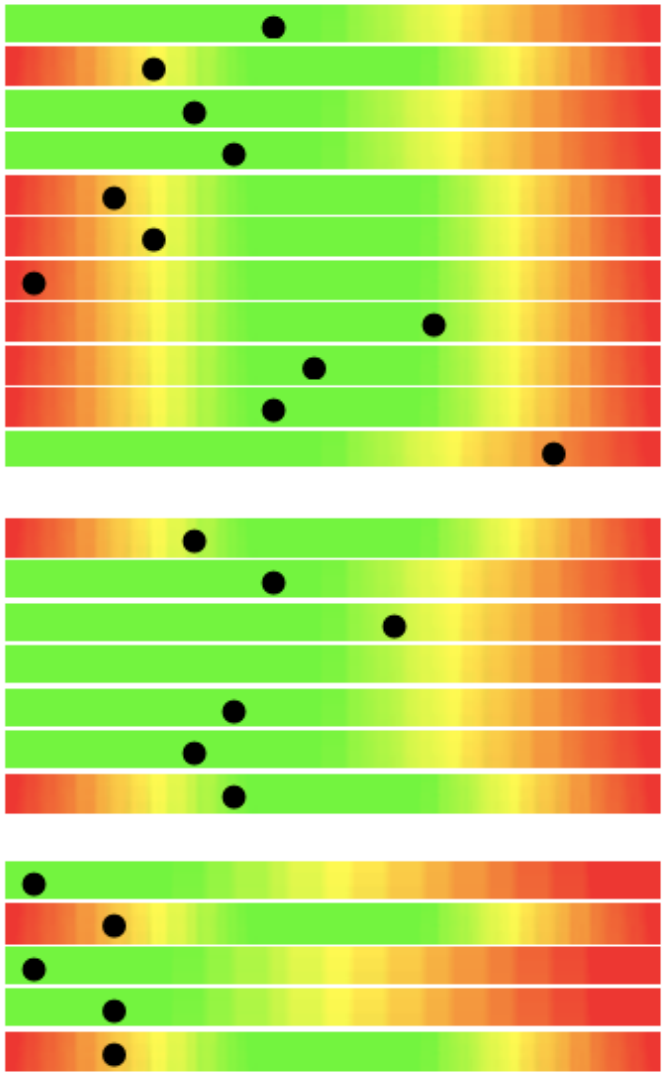
- You need enough B6 to maintain a healthy microbiome
- B6 – non-activated, pyridoxine
- P5P – phosphorylated B6 - ACTIVE
- B6 deficiency leads to systematic oxidative stress including oxidative stress in the microbiome
- Conversion of B vitamins can happen with opportunistic microbes leading to a pro-inflammatory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

Amino Acids

BLOOD - Li HEPARI	Result	Range	Units
AMINO ACIDS, Plasma			
Essential Amino Acids			
Arginine	85.0	28.0 - 108	umol/L
Histidine	72.1	65.0 - 104	umol/L
Isoleucine	53.3	30.0 - 75.0	umol/L
Leucine	*73.4 *L*	77.0 - 155	umol/L
Lysine	134	105 - 207	umol/L
Methionine	24.0	15.0 - 32.0	umol/L
Phenylalanine	55.9	42.0 - 62.0	umol/L
Taurine	43.3	27.0 - 95.0	umol/L
Threonine	156	75.0 - 197	umol/L
Tryptophane	17.0	15.0 - 53.0	umol/L
Valine	*147 *L*	150 - 250	umol/L
Total Branched Chain AAs	*273 *L*	324 - 557	umol/L
Non-Essential Amino Acids			
Alanine	344	218 - 474	umol/L
Asparagine	53.6	26.0 - 74.0	umol/L
Aspartate	0.5	0.0 - 6.0	umol/L
Cystine	38.0	31.0 - 50.0	umol/L
GABA	31.8	0.0 - 50.0	umol/L
Glutamic Acid	23.6	6.0 - 47.0	umol/L
Glutamine	476	340 - 740	umol/L
Proline	126	97.0 - 240	umol/L
Tyrosine	70.6	26.0 - 80.0	umol/L
Large Neutral Amino Acids (LNAA)	399.6		umol/L



Intermediary Metabolites			
alpha-Aminoadipic Acid	3.2	0.0 - 6.0	umol/L
alpha-Aminobutyric Acid	8.5	5.0 - 35.0	umol/L
beta-Aminoisobutyric Acid	2.5	0.0 - 10.0	umol/L
Cystathionine	1.0	0.0 - 3.0	umol/L
Citrulline	*9.3* *L	10.0 - 55.0	umol/L
Ornithine	47.0	36.0 - 96.0	umol/L
Urea.	*1.0* *L	2.8 - 8.1	mmol/L
Glycine	377	100 - 384	umol/L
Serine	130	70.0 - 175	umol/L
Phosphoserine	7.3	2.0 - 14.0	umol/L
Sarcosine	*38.5* *H	0.0 - 19.5	umol/L
Dietary Peptide Related Markers			
1-Methyl Histidine	12.1	1.0 - 42.0	umol/L
3-Methyl Histidine	2.5	0.0 - 5.0	umol/L
beta-Alanine	10.7	0.0 - 12.0	umol/L
Anserine	0.0	0.0 - 43.0	umol/L
Carnosine	3.4	0.0 - 10.0	umol/L
Hydroxyproline	11.4	0.0 - 53.0	umol/L
Hydroxylysine	3.1	2.0 - 5.0	umol/L
Amino Acid Functional Ratios			
Phenylalanine/Tyrosine	0.79	< 2.00	RATIO
Glutamate/Glutamine	*0.05* *L	0.06 - 0.23	RATIO
Hydroxyproline/Proline	0.09	< 0.50	RATIO
a-Amino-n-Butyrate/Leucine	0.12	< 0.2	RATIO
Tryptophan/LNAA	0.04	0.04 - 0.10	RATIO



Mast Cells

- Excitatory mast cells are caused by inflammation
- The more toxicants, the more excitable the mast cells
- Systematic inflammatory response
- Destroys BBB, vascular barrier and gut barrier
- The more histamine = the more damage

Mast Cells

- Bioflavonoids inhibit mast cell degranulation which reduces histamine release

J Neuroimmunol. 2009 Dec 10;217(1-2):20-7. doi: 10.1016/j.jneuroim.2009.08.012. Epub 2009 Sep 18.

Flavonoids, a prenatal prophylaxis via targeting JAK2/STAT3 signaling to oppose IL-6/MIA associated autism.

Parker-Athill E[1], Luo D, Bailey A, Giunta B, Tian J, Shytle RD, Murphy T, Legradi G, Tan J.

Author information

- Luteolin and diosmin both in vitro and in vivo diminished behavioural deficits in social interaction following IL-6 challenge
- Diosmin (10 mg/kg/day) was able to block MIA induced abnormal behaviour and neurological abnormalities

Abstract

Maternal immune activation (MI offspring. Reports have shown that increased Inter development, and may impair social behaviors in t -6. The current study investigated the effects of luteol JAK2/STAT3 (Janus tyrosine kinase-2/signal transdu as behavioral phenotypes of MIA offspring. Lu vitro and in vivo following IL-6 challenge as well ntly, our results showed that diosmin (10mg/kg A-induced abnormal behavior and neuropathological abnormalities in MIA/adult offspring. Diosmin's molecular inhibition of JAK2/STAT3 pathway may underlie the attenuation of abnormal social interaction in IL-6/MIA adult offspring.

Comment in

Multiple pathways in prevention of immune-mediated brain disorders: Implications for the prevention of autism. [J Neuroimmunol. 2009]

PMID: 19766327 DOI: 10.1016/j.jneuroim.2009.08.012

Eur J Pharmacol. 2016 Apr 15;777:60-9. doi: 10.1016/j.ejphar.2016.02.062. Epub 2016 Feb 27.

Astaxanthin ameliorates aluminum chloride-induced spatial memory impairment and neuronal oxidative stress in mice.

Al-Amin MM[1], Reza HM[2], Saadi HM[2], Mahmud W[2], Ibrahim AA[2], Alam MM[2], Kabir N[2], Saifullah AR[2], Tropa ST[2], Quddus AH[3].

Author information

Abstract

Aluminum chloride induces neurodegenerative disease in animal model. Evidence suggests that aluminum intake results in the activation of glial cells and generation of reactive oxygen species. By contrast, astaxanthin is an antioxidant having potential neuroprotective
avioral brain
function and neu
) control
(distilled water),
tests; radial arm
maze and open
g 42 days of
treatment. Alumi
ike behavior.
Moreover, alumi
oxide (NO),
glutathione (GSH
ation of
astaxanthin and aluminum has shown improved spatial memory, locomotor activity, and OS. These results indicate that astaxanthin improves aluminum-induced impaired memory performances presumably by the reduction of OS in the distinct brain regions. We suggest a future study to determine the underlying mechanism of astaxanthin in improving aluminum-exposed behavioral deficits.

Astaxanthin improves aluminum-induced impaired memory performances presumably by the reduction of oxidative stress in the distinct brain regions

KEYWORDS: Behavior; Glutathione; Memory; Nitric oxide; Superoxide dismutase

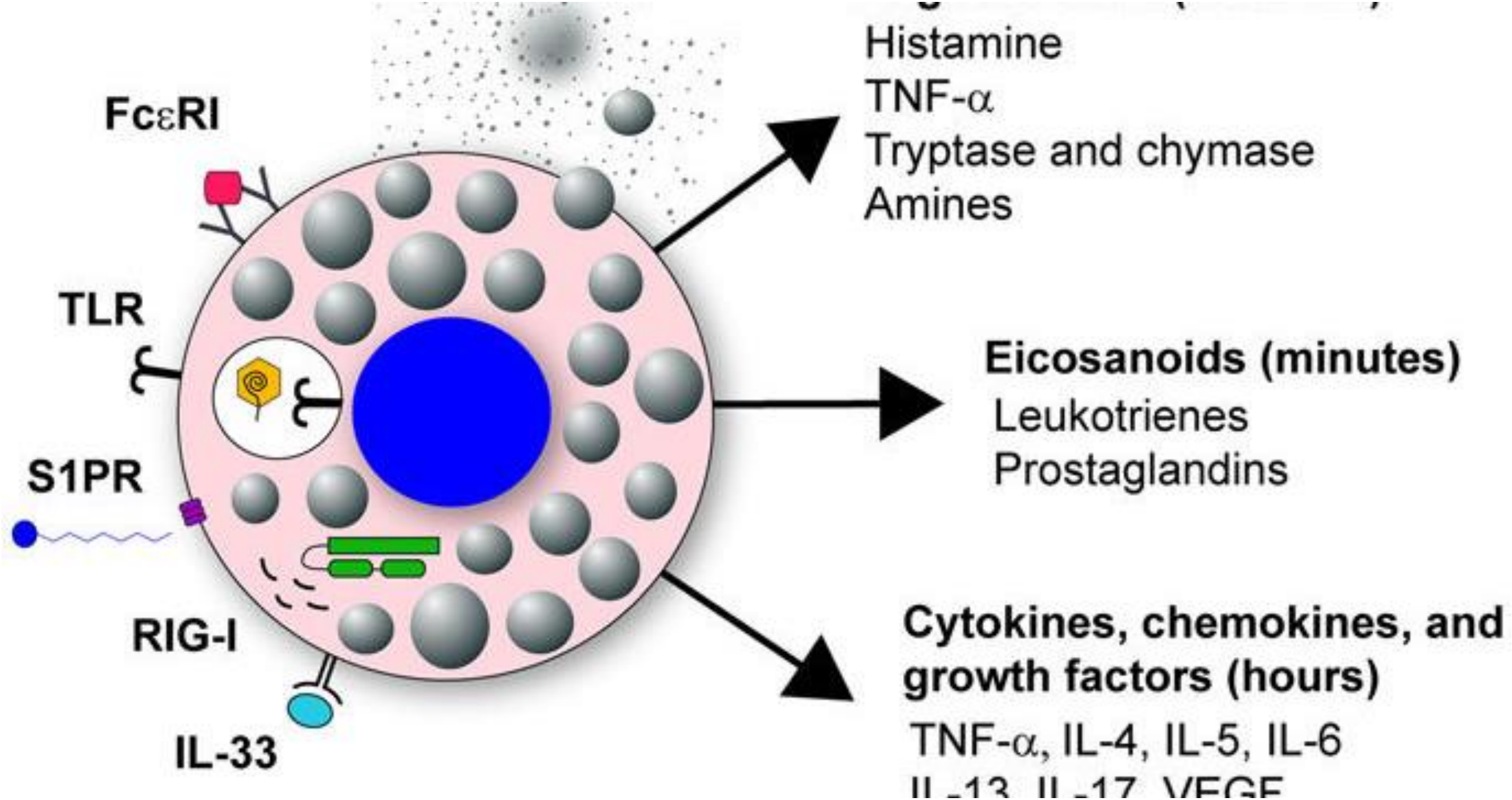
> Arch Pharm Res. 2008 Oct;31(10):1303-11. doi: 10.1007/s12272-001-2110-5. Epub 2008 Oct 29.

Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells

Hyo-Hyun Park [1], Soyoung Lee, Hee-Young Son, Seung-Bin Park, Mi-Sun Kim, Eun-Ju Choi, Thoudam S K Singh, Jeoung-Hee Ha, Maan-Gee Lee, Jung-Eun Kim, Myung Chul Hyun, Taeg Kyu Kwon, Yeo Hyang Kim, Sang-Hyun Kim

Affiliations + expand

PMID: 18958421 DOI: 10.1007/s12272-001-2110-5

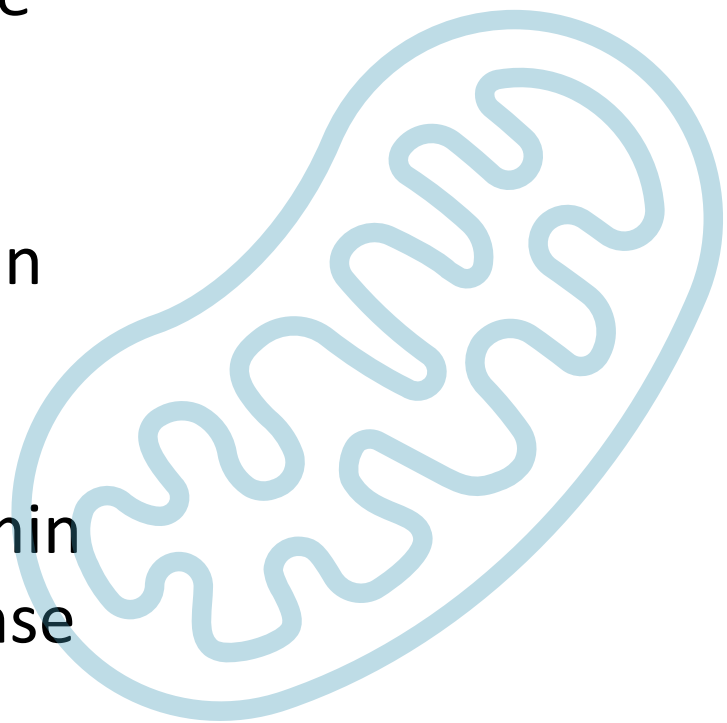

FcεRI
TLR
S1PR
RIG-I
IL-33
Histamine
TNF-α
Tryptase and chymase
Amines
Eicosanoids (minutes)
Leukotrienes
Prostaglandins
Cytokines, chemokines, and growth factors (hours)
TNF-α, IL-4, IL-5, IL-6
IL-13, IL-17, VEGF

ALTERNATIVE
MEDICINE REVIEW

NEURODEGENERATION FROM MITOCHONDRIAL INSUFFICIENCY: NUTRIENTS, STEM CELLS, GROWTH FACTORS, AND PROSPECTS FOR BRAIN REBUILDING USING INTEGRATIVE MANAGEMENT

Mitochondrial Medicine is regeneration medicine

- Neuroregeneration relies on mitochondrial medicine
- Heal membranes (BBB, vascular, nerve cell membranes)
- Mitochondrial supports – B vitamins, CoQ10, vitamin E, vitamin K, acetyl-L-carnitine, phosphatidylserine, glycerophosphocholine and omega's
- Restoring redox is also essential – glutathione, vitamin E, vitamin C which helps regulates histamine response and stop the inflammatory cascade
- Dr. Anderson's tripod approach – Reduce histamine release, remove histamine and support redox balance



COMT V158M

Present in 80% of the population
Slows COMT by 300%

COMT Related Conditions

High risk for BC and OV CA	Drug/alcohol dependence
Anger/Aggression	Depression/Anxiety
Fibromyalgia	Bipolar
Cognitive Decline	Insomnia
High risk behaviour	Dysphagia
Uterine leimyoma	Mood swings
Schizophrenia	OCD
Chronic Pain	ADHD
Panic Disorder	HTN
Type II Diabetes	Recurrent Miscarriages
Adenomyosis	Preterm Birth
Narcolepsy	Disc degeneration

COMT (catechol-O-methyl transferase)

- BREAKS DOWN **ESTROGEN**
- Controls breakdown of **epinephrine, dopamine and norepinephrine**
- Introduces a methyl group to catecholamine by SAM
- **Determines the amount of methyl donors a person can tolerate** (can use hydroxyB12)
- **SNPS – advantage is more DOPAMINE**
- Controls brain response to STRESS
- **Very sensitive to lead**

COMT Workarounds

- Adequate SAM (S-adenosyl methionine) – **not too much**
- **Inositol**, B6 (no P5P), B12 (HYDROXY)
- Magnesium Bisglycinate
- DIM
- Lithium orotate
- Folate, methyl folate – **not too much**
- Curcumin
- Melatonin
- L-theanine
- Mitochondrial support – vitamin E/K, carnitine

COMT related to Anxiety and Depression

- A functional variant in the catechol-*O*-methyltransferase (COMT) gene, the Val158Met (‘val/met’) polymorphism, has been associated in some prior studies with several phenotypes, including neuroticism
- COMT V158M slows activity of COMT leading to oxidative stress in the brain
- COMT is related to creativity, OCD, panic attacks, increased pain sensation, anxiety and depression.
- COMT increases risk of addiction

COMT

- Methylation support increases production of dopamine and epi / norepi which
- Methyl donors also help to metabolize histamine by converting histamine into methyl histamine
- COMT bottleneck!

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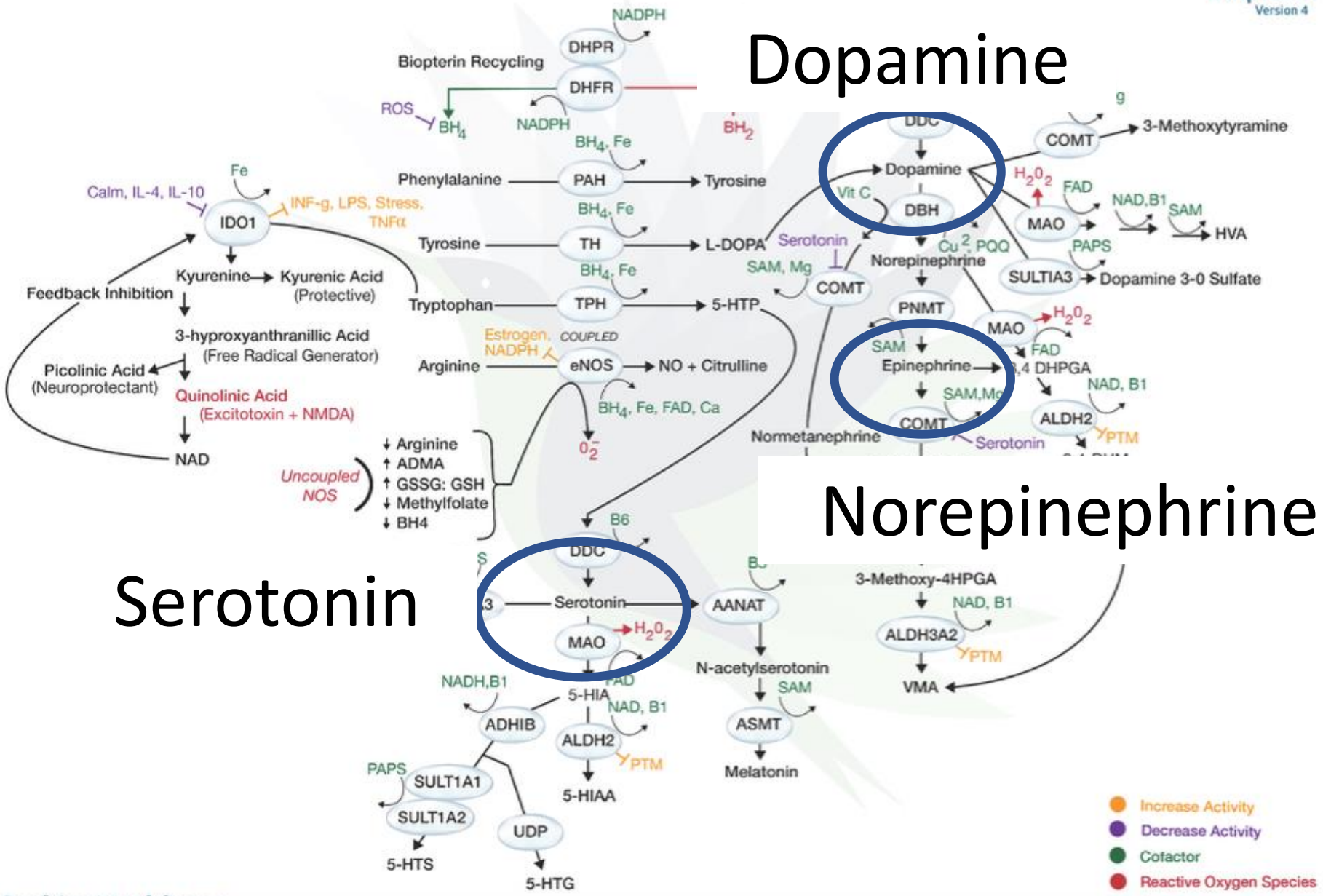
Pathway Planner

Biopterin

Version 4



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Neuropsychopharmacology (2005) 30, 2092–2102

www.neuropsychopharmacology.org

COMT Polymorphisms and Anxiety-Related Personality Traits

Murray B Stein*[,1], Margaret Daniele Fallin[2], Nicholas J Schork[1] and Joel Gelernter[3]

[1]Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

ORIGINAL ARTICLE | VOLUME 51, ISSUE 7, P591-601, APRIL 01, 2002

Evidence for a susceptibility locus for panic disorder near the catechol-*O*-methyltransferase gene on chromosome 22

Steven P. Hamilton • Susan L. Slager • Gary A. Heiman • ... Myrna M. Weissman • Abby J. Fyer • James A. Knowles • Show all authors

DOI: https://doi.org/10.1016/S0006-3223(01)01322-1

Behavioral and Brain Functions

Research | Open access | Published: 31 December 2011

A novel SNP in *COMT* is associated with alcohol dependence but not opiate or nicotine dependence: a case control study

Joanne Voisey, Christopher D Swagell, Ian P Hughes, Bruce R Lawford, Ross MD Young & C Phillip Morris

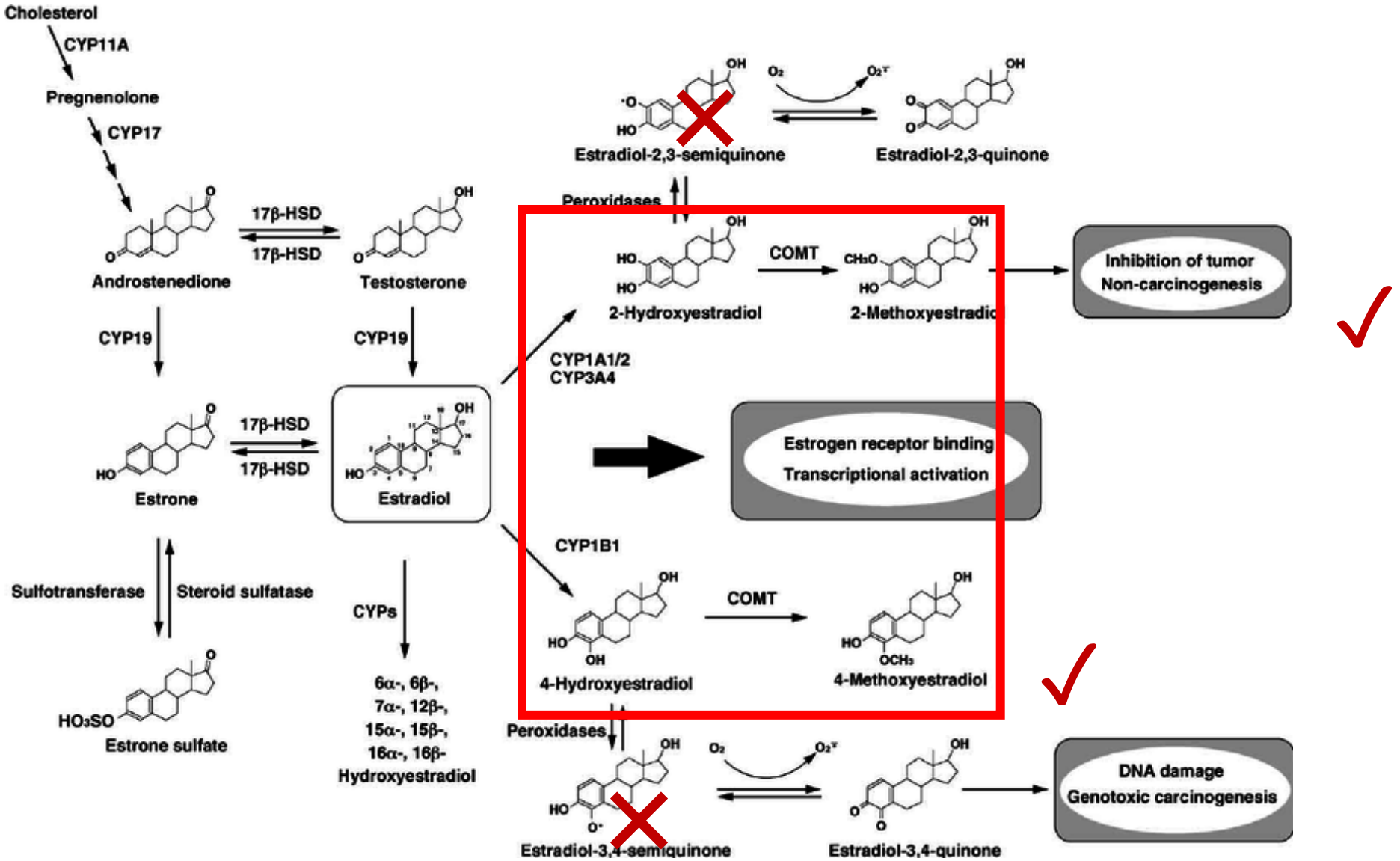
Behavioral and Brain Functions **7**, Article number: 51 (2011) | Cite this article

Methyl donors: COMT and estrogen

- COMT is one of several enzymes that degrade or inactivate catecholamines (such as dopamine, epinephrine, and norepinephrine), and catecholestrogen.
- The enzyme introduces a methyl group to the catecholamine, which is donated by S-adenosyl methionine (SAM)
- The methyl group can directly be delivered by dietary methyl donors, including methionine, folate, methylcobalamin, betaine, and choline
- Polymorphism of catechol-O-methyltransferase and prevalence of uterine leiomyomata.

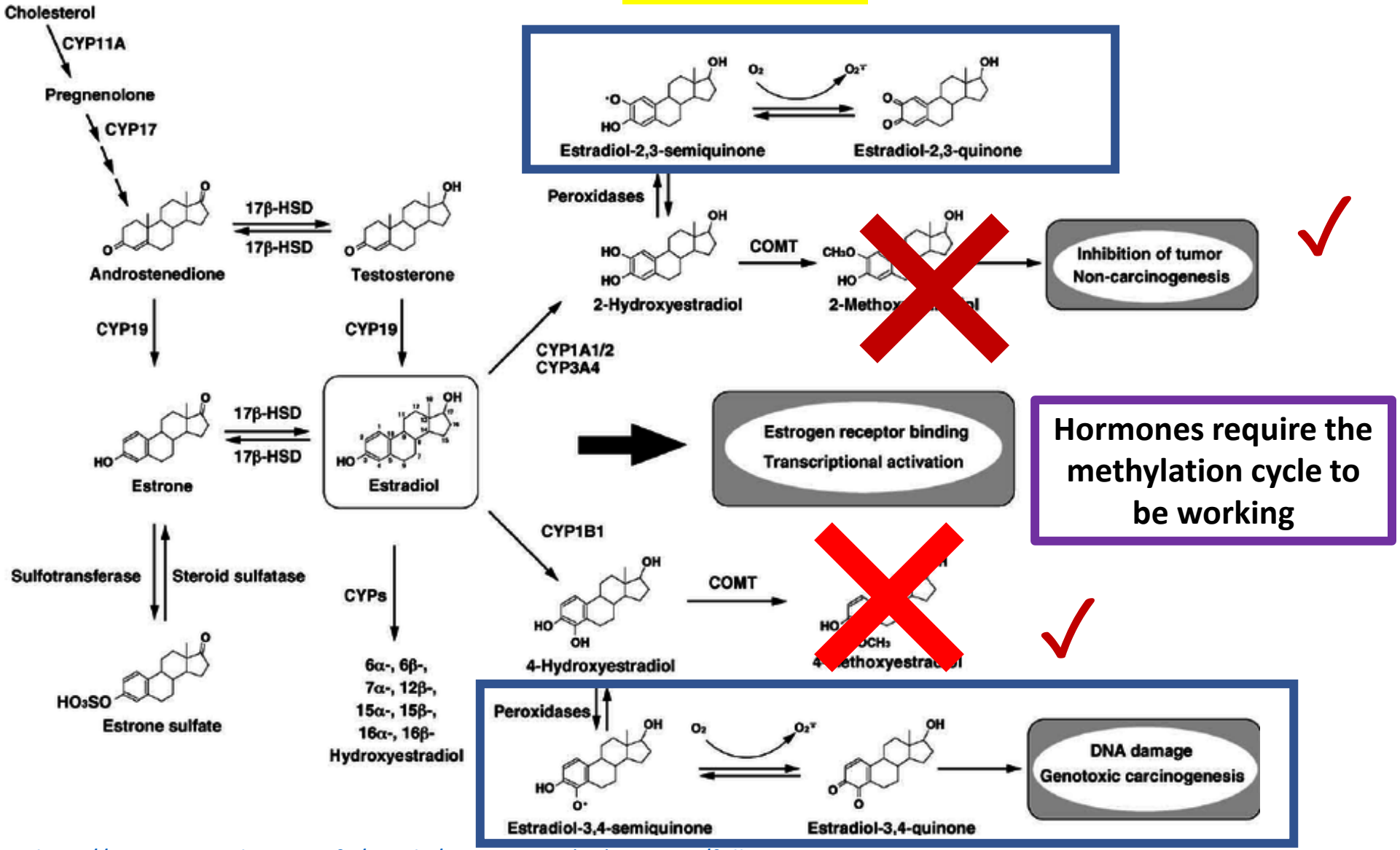
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3798916/

COMT: Catechol-*O*-methyltransferase



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

Estrogen Dominance? When hormones don't get detoxified



Hormones require the methylation cycle to be working

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

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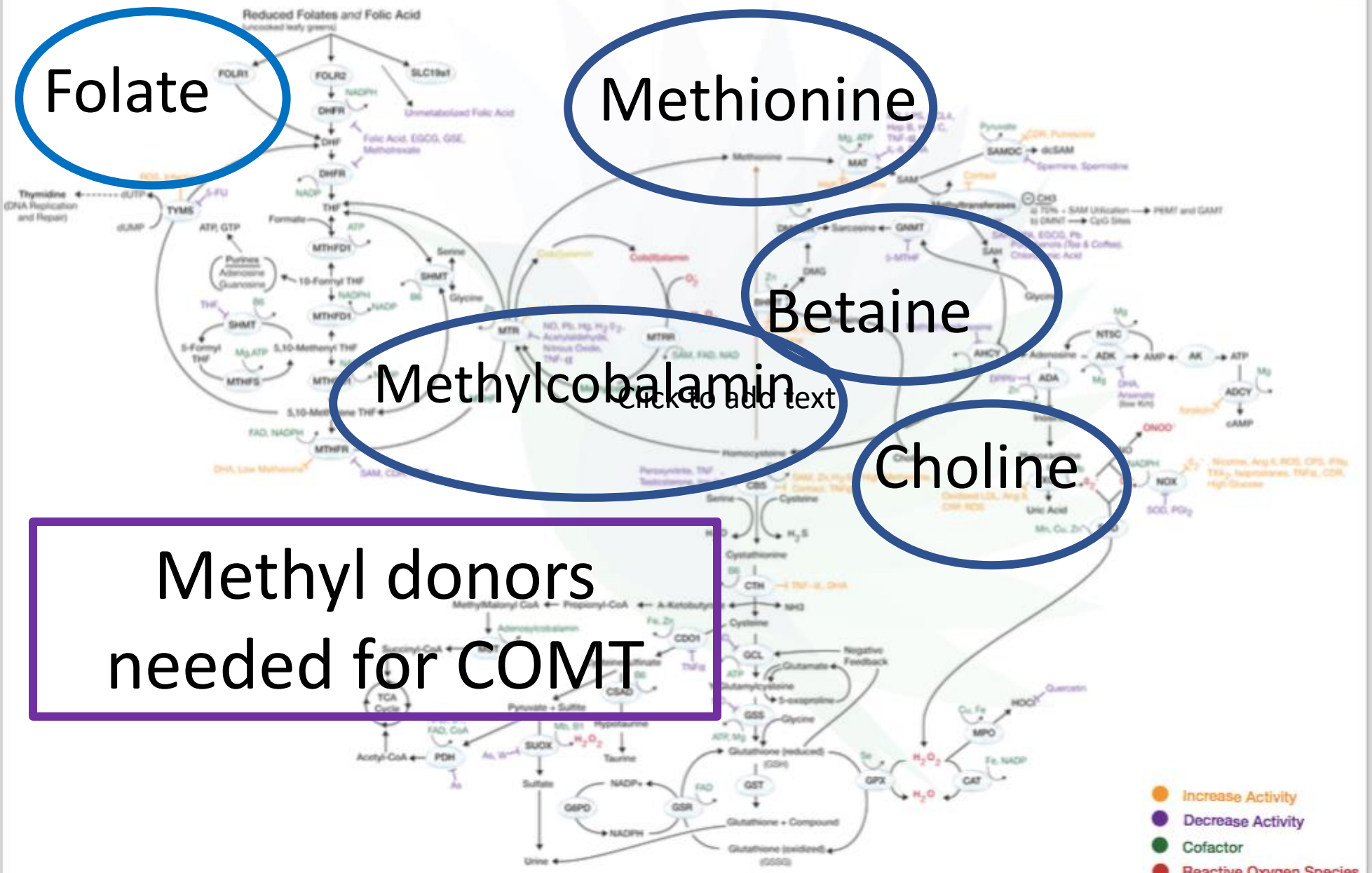
Pathway Planner

Folate, Methionine, Transsulfuration

Version 4

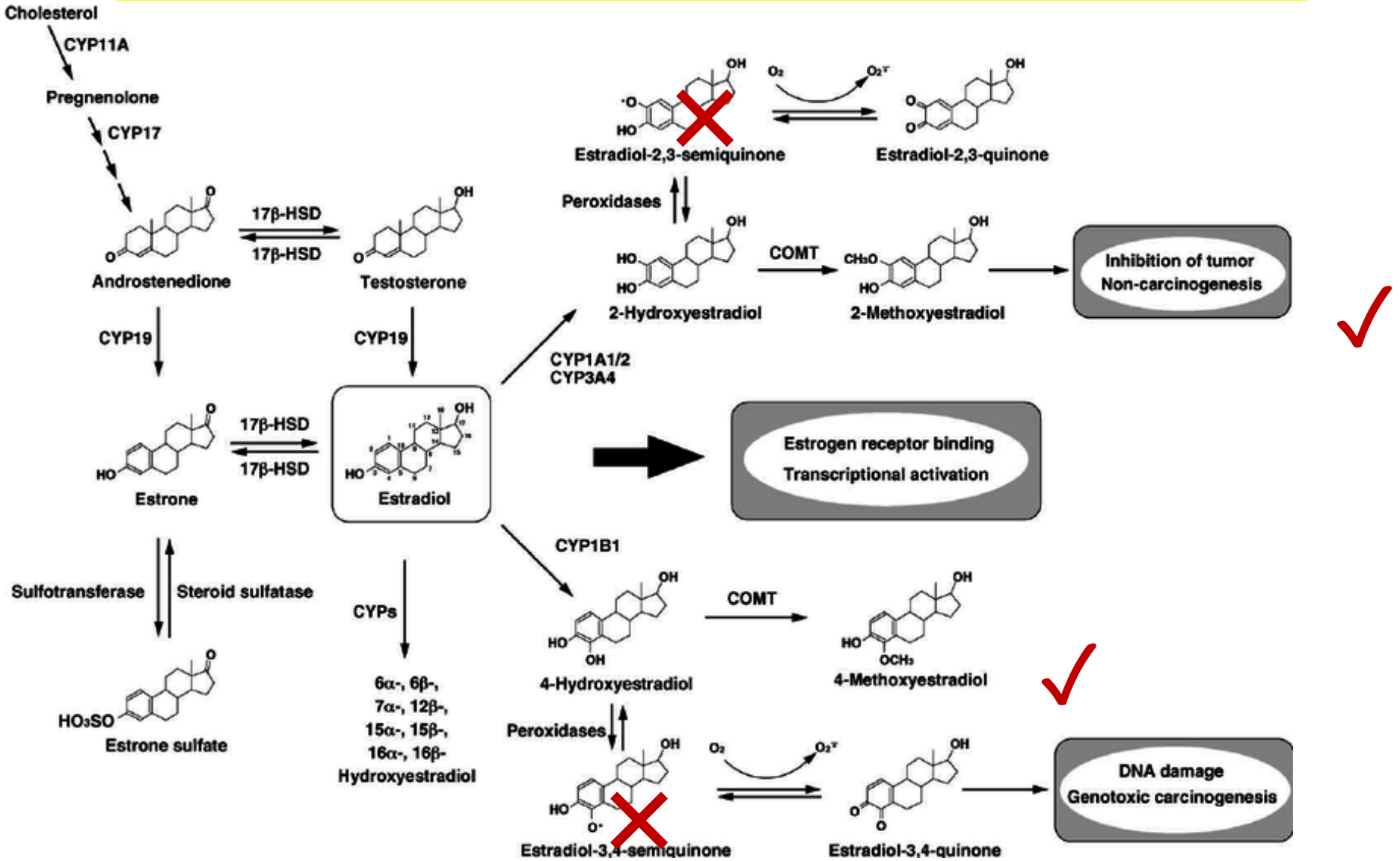


Methyl donors needed for COMT

Cytochrome P450-mediated metabolic pathways of estradiol

- Estradiol is biosynthesized by both CYP19 and 17 b -hydroxysteroid dehydrogenase (17 b -HSD) from androstenedione via testosterone or estrone.
- Estradiol is metabolized to 2- and 4-hydroxyestradiol estradiol metabolites by catechol O -methyltransferase (COMT).
- 2-Methoxyestradiol appears to be non-carcinogenic and inhibits the proliferation of cancer cells.
- 4-Hydroxyestradiol undergoes metabolic redox cycling to generate free radicals such as superoxide and the reactive semiquinone/quinone intermediates, which cause DNA damage.

Making and breaking down hormones



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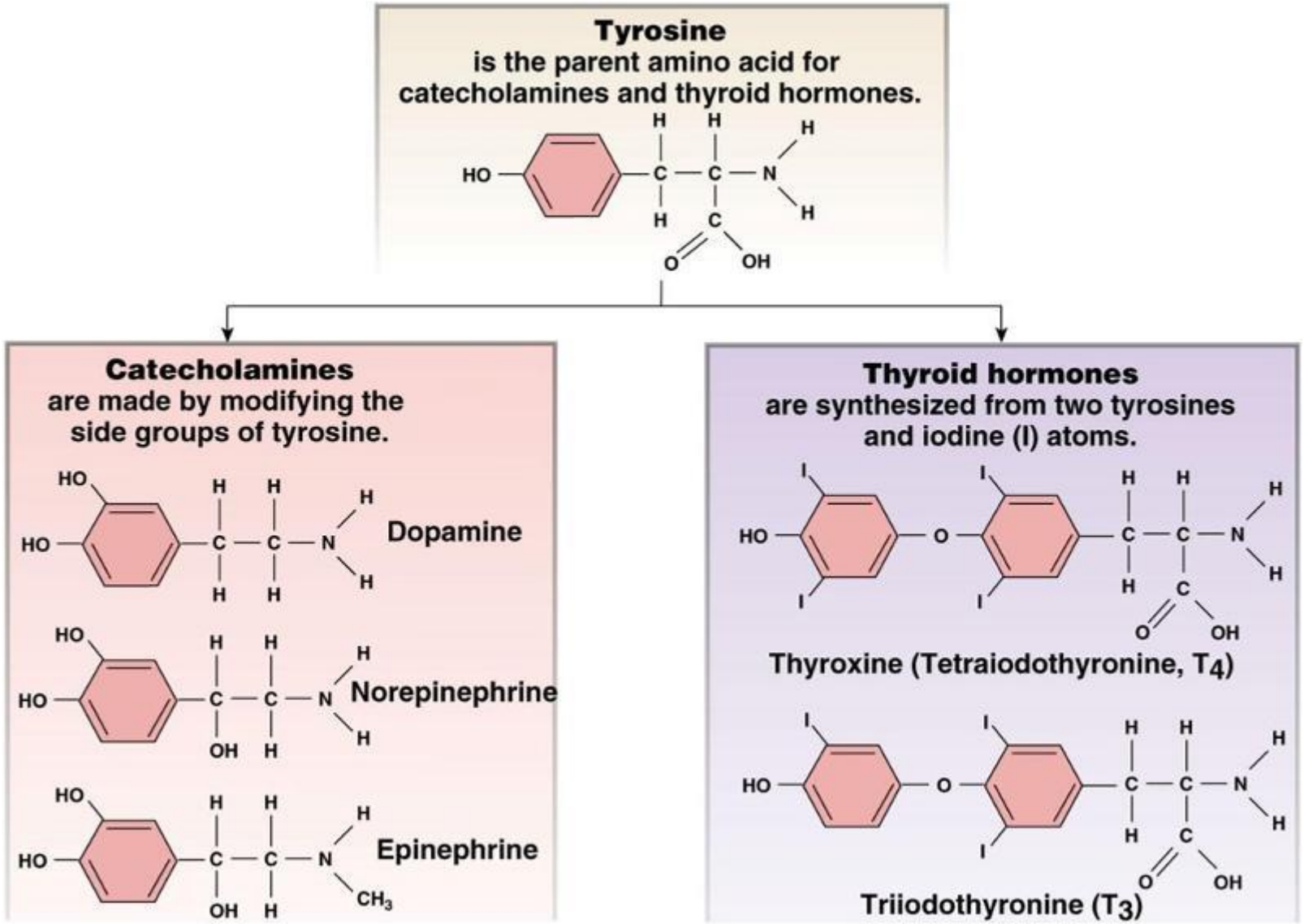
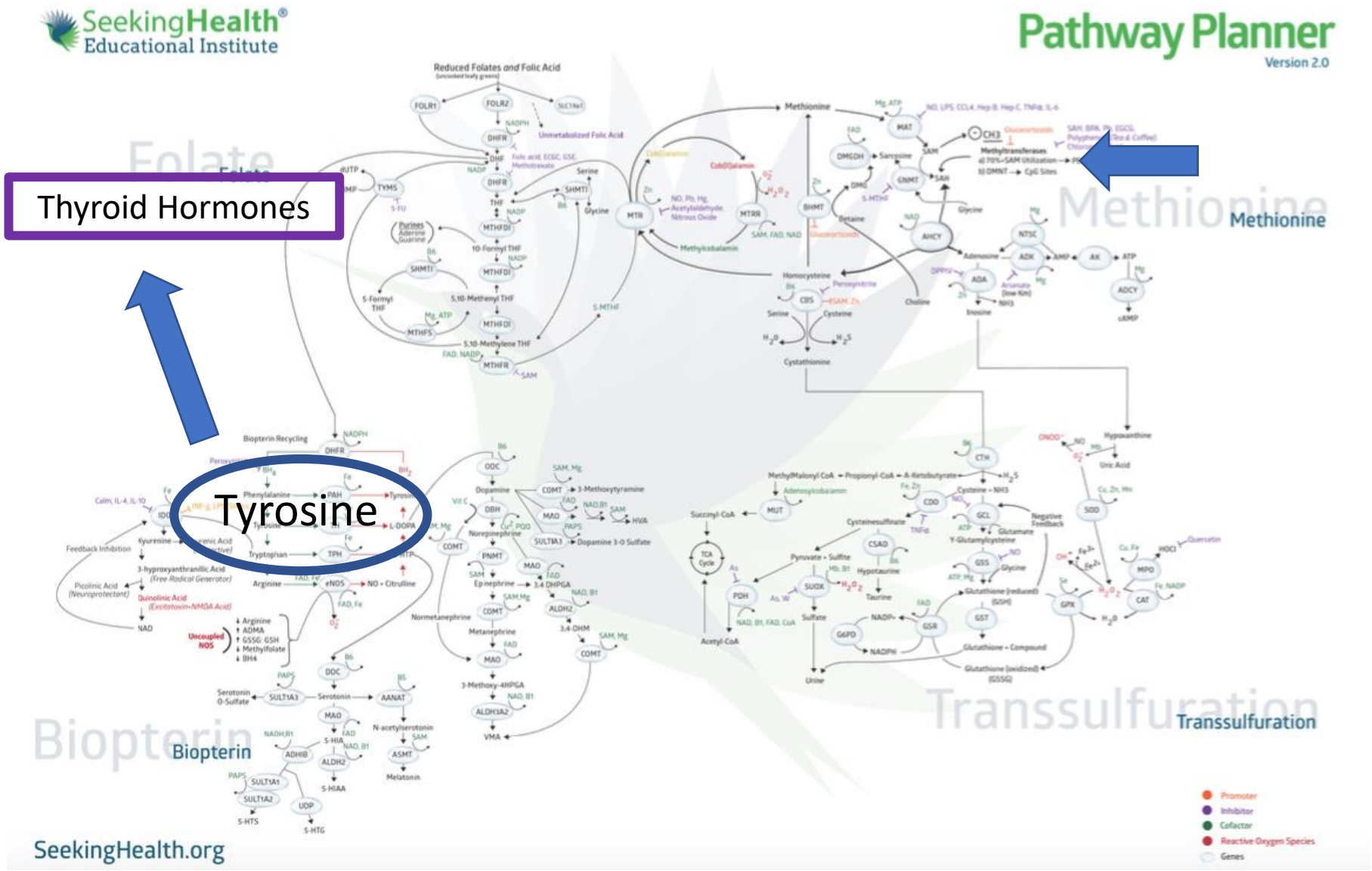


https://www.easynotecards.com/notecard_set/84284#&image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Thyroid Hormones
Tyrosine
Folate
Methionine
Biopterin
Transsulfuration
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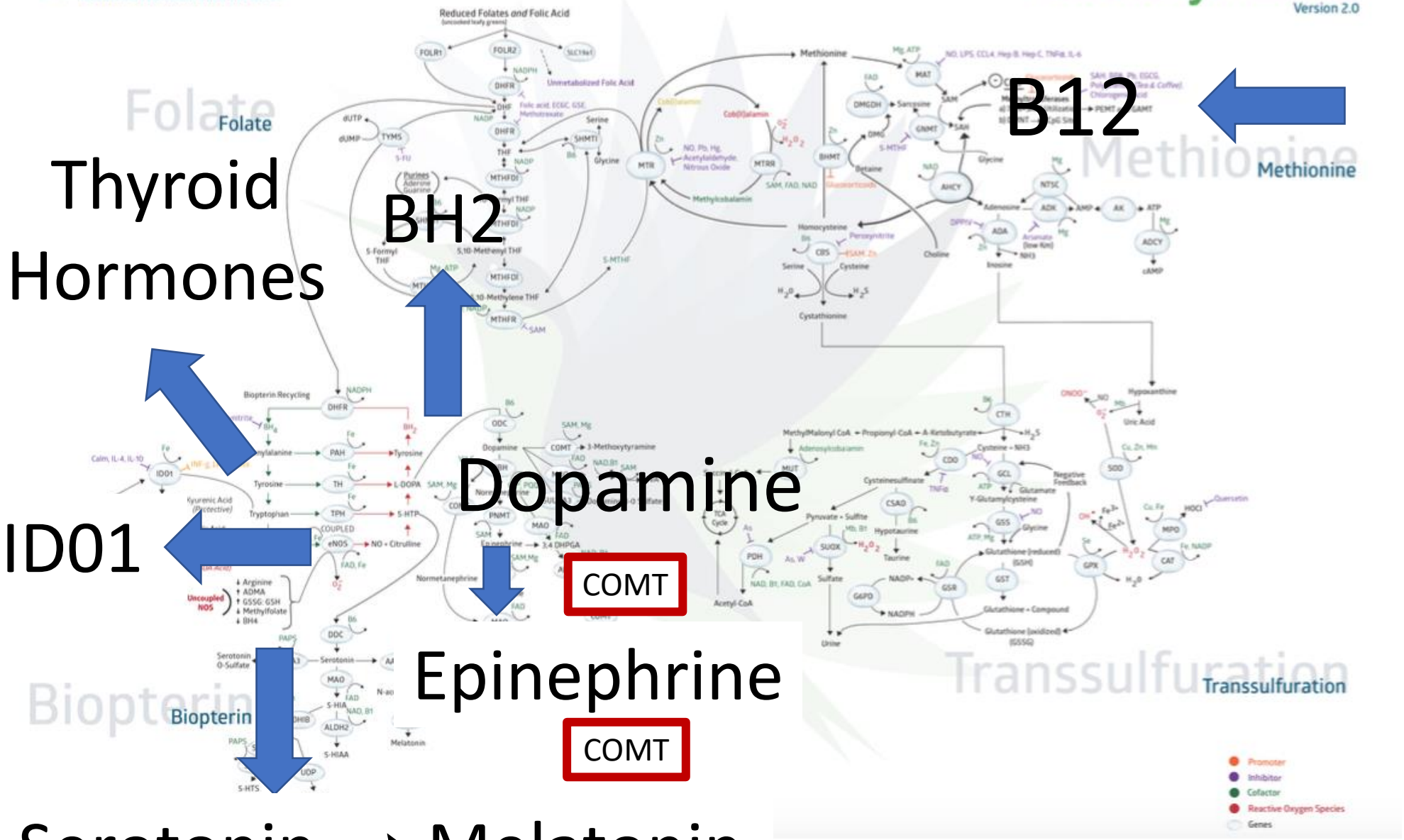


Thyroid Hormones

BH2

B12

ID01

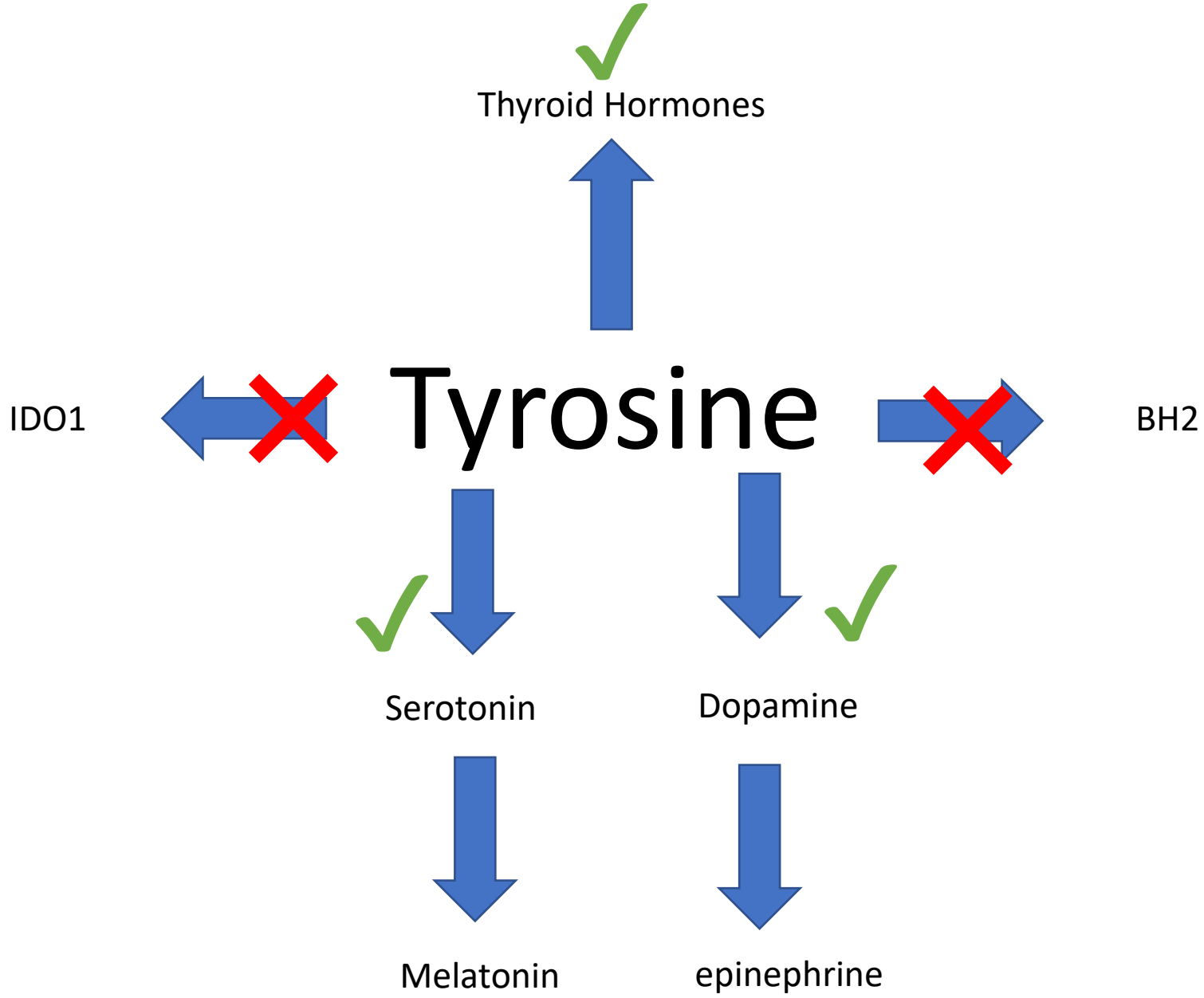
Dopamine

COMT

Epinephrine

COMT

Serotonin → Melatonin


Thyroid Hormones
IDO1
Tyrosine
BH2
Serotonin
Dopamine
Melatonin
epinephrine

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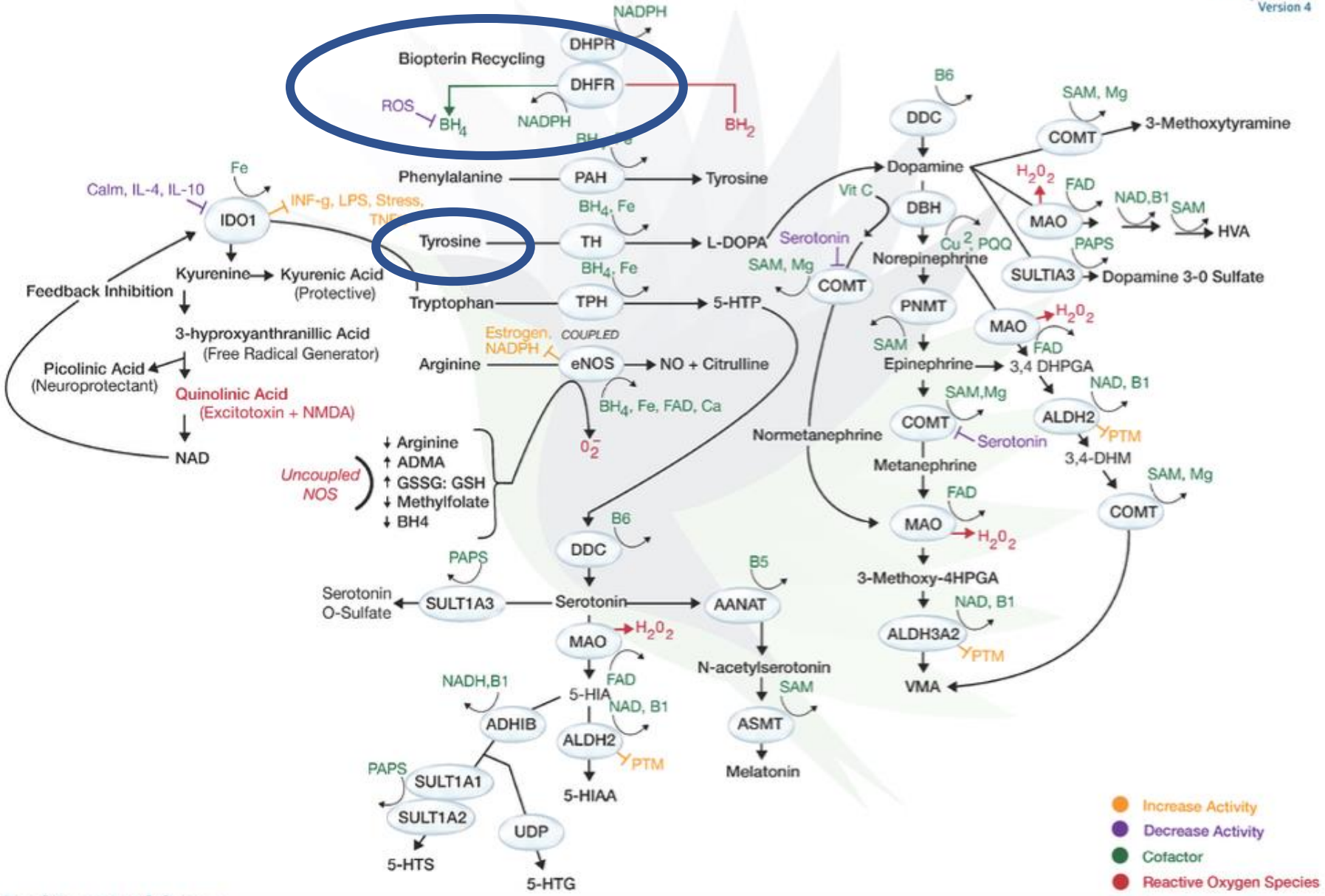
Pathway Planner

Biopterin

Version 4



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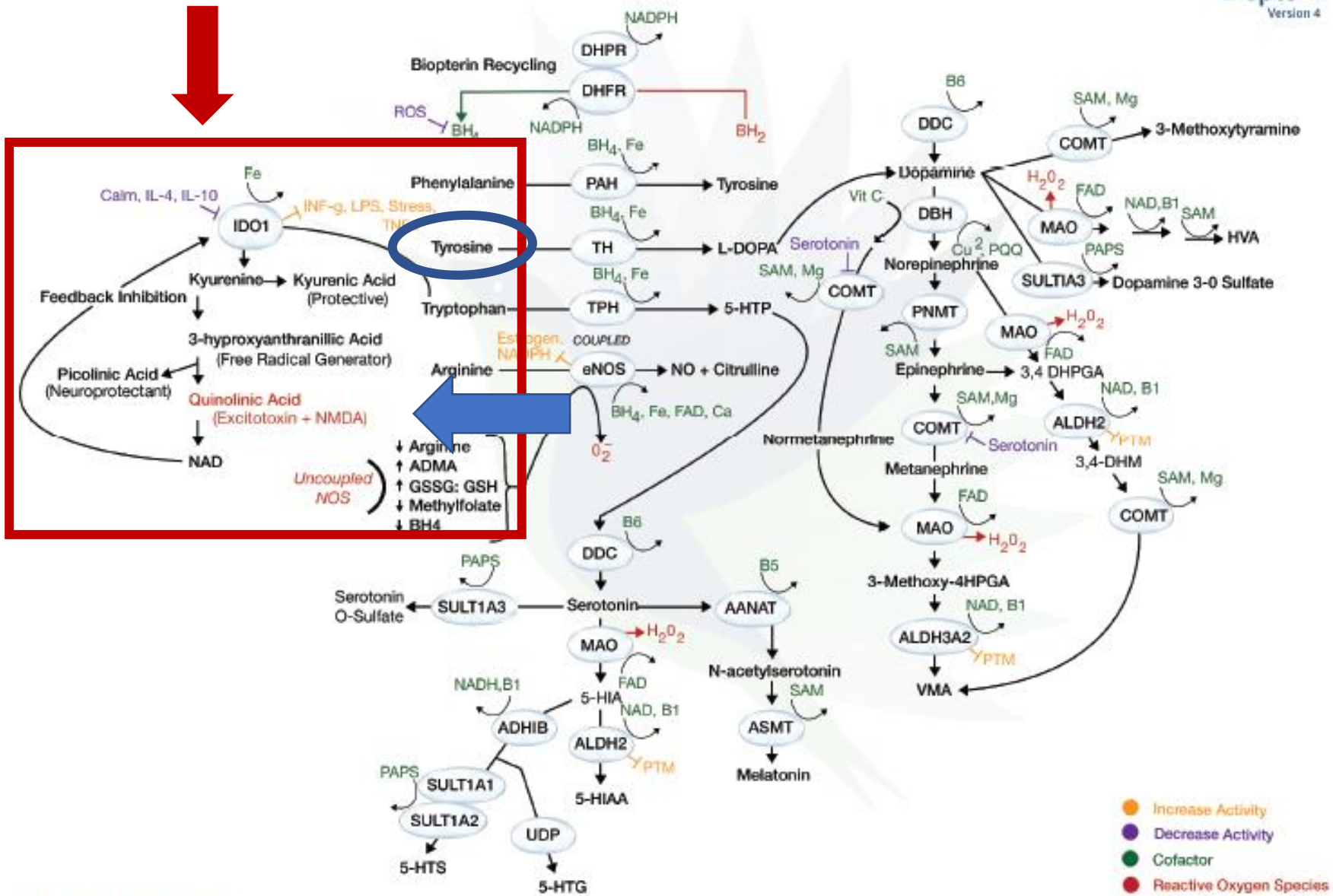
Biopterin

Version 4



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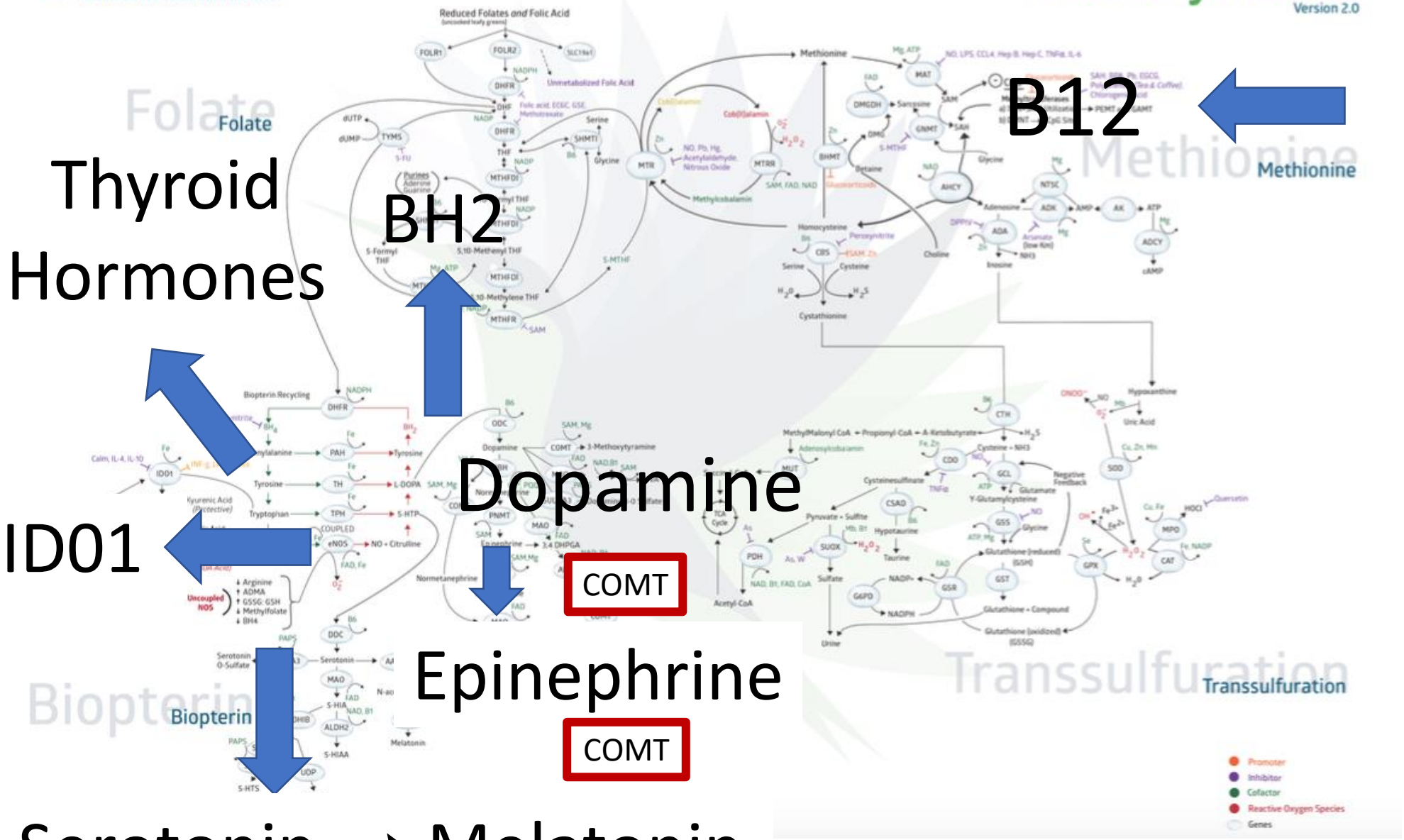


Thyroid Hormones

BH2

B12

ID01

Dopamine

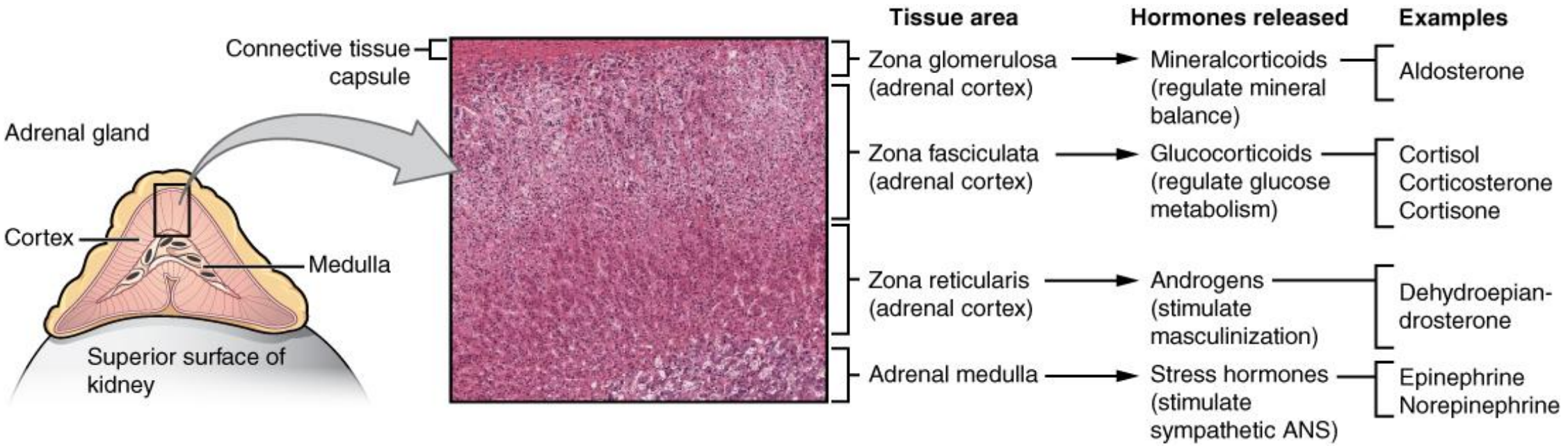
COMT

Epinephrine

COMT

Serotonin → Melatonin

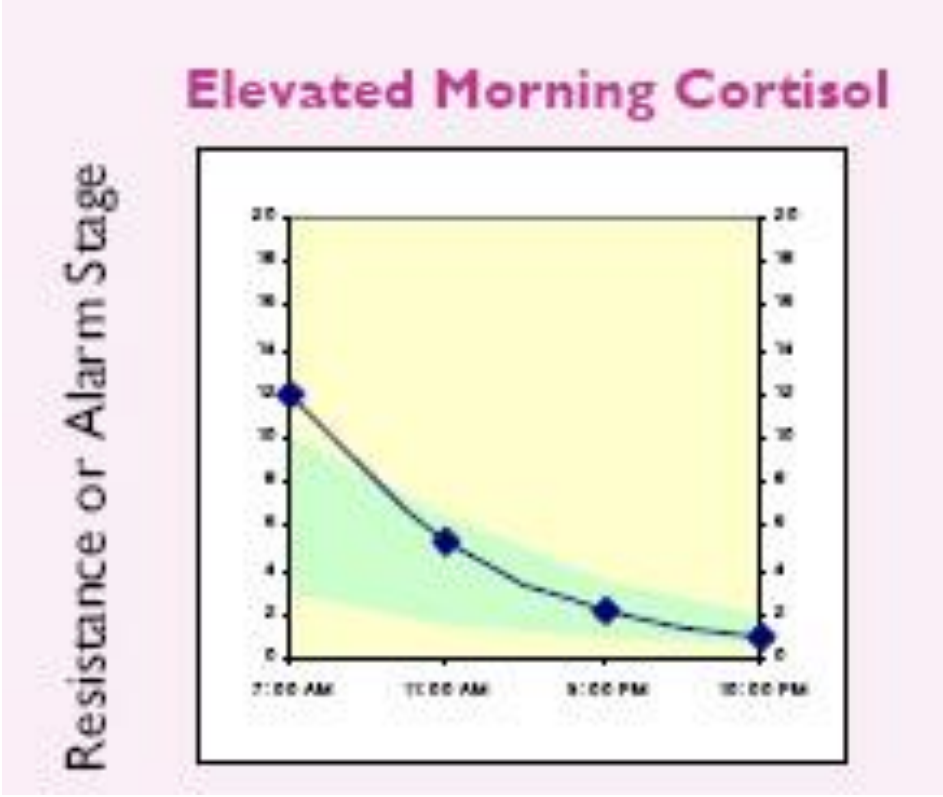
Adrenal Glands

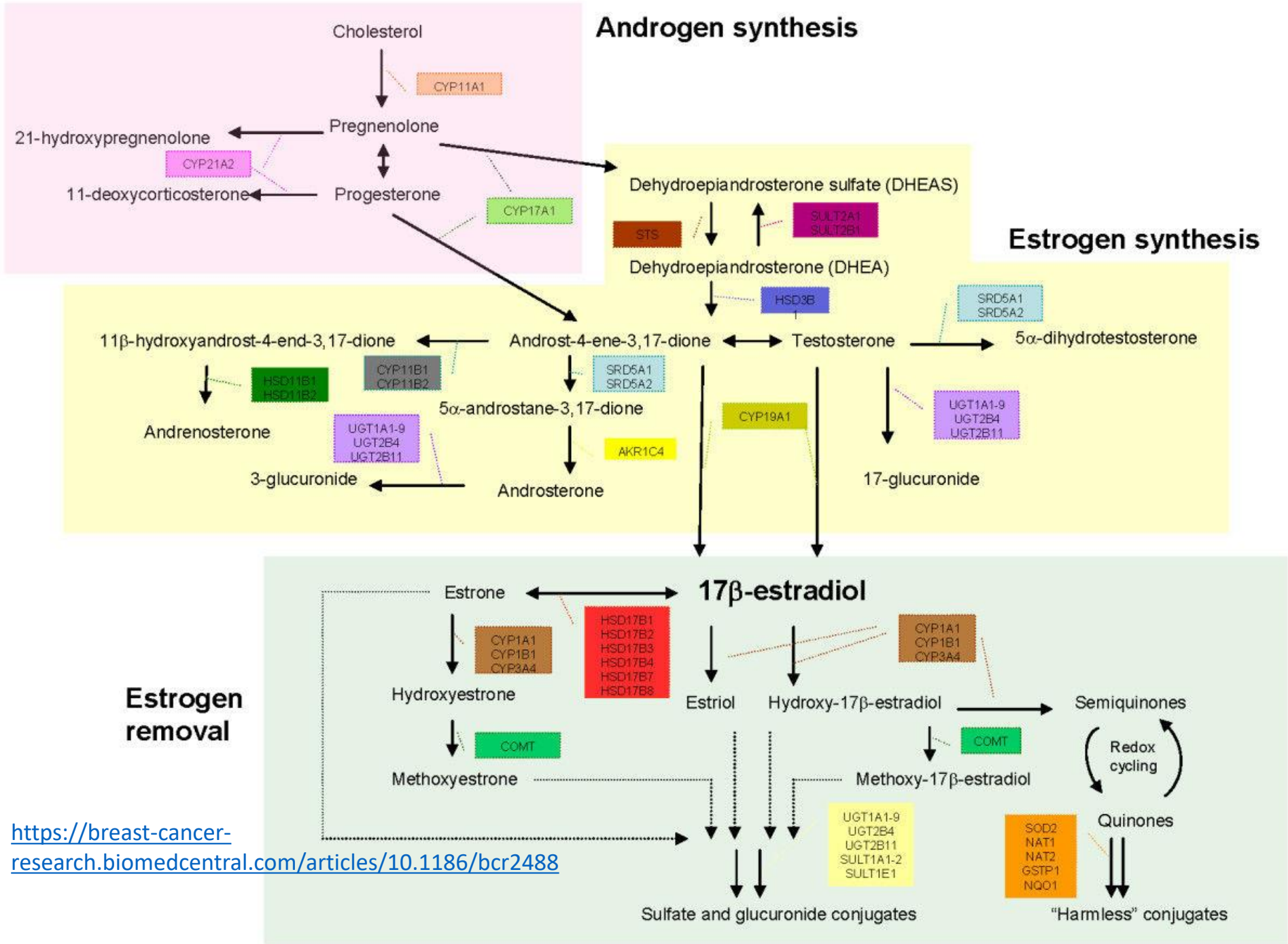


https://cnx.org/contents/FPtK1zmh@6.27:kaX2y2XZ@3/The-Adrenal-Glands

Cortisol Curve

- Cortisol is made in the adrenal glands and secreted with the same regularity every day
- There should be a higher amount of cortisol in the am
- Koenisburg potassium loss urine testing
- Serotonin testing





https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr2488

> Int J Tissue React. 2001;23(3):73-9.

The suppressive mechanism of histamine release from rat peritoneal mast cells of iodine-enriched eggs

H Inoue [1], H Funayama, K Sekimoto, E Miura, N Kumagai

Affiliations + expand

PMID: 11517853

> Sci Rep. 2023 Apr 3;13(1):5398. doi: 10.1038/s41598-023-32552-1.

Dietary iodine attenuates allergic rhinitis by inducing ferroptosis in activated B cells

Yutaka Nakamura [1], Yozen Fuse [2], Seiga Komiyama [1], Takahiro Nagatake [3 4], Jun Kunisawa [4], Koji Hase [5 6 7]

Affiliations + expand

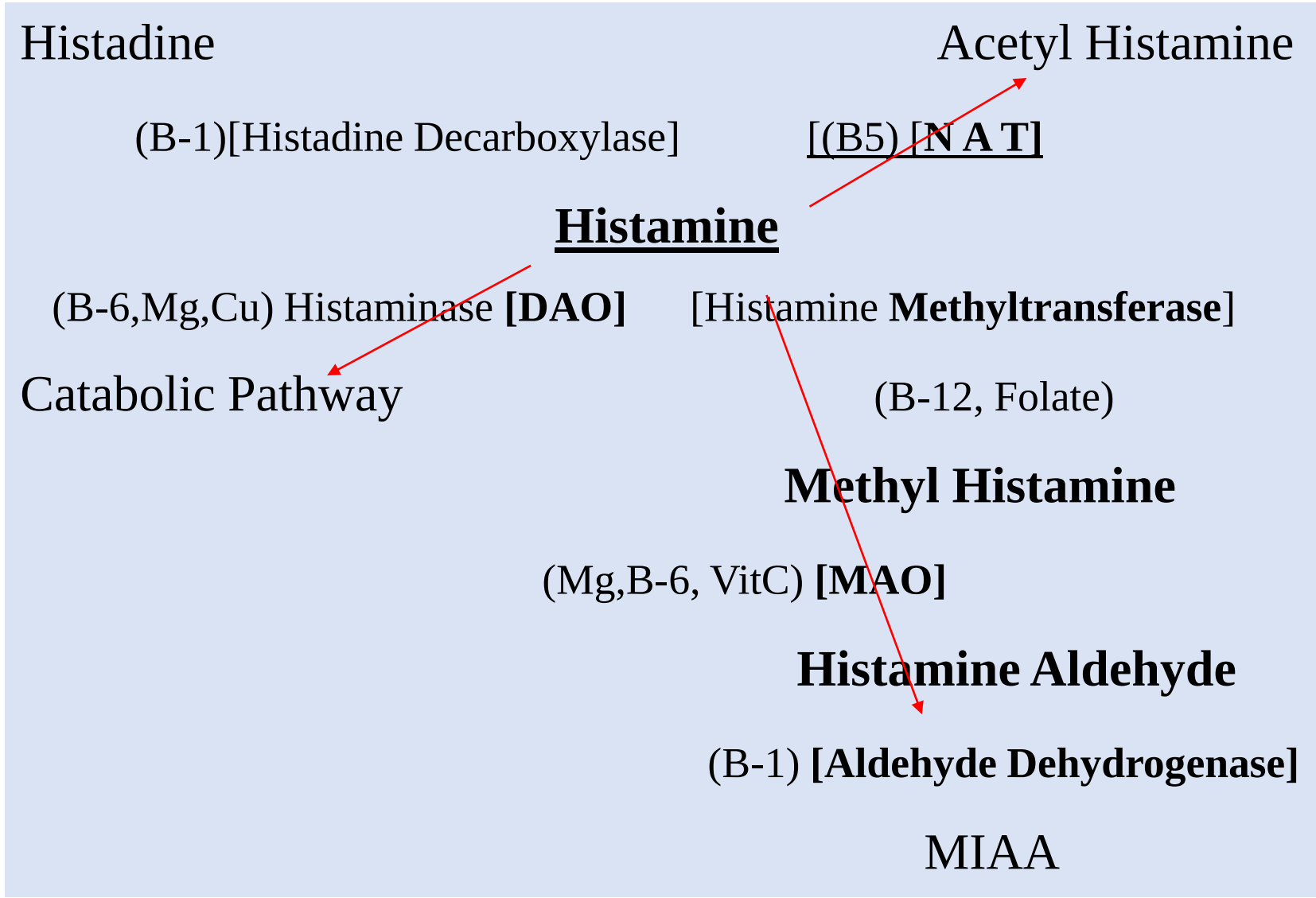
PMID: 37012320 PMCID: PMC10070403 DOI: 10.1038/s41598-023-32552-1

Free PMC article

MAO (monoamine oxidase)

- A family of enzymes that catalyze the oxidation of monoamines
- Monoamines are neurotransmitters such as phenylalanine, tyrosine, tryptophan, serotonin, melatonin, dopamine, noradrenaline and adrenaline and the thyroid hormones
- Involved in the regulation of cognitive processes such as emotion, arousal, and certain types of memory
- **“Warrior Gene”** – on the X chromosome so males have a greater tendency towards aggression

EXCEPTIONAL ND


Histadine
Acetyl Histamine
(B-1)[Histadine Decarboxylase]
[(B5) [N A T]
Histamine
(B-6,Mg,Cu) Histaminase [DAO]
[Histamine Methyltransferase]
Catabolic Pathway
(B-12, Folate)
Methyl Histamine
(Mg,B-6, VitC) [MAO]
Histamine Aldehyde
(B-1) [Aldehyde Dehydrogenase]
MIAA

MAO (monoamine oxidase)

- Acetylation - B5 – 1 gram to 2 grams?
- Homozygous MAO A or MAO B
  - Histamine surges
  - If they are already anxious, they become more anxious, shaky and can’t sleep
- Methyl aggravators leading to increase histamine / bottlenecking at COMT… go back and support other histamine pathways, reduce inflammation in gut, heal membranes, provide antioxidants

EXCEPTIONAL ND

MAO

Anything that injure mitochondria such as oxidative stress, toxin exposure, and the aging process in general will cause an increase in MAO activity regardless of genetics

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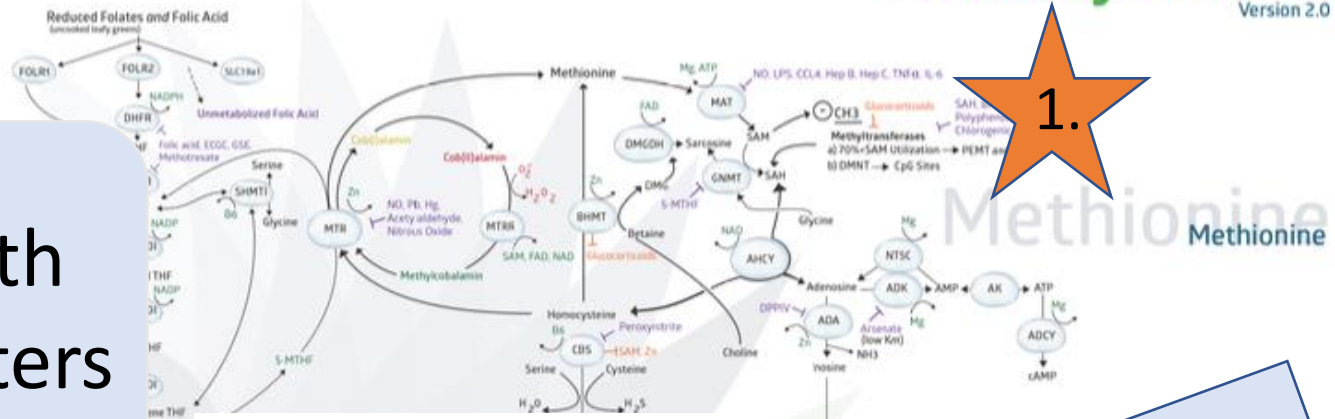
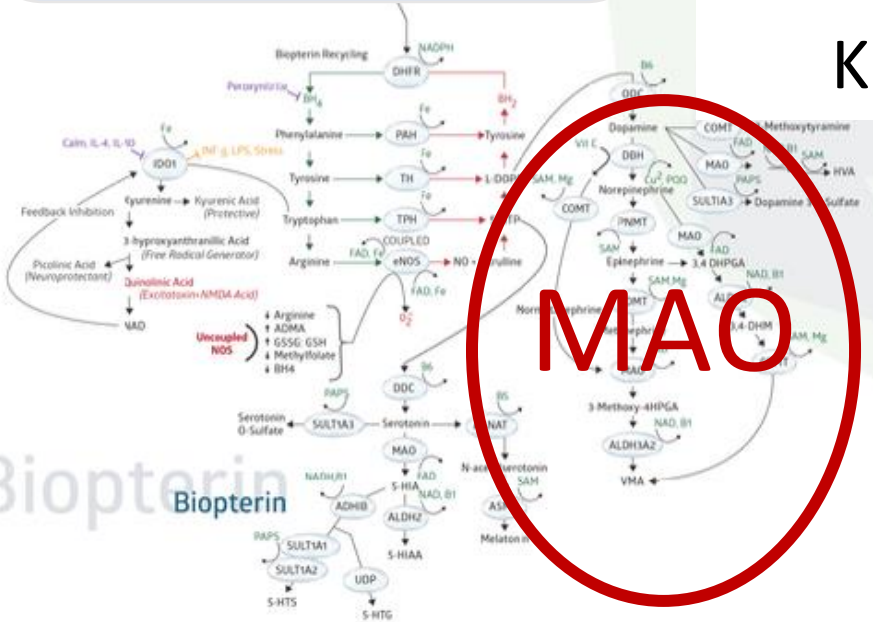
1.

3.
Then deal with
Neurotransmiters

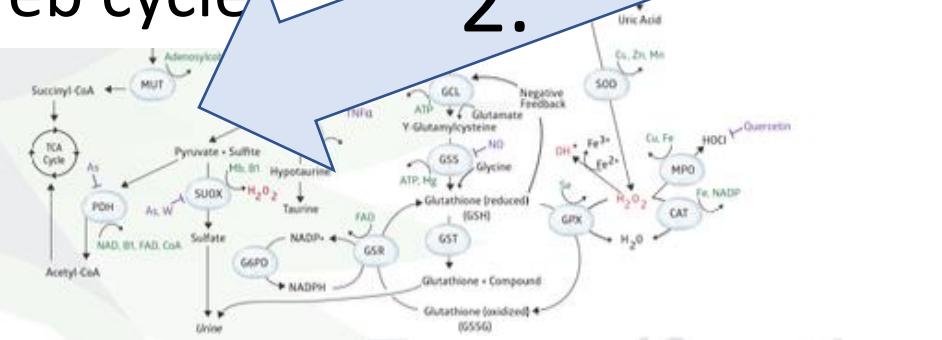
Pick up energy at
Kreb cycle

2.





MAO



Promoter
Inhibitor
Cofactor
Reactive Oxygen Species
Genes

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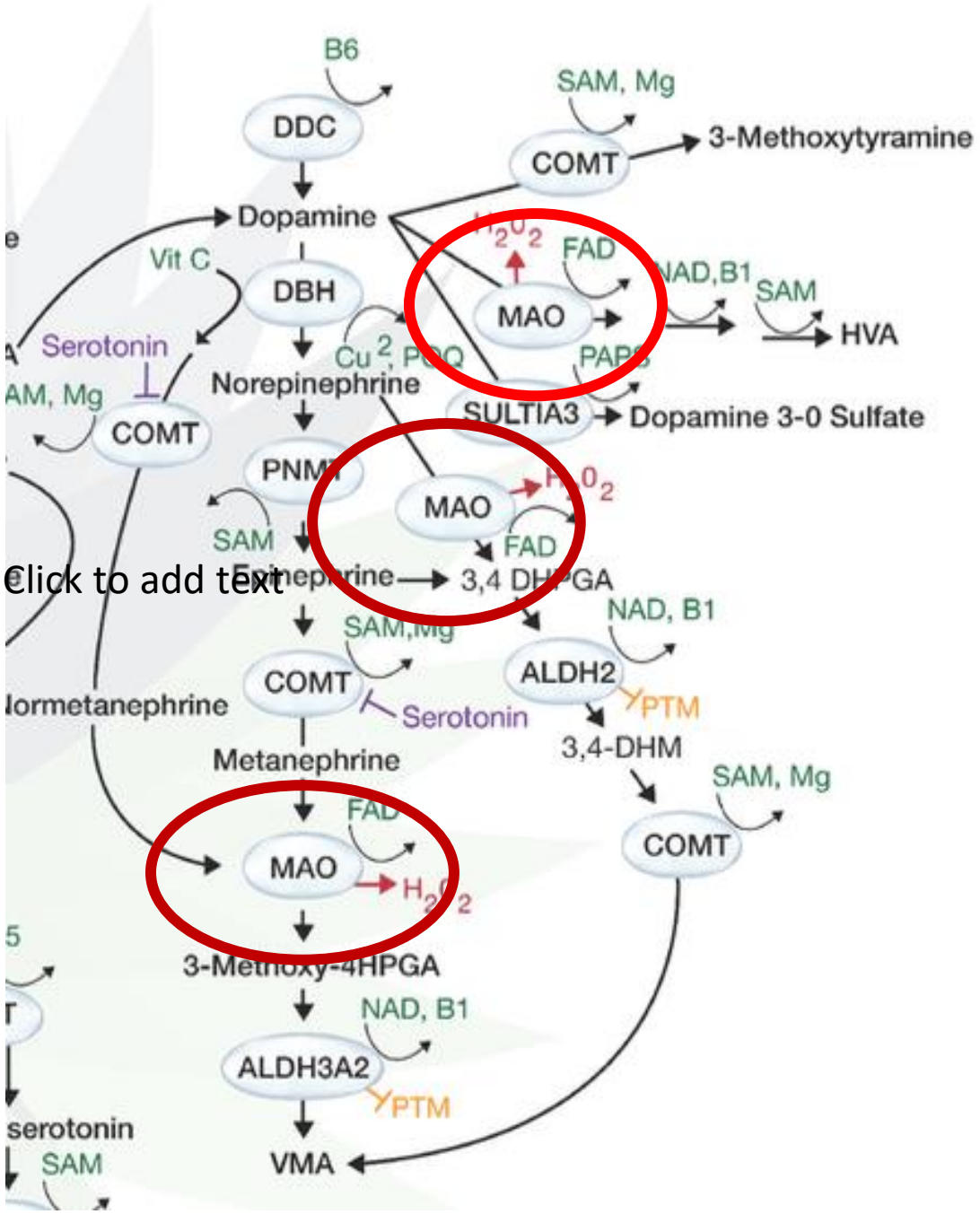
MAO



Click to add text

MAO Related Conditions

Aggression
OCD / ODD
Depression
Tics / Tourette Syndrome
ADD
Substance Abuse
Migraines
Mood swings
Anxiety

Original

Autism: The role of cholesterol in treatment

Alka Aneja, MD & Elaine Tierney

Pages 165-170 | Published online: 11 Jul 2009

- Cholesterol is essential for neuroactive steroid production, growth of myelin membranes and normal embryonic and fetal development
- Cholesterol modulates the oxytocin receptor, ligand activity and G-protein coupling of the serotonin-1A receptor
- Overgrowth of yeasts (which feed on carbyhydrates) depletes biotin needed to produce cholesterol

spectrum disorders (ASDs), as observed in Smith-Lemli-Opitz syndrome (SLOS) and some subjects with ASDs in the Autism Genetic Resource Exchange (AGRE). A clinical diagnosis of SLOS can be confirmed by laboratory testing with an elevated plasma 7DHC level

MAO Workarounds

- St. John's Wort
- 5-HTP
- Lavender
- Vitamin C
- B6
- B2 (cofactor)
- Support acetylation histamine pathway – B5