VibrantWellness

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# Neurotransmitter Interpretive Guide

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# WHAT ARE NEUROTRANSMITTERS?

The nervous system is one of the most complex and highly organized systems in the body. It allows the body to communicate and 'sense' the outside world and control many internal bodily functions. The nervous system is comprised of neurons, which are specialized nerve cells that receive sensory input, process signals, and transmit information. It is composed of two branches, the central nervous system, which includes the nerves in the brain and spinal cord and the peripheral nervous system, which includes all other nerve cells in the body. When the nervous system receives messages, or input, they initially travel through the neurons as electrical signals. Once the messages reach the end of the neuron, they stimulate the release endogenous chemicals, called neurotransmitters, from synaptic vesicles. The neurotransmitters cross the synaptic cleft, which is the space between the cells, where they can interact with postsynaptic receptors on the cell receiving the messages. This allows for communication between neurons or other body tissues and cells.

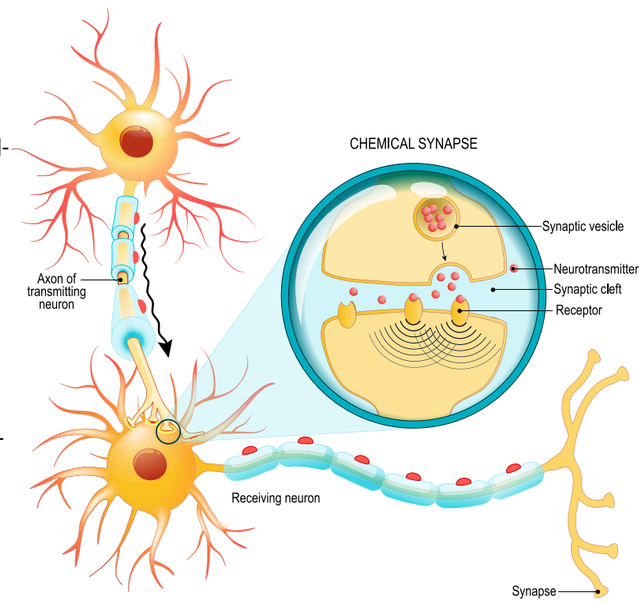
*A neurotransmitter is an endogenous chemical messenger that is secreted by a neuron in response to an electrical signal, and crosses a synapse to communicate with another cell, such as another neuron, gland or muscle celli.*

Neurotransmitters are classified into two main categories, inhibitory or excitatory, based on their ability to generate action potentials, which is another term used to describe an electrical signal in the neuron. Some neurotransmitters can be classified as both inhibitory and excitatory, depending on the location or context of signaling.

**Inhibitory:** Inhibitory neurotransmitters act as the "brakes" or "off switch" in nervous system communication. They decrease or inhibit the generation of action potentials by opening ligand-gated potassium ion channels, leading to an increase in negative charge inside the neuron and local hyperpolarization. Inhibitory neurotransmitters include gamma-aminobutyric acid (GABA), serotonin, glycine, and acetylcholine.

**Excitatory:** Excitatory neurotransmitters act as an "accelerator" or "on switch" within the nervous system by firing off action potentials, which is the generation of electrical signals that excite other neurons. Excitatory neurotransmitters cause an opening of ligand-gated sodium ion channels, which allows sodium to flow into the cell and become less negative, leading to local depolarization. Excitatory neurotransmitters include acetylcholine, dopamine, norepinephrine, epinephrine, glutamate, histamine, phenethylamine (PEA).

Neurotransmitters are also further categorized based on their type. Monoamine neurotransmitters include serotonin, epinephrine, norepinephrine and dopamine, amino acid neurotransmitters include GABA and glutamate, trace amines include PEA, tyramine and tryptamine, and acetylcholine is listed in a category by itself.




Neurotransmitters are involved in an intricate symphony of communication within the nervous system. They are involved in many physiological processes in the body, from regulating mood, heart rate, sleep regulation, digestion, appetite, muscle movement, breathing, learning, memory, motivation, pain and many more functions. Imbalances in neurotransmitters are seen in many conditions and disease states. Well established associations include depression with low serotonin levels, Parkinson's disease with low dopamine, and epilepsy with high glutamate levels. Understanding a patients' neurotransmitter levels can allow for individualized treatment and interventions to help improve any symptoms or conditions they are experiencing.



# Conditions associated with neurotransmitter imbalance

Neurotransmitter testing can provide insightful information for various conditions, but are most commonly used with neurological and mental health disorders. Ideal candidates for neurotransmitter testing includes anyone with the following conditions or symptoms:

- Addictive behaviors
- ADHD/ADD
- Alzheimer's Disease
- Altered pain response
- Anger
- Anxiety
- Appetite (poor/excess)
- Autism spectrum disorder
- Autoimmune disease
- Autonomic nervous system disorders
- Bipolar disorder
- Brain fog
- Cancer
- Cardiovascular disease
- Chronic Fatigue
- Constipation/diarrhea
- Compulsive behaviors
- Dementia
- Depression
- Developmental problems
- Difficulty concentrating
- Diabetes
- Dysmotility
- Eating disorders
- Epilepsy
- Fatigue
- Fibromyalgia
- Headaches
- Hormonal Imbalances
- Hyperactivity
- Huntington's Disease
- IBS
- Insomnia
- Irritable bowel disease
- Irritability
- Low libido
- Low motivation
- Medication adjustments
- Memory impairments
- Migraines
- Mood disorders
- Motor dysfunction
- Movement disorders
- Multiple sclerosis
- Muscle twitching/spasms
- Obsessive compulsive disorder
- Panic attacks
- Parkinson's disease
- Reflux
- Schizophrenia
- Seizures
- Sensory processing disorders
- Scoliosis
- Tremors
- Weight issues
- Vomiting

# VIBRANT LABS

Additional tests that may be useful in conjunction with neurotransmitter test interpretation:

Micronutrient Test

Neurotransmitters require specific nutrient cofactors and amino acids for enzymatic reactions responsible for neurotransmitter synthesis and degradation. When a neurotransmitter test is paired with a micronutrient test, it's easier to understand whether an intermediate or neurotransmitter is low/high due to nutrient or amino acid deficiencies. It is also helpful to guide treatment protocols and interventions when micronutrient levels are known. Specific nutrients that are important for neurotransmitter pathways include: choline, B2, B3, B5, B6, folate, B12, magnesium, copper, vitamin C, zinc, Vitamin D, glutamine, cysteine

Gut Zoomer

Gastrointestinal dysfunction can play a significant role in neurotransmitter imbalances. Digestive insufficiency and malabsorption can impair the body's ability to absorb essential micronutrients and amino acids that are essential for neurotransmitter synthesis and degradation. Dysbiosis can contribute to proinflammatory cytokine and lipopolysaccharide (LPS) release that can influence neurotransmitter pathways. The gut can also be a major site of neurotransmitter synthesis, such as seen with the enterochromaffin cells, which are responsible for producing over 90% of the body's serotonin. The gut-brain axis is also a critical connection that may influence neurotransmitter levels. Understanding digestive processes and the ecosystem of the gut can provide better guidance for treatment.

Urinary Hormones

Hormones and neurotransmitters have influential relationships on each other. Specific hormones, such asestrogen, may increase neurotransmitters such as serotonin. Cortisol, also measured on the Urinary Hormones test, has been shown to affect neurotransmitter pathways, such as the activation of the kynurenine pathway. In the CNS, sex hormones act via steroid receptors. They also have an effect on different neurotransmitters such asGABA, serotonin, dopamine, and glutamate[3]. By understanding other factors that contribute to neurotransmitter levels, more targeted interventions can be addressed.

Wheat Zoomer

Immune sensitization to gluten has been shown to affect neurotransmitter balance. In particular, anti-gliadin antibodies have been shown to react against glutamic acid decarboxylase (GAD65), an enzyme responsible for converting glutamate to GABAvi. Identifying dietary influences that affect neurotransmitter imbalances can provide another avenue for treatment and interventions.

Total Tox Bundle (Heavy Metals, Environmental Toxins, and Mycotoxins)

Environmental toxins can interfere with neurotransmitter balance in the body. They can alter neuron functioning in multiple ways, including inhibition of enzymes, affecting receptors, interfering with clearance, influencing depolarization and more. One example is the exposure of organophosphate pesticides, which can block acetylcholinesterase, the enzyme responsible for breaking down acetylcholine, leading to higher levels of the neurotransmitter. Understanding environmental toxin levels can allow for proper avoidance of agents leading to neurotransmitter imbalances and guidance for treatment and interventions.

Neural Zoomer Plus:

The Neural Zoomer Plus provides valuable information about antibodies associated with neurological autoimmunity and cognitive decline. Understanding neural autoimmunity can help with the interpretation of neurotransmitters and understanding the causative factors leading to abnormal levels. The Neural Zoomer Plus includes markers such as: anti-acetylcholine, anti-glutamate, anti-dopamine receptor 1 and 2, anti-glycine, anti-NMDA receptor, anti-hydroxytryptamine, and anti-GABA.

Methylation & Genetic Tests:

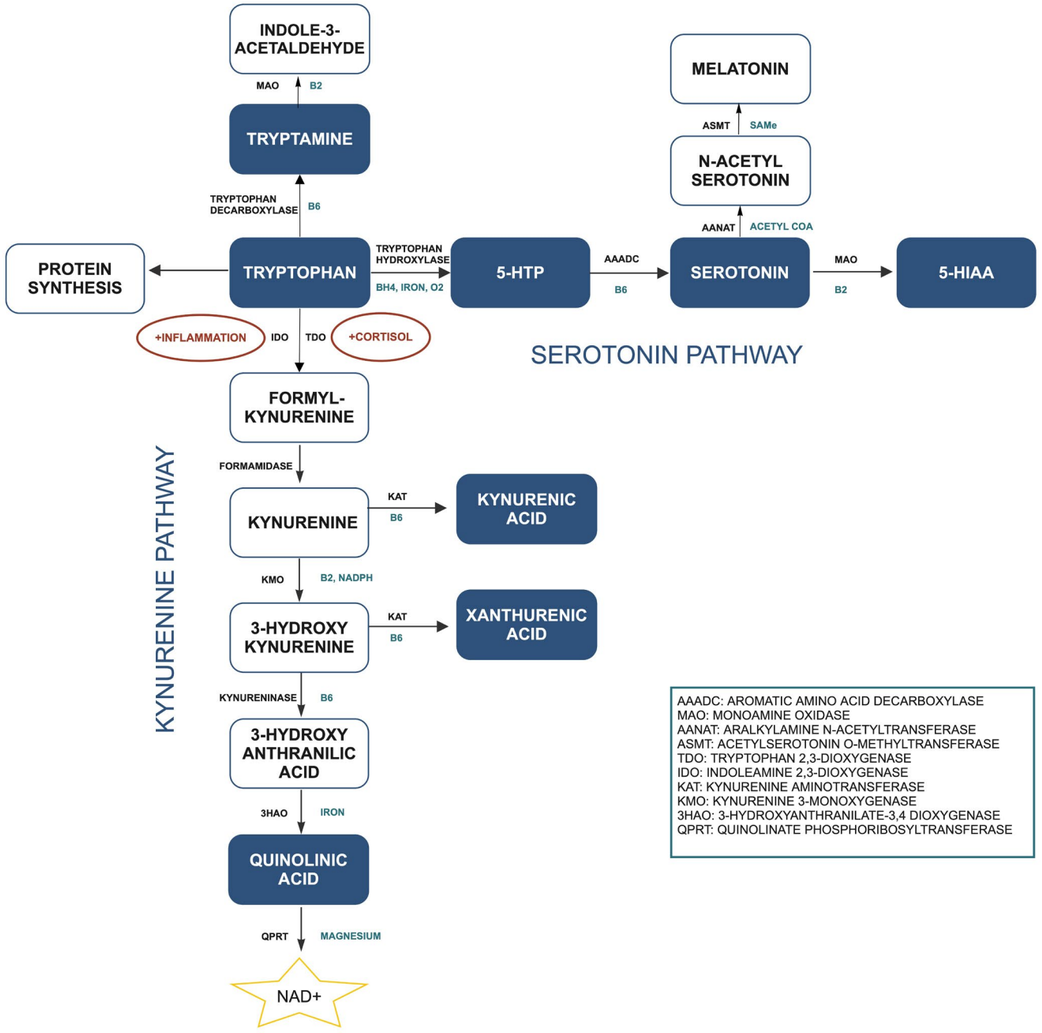
Understanding genetic influences on enzymes that regulate neurotransmitters is helpful to guide treatment and intervention protocols. Particular importance is placed on MTHFR, COMT and MAO enzymes as they play a critical role in neurotransmitter synthesis and degradation.



# GENERAL INTERPRETATION GUIDELINES

1. **FOLLOW THE PATHWAYS:** Each marker tested is part of enzymatic reactions and any variability in the enzymatic reaction can influence the level of the specific marker. Assess for nutrient cofactors, medications, supplements, genetic polymorphisms, and other factors that may impact the enzymes involved.
2. **LOOK FOR TRENDS:** There are many factors that can impact multiple neurotransmitters and pathways. Understanding these trends in the neurotransmitters cascade can help identify appropriate interventions. One example is vitamin B6, which is an important nutrient cofactor in the synthesis of multiple neurotransmitters such as serotonin, dopamine, tryptamine and tyramine. Therefore, a single nutrient deficiency can impact multiple neurotransmitters. Another example relates to COMT, which is an important enzyme that aids the degradation of dopamine, norepinephrine and epinephrine and therefore any genetic SNP involved with this enzyme can impact multiple catecholamines.
3. **BALANCE INHIBITORY & EXCITATORY NEUROTRANSMITTERS:** The total level of excitatory neurotransmitters can impact excitation in the nervous system and the total level of inhibitory neurotransmitters can impact inhibition in the nervous system. This is important because even if the neurotransmitters are within normal limits, but many excitatory neurotransmitters are in the upper level of normal and many inhibitory neurotransmitters are on the lower level of normal, there could be excess excitation in the nervous system and interventions to balance that discrepancy would be important.
4. **SUPPORT INHIBITION FIRST:** When balancing neurotransmitters most practitioners prefer to start with interventions that support inhibitory neurotransmitters first before balancing excitatory neurotransmitters. There are some exceptions to this, however, this seems to best tolerated in most patients.
5. **ADDRESS ROOT CAUSES:** Even though the results may indicate abnormal neurotransmitter levels, the focus should be on addressing root causes of the imbalance. A good example of this deals with the serotonin and the kynurenine pathway. When there are elevated levels of stress (cortisol), infections, or inflammation, tryptophan can be shifted away from serotonin synthesis and used for the kynurenine pathway. While supplementing with 5-HTP might help to remedy lower serotonin levels, and may be helpful in the short term, the real issue might be a subclinical infection, factors that increase inflammation, or uncontrolled stress.
6. **UNDERSTAND THE SYMBIOSIS:** Neurotransmitters are the communication messengers of the nervous system and are impacted by multiple factors. Imbalanced hormone levels can result in increased or decreased neurotransmitters, therefore it's important to understand the relationship between imbalanced hormones and imbalanced neurotransmitters. Elevated levels of environmental toxins can have a negative effect on neurotransmitter balance. While these are just two examples, the concept of symbiosis is important as it relates to neurotransmitter levels.
7. **PAIR RESULT WITH CLINICAL SYMPTOMS:** The neurotransmitter test provides a snapshot in time of the nervous system's communication. Even though the neurotransmitters may be a representation of the central nervous system, the results provide the totality of the neurotransmitters in the body. Therefore, there may be elevated levels in the periphery and lower amounts in the CNS, or vice versa. As such, it's important to assess the patient's symptoms in conjunction with test results, so that they act like another tool for the practitioners' assessment of the patient's neurochemistry.

# TRYPTOPHAN METABOLISM






# TRYPTOPHAN

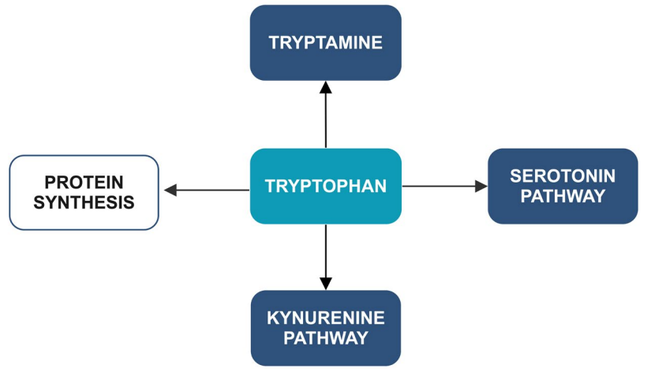
## What is tryptophan?

Tryptophan is an essential large neutral amino acid that plays an important role in multiple physiological functions and as a precursor for multiple pathways in the body. Tryptophan is abundant in a variety of different protein-rich food sources, however, it is the least abundant amino acid in cells[5]. Tryptophan transport into the brain utilizes the same transport system as all other large neutral amino acids (LNAA). Due to the competition with other amino acids, and the fact that tryptophan is the least abundant amino acid in protein, tryptophan absorption into the brain is often very limited. Increasing tryptophan concentrations in relation to other amino acids or decreasing other competitive amino acids (LNAA) are two ways to increase absorption into the brain[6]. A meal higher in carbohydrates and lower in protein stimulates insulin release, which directs amino acids into muscle tissue while tryptophan remains in the bloodstream[7]. This action diminishes plasma levels of the amino acids (LNAA) that compete with tryptophan for transport into the brain and therefore preferentially allows tryptophan to cross the blood brain barrier (BBB)[8]. Since tryptophan is a precursor for serotonin, melatonin, tryptamine and the kynurenine pathways, varying tryptophan levels can affect all of the corresponding markers.

## What are the functions and pathways of tryptophan?

Tryptophan plays an important role in regulating mood, sleep, skeletal muscle, cognition, and behavior. A synopsis of tryptophan's main roles are identified below.

1. **Biosynthesis of proteins:** Roughly 1-5% of tryptophan is used to form proteins in the body.
2. **Serotonin & Melatonin synthesis:** Tryptophan is a precursor to serotonin and melatonin synthesis. Tryptophan is converted to 5-HTP by the enzyme tryptophan hydroxylase, which requires the nutrient cofactors BH4 and iron. 5-HTP can then be converted to serotonin by the enzyme L-aromatic amino acid decarboxylase, which requires the nutrient cofactor vitamin B6. Serotonin can then synthesize melatonin, or it can be broken down to 5-HIAA. Roughly 1-5% of tryptophan is metabolized to 5-HTP for serotonin production in the body and only 1% is used for serotonin synthesis in the brain[9].
3. **Kynurenine Pathway:** Tryptophan is catabolized by the rate limiting enzymes of the kynurenine pathway, indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). This pathway forms many intermediates, including kynurenic acid, xanthurenic acid and quinolinic acid and the end product, nicotinamide adenine dinucleotide (NAD+). Factors such as inflammation, infections and high cortisol can upregulate tryptophans' catabolism toward the kynurenine pathway and shift tryptophan's use away from other pathways, including protein and serotonin synthesis. Roughly 90-95% of tryptophan is utilized in the kynurenine pathway[9].
4. **Tryptamine synthesis:** Tryptophan can also be metabolized to form tryptamine with vitamin B6 as a cofactor.



## LOW TRYPTOPHAN

Low tryptophan levels can impact multiple biochemical pathways potentially resulting in lower protein synthesis, lower serotonin and melatonin levels and lower kynurenine pathway intermediates, including NAD+. Some symptoms of low tryptophan may include low mood10, depression, panic attacks, memory impairments[11], impaired cognition, poor sleep, skeletal muscle atrophy[12], PMS[13], poor olfactory function[14], motion sickness, and obsessive-compulsive behaviors. Low levels are often due to insufficient intake from poor food sources, digestive insufficiency, or poor absorption due to factors such as fructose malabsorption[15]. Additionally, tryptophan levels may be lower if there is a higher need for any of the pathways, and therefore, it's important to assess tryptophan levels in conjunction with the corresponding pathways and intermediates.

## HIGH TRYPTOPHAN

High tryptophan levels can impact multiple biochemical pathways involving tryptophan. High levels are often due to direct supplementation or amino acid-based supplements/formulas. Insufficient nutrient cofactors for the conversion of tryptophan to other intermediates, such as 5-HTP, can impact tryptophan levels. If tryptophan is high and 5-HTP is low/suboptimal, there may be a deficiency/insufficiency of the nutrient cofactors BH4 and iron, which are required for tryptophan hydroxylase. There are many nutrients that are also important for BH4 synthesis and regeneration, including 5-MTHF, magnesium, zinc, and niacin[18]. Defects in methylation may impair BH4 synthesis and consequently tryptophan hydroxylase enzyme activity. Genetic polymorphisms of TPH1 and TPH2 may interfere with tryptophan metabolism and can be related to many conditions, such as depression, aggression, schizophrenia, and suicidality[16]. Higher levels of tryptophan can decrease absorption of other LNAA into the brain, including tyrosine and can therefore affect neurotransmitters like dopamine. Symptoms of increased anger, hostility and aggression were seen in women with higher tryptophan levels, but not men[17]. When tryptophan is elevated, caution is required with certain medications, such as selective serotonin reuptake inhibitors (SSRI's) and monoamine oxidase inhibitors (MAOIs) due to the risk of serotonin syndrome.

### Clinical Pearl:

Even if tryptophan levels are sufficient in the body, they compete with other large neutral amino acids for absorption into the brain. Therefore, it's important to assess tryptophan levels in conjunction with other amino acids. Assessing intermediates along the different tryptophan pathways can provide useful information about how tryptophan is being utilized in the body.



## Tryptophan Considerations

| | LOW TRYPTOPHAN | HIGH TRYPTOPHAN |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **L-Tryptophan[17]:** up to 50mg/kg/day for up to 6 weeks.<br>  • May competitively inhibit absorption of other large neutral amino acids into the brain, therefore caution is warranted if other neurotransmitters are low, such as dopamine. | • Discontinue supplements with L-tryptophan<br>• Support nutrient cofactors for tryptophan hydroxylase:<br>  • **BH4:** Nutrient cofactors for synthesis and regeneration of BH4 listed below[18]<br>  • 5-Methyltetrahydrofolate/folate: 400-800mcg<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>  *Note: Inflammation and oxidative stress may decrease BH4 levels[19]*<br>  • **Iron:** 15-30mg |
| DIETARY CONSIDERATIONS | **Increase tryptophan rich foods[17]:**<br>• Turkey, chicken, duck, eggs, beef, pork chops, salmon, cod, soy, legumes, seeds (sesame, chia, pumpkin, sunflower), dairy, oats<br>• Alpha-Lactalbumin is a whey protein that contains a rich source of tryptophan[20]<br>• Note: Collagen does not contain tryptophan<br>• Note: a typical diet provides .5-.2 grams of L-tryptophan daily | **Limit intake of tryptophan rich foods**<br>• Consider increasing foods higher in other amino acids,such as collagen, to deplete tryptophan levels.<br>*Consider these dietary interventions if marers such as serotonin are elevated and there are no other reasons for high tryptophan* |
| LIFESTYLE CONSIDERATIONS | • **Avoid exhaustive exercise[21]**<br>  • One study showed that exhausted exercise increased immune activation, decreased tryptophan concentrations by 12%, while also increasing kynurenine levels | *Lifestyle interventions to do not significantly affect high tryptophan levels* |
| TESTING CONSIDERATIONS | • **Gut Zoomer:** to assess for digestive insufficiency<br>• **Micronutrients:** to assess for nutrient deficiencies/ insufficiencies | • **Methylation Panel:** to assess for methylation impairments<br>• **Micronutrients:** to assess for nutrient deficiencies/ insufficiencies |

# 5-HTP

## What is 5-HTP:

5-Hydroxytryptophan (5-HTP), also known as oxitriptan, is an aromatic amino acid and metabolic intermediate in the biosynthesis of the neurotransmitter serotonin. Serotonin is an inhibitory neurotransmitter that is commonly referred to as the 'happiness molecule,' and plays an important role in mood, cognition, reward, learning, memory, sleep, pain, and satiety[22]. 5-HTP is a commonly used over the counter dietary supplement because its direct end product is serotonin synthesis, whereas tryptophan supplementation may be used for other pathways. 5-HTP is also preferentially used to boost serotonin levels within the CNS because it readily crosses the blood brain barrier (BBB). Serotonin is too large to cross the BBB and tryptophan requires active transport and competes with other LNAA[24].

## What are the functions of 5-HTP?

The main function of 5-HTP is to synthesize serotonin in the body, which can then be used to synthesize melatonin. In human studies, supplementation with 5-HTP has shown therapeutic benefits in patients with fibromyalgia, dementia of the Alzheimer's type (DAT), depression, panic disorder, migraines, ataxia, myoclonus, obesity (for weight management due to appetite suppression) and sleep disorders[22]. Oral intake of 5-HTP has been shown to significantly increase plasma human prolactin levels[22]. Another benefit of 5-HTP is its ability to scavenge free radicals and preserve membrane fluidity in situations of increased oxidative stress[22]. Research has shown that 5-HTP may also increase cortisol levels, particularly in individuals with affective disorders who were unmedicated[23].

## 5-HTP metabolism and pathways:

5-HTP is produced from the amino acid tryptophan through the enzymatic action of tryptophan hydroxylase, which is the rate-limiting enzyme in serotonin synthesis. This enzyme requires nutrient cofactors, including BH4 and iron and it's also dependent on oxygen[17]. Any factor that may decrease these nutrient cofactors, including nutrient deficiencies important for BH4 synthesis and regeneration, such as 5- methyltetrahydrofolate/folate, niacin, zinc and magnesium, may impair tryptophan hydroxylase enzyme activity[18]. Additional factors, such as MTHFR genetic SNPs or poor methylation, may also impair BH4 synthesis and consequently tryptophan hydroxylase enzyme activity. 5-HTP is normally rapidly converted to serotonin (5-HT) by the aromatic amino acid decarboxylase (AAADC), which requires vitamin B6 as a nutrient cofactor.




## LOW 5-HTP

Low levels of 5-HTP often result in lower levels of serotonin and melatonin since it is a precursor for their synthesis. Low 5-HTP often mimic symptoms of low serotonin and melatonin levels including depression, poor sleep, heightened pain response, lack of joy and constipation to name a few. Deficiencies in nutrient cofactors essential for tryptophan hydroxylase function, including BH4, iron and oxygen, may impair enzymatic activity and result in lower 5-HTP levels. Multiple factors can decrease the activity of tryptophan hydroxylase, including stress, insulin resistance, and nutrient deficiencies, particularly vitamin B6 and magnesium[24]. These factors may also upregulate the tryptophan 2,3-dioxygnase enzyme and shift tryptophan's use towards the kynurenine pathway and away from serotonin synthesis[24]. Some studies have shown that combination therapy of 5-HTP with SSRIs may improve an individual's response to treatment by providing additional building blocks for serotonin synthesis since SSRIs only act to prevent reuptake25. Extreme caution is warranted with combination therapy due to the potential risk of serotonin syndrome. It's important to assess 5-HTP levels in combination with serotonin levels; for example, if 5-HTP is low, but serotonin is high due to decreased breakdown or slowed MAO activity, then supplementing or supporting 5-HTP may not be recommended.

## HIGH 5-HTP

Elevated 5-HTP levels may result in increased serotonin levels within the CNS since it can cross the BBB. Symptoms of high5-HTP may mimic symptoms of high serotonin and can include symptoms such as nausea[24], vomiting, diarrhea, appetite suppression and reduced carbohydrate cravings[26] to name a few. The risk of serotonin syndrome is also a concern with high 5-HTP levels. Elevated levels are often a result of direct supplementation with 5-HTP or high tryptophan intake. Since vitamin B6 is required as a cofactor for the AAADC enzyme to convert 5-HTP to serotonin, a deficiency can result in higher levels of 5-HTP due to decreased enzymatic function, which will often be combined with lower serotonin levels. High 5-HTP can result in decreased dopamine, epinephrine, and norepinephrine production due to competitive inhibition with the AAADC enzyme, which is required for conversion of 5-HTP to serotonin and for dopamine synthesis. Caution is warranted if 5-HTP levels are elevated in conjunction with taking medications that may increase serotonin, such as SSRIs and MAOI, due to the risk of serotonin syndrome.

## Clinical Pearl:

If 5-HTP is high due and serotonin is low, consider a vitamin B6 deficiency. Look at other enzymatic reactions that require vitamin B6 to determine if the pattern matches. The enzyme chart at the end of the document may be helpful. If 5-HTP is low and kynurenine markers are high, assess for factors that increase the kynurenine pathway. The presence of inflammation, high cortisol and infections upregulate the kynurenine pathway and "steal" tryptophan away from 5-HTP synthesis towards the kynurenine pathway.

# 5-HTP CONSIDERATIONS

| | LOW 5-HTP | HIGH 5-HTP |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **5-HTP[24]:** 50-600mg<br>  • Initial dose typically starts at 50mg TID<br>  • Typical to dose before bed due to potential melatonin synthesis<br>  • Controlled release available<br>• **L-Tryptophan:** 500-2000mg/day<br>*Precursor for 5-HTP synthesis*<br>• Support nutrient cofactors for tryptophan hydroxylase:<br>  • **BH4:** Nutrient cofactors for synthesis and regeneration of BH4 listed below[18]<br>  • 5-Methyltetrahydrofolate or folate: 400-800mcg<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>*Note: Inflammation and oxidative stress may decrease BH4 levels[19]*<br>  • **Iron:** 15-30mg | • Support nutrient cofactors for aromatic amino acid decarboxylase: *(Converts 5-HTP to serotonin)*<br>  • **Vitamin B6** (pyridoxal 5-phosphate): 10-50mg<br>• *If serotonin and tryptophan are elevated, see interventions for high tryptophan levels o Vi* |
| DIETARY CONSIDERATIONS | Increase tryptophan rich foods[17]:<br>• Turkey, chicken, duck, eggs, beef, pork chops, salmon, cod, soy, legumes, seeds (sesame, chia, pumpkin, sunflower), dairy, oats<br>• Alpha-Lactalbumin is a whey protein that contains a rich source of tryptophan[21]<br>• Note: Collagen does not contain tryptophan<br>• *Note: a typical diet provides .5-.2 grams of L-tryptophan daily* | • *Decrease carbohydrates and increase protein for more competitive inhibition of tryptophan as a precursor for 5-HTP* |
| LIFESTYLE CONSIDERATIONS | • **Aerobic exercise[27]:**<br>  • Animal studies have shown an increase in 5-HTP levels in the brain after 30 minutes of swimming per day | |
| TESTING CONSIDERATIONS | **Gut Zoomer:** to assess for digestive insufficiency (if tryptophan is also low)<br>**Micronutrients:** to assess for nutrient deficiencies/insufficiencies<br>**Methylation Panel:** to assess for methylation impairments related to BH4<br>**Infection Panel:** If kynurenine pathway is upregulated<br>**Other tests:** Cortisol, CBC, iron panel, CRP, other inflammatory markers | **Micronutrients:** to assess for nutrient deficiencies/insufficiencies |



# SEROTONIN

## What is serotonin:

Serotonin, 5-hydroxytryptamine (5-HT), is a biogenic monoamine that functions as both a neurotransmitter in the central nervous system and a hormone in the periphery.  Serotonin's role as a neurotransmitter is inhibitory and it has been coined the "happiness molecule."

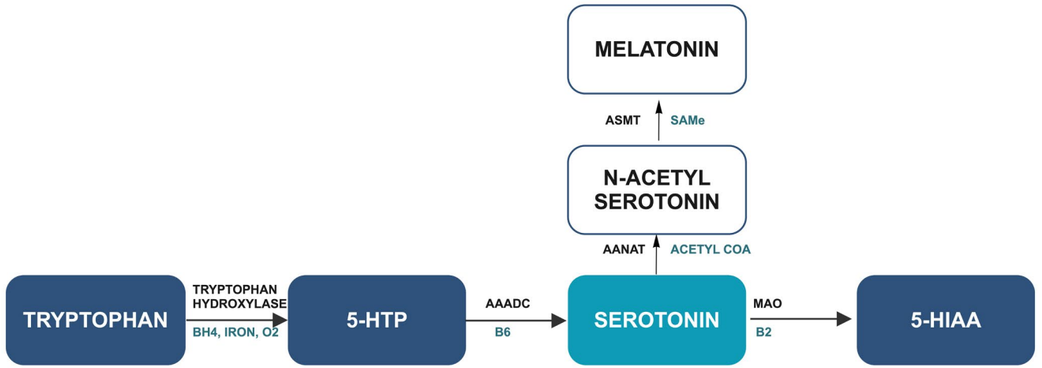
## What are the functions of serotonin?

In the CNS, serotonin plays important neuromodulatory roles, influencing mood, pain perception, memory, anger, aggression, reward, attention, fear, stress responses, appetite, addiction, sexual function, motor control, sleep/circadian rhythms, emesis, respiratory drive, and body temperature[28]. Serotonin is most well-known for its role in depression, which is why it's a commonly targeted neurotransmitter with medications to treat depression, such as SSRIs. Since serotonin is used as a precursor to synthesize melatonin, it plays an important role in regulating sleep and circadian rhythm. There are a multitude of different serotonin receptors in the body (5-HT1-5-HT7), some of which have several subtypes, that each play different physiological functions, and with many different medications created to target them. Serotonin also influences other neurotransmitters in the body, particularly inhibiting dopaminergic function, which can also reduce other catecholamines as well[29]. There is an important relationship between serotonin and estrogen levels, where estrogen influences serotonin levels via a few main mechanisms. The first is through increased production of tryptophan hydroxylase, which is the rate limiting step in serotonin synthesis[31]. The second is by inhibiting the expression of the serotonin reuptake transporter (SERT), acting similarly to many SSRI medications. Lastly, it also inhibit serotonin's degradation by MAOa[32]. Therefore, hormones may act as another influencer in serotonin levels.

It's important to note that serotonin does not cross the BBB, but peripheral serotonin production may influence CNS levels through vagal afferent communication. Serotonin levels in the brain may be influenced by the levels of precursors available as well as sufficient nutrient cofactors for enzymatic reactions. In the periphery, serotonin functions include vasoconstriction via smooth muscle stimulation, platelet aggregation, uterine contraction, intestinal peristalsis, and bronchoconstriction[28]. Serotonin is present in enteric neurons, blood platelets and enterochromaffin cells of the gut. 90%+ of serotonin is produced in the GI tract from enterochromaffin cells where it functions as an important gastrointestinal signaling molecule, acting as a sensory inducer, initiating peristaltic and secretory reflexes, and transmitting information to the CNS[33]. Research has also found that interleukin-33 (IL-33), released in response to environmental stresses, could be the trigger of 5-HT release from enterochromaffin cells[34]. After serotonin is released from the enterochromaffin cells, it can enter portal circulation and be taken up by the platelets, affecting blood clotting. If there is excess serotonin production in the periphery, it could deplete tryptophan levels and decrease availability to be transported into the brain[36]. Individuals with autism spectrum disorder display lower concentrations of serotonin in the brain, however, many show elevated concentrations of serotonin in the blood, a term referred to as 'serotonin anomaly'[34]. Research has not yet confirmed whether the higher blood levels are coming from increased gastrointestinal production of serotonin or another mechanism.

## Serotonin metabolism and pathways:

Serotonin is formed from the hydroxylation and decarboxylation of tryptophan. Tryptophan hydroxylase (Tph) converts tryptophan to 5-HTP and requires BH4, iron and oxygen as cofactors. There are two types of TPH enzymes, TPH1 and TPH2. Tph1 is expressed primarily in the enterochromaffin cells of the gastrointestinal tract, pineal gland, placenta and T cells and accounts for most of the peripheral serotonin[36]. Tph2 is expressed solely in the serotoninergic neurons of the raphe nuclei and the enteric nervous system and accounts for serotonin production in the brain[36]. 5-HTP is then decarboxylated to serotonin by aromatic amino acid decarboxylase, which requires vitamin B6 as a nutrient cofactor. Serotonin can be broken down to 5-HIAA by MAOa enzyme within the cytosol of the neuron, which requires vitamin B2 as a cofactor. Since serotonin is a charged molecule and MAO is located intracellularly, serotonin must be transported via serotonin reuptake transporter in order to be degraded. Many factors can also influence SERT activity, which as certain nutrients and hormones. The second major pathway for serotonin catabolism is sulfate conjugation by phenol sulfotransferase (PST)[37]. Serotonin can also be converted into melatonin in the pineal gland, using S-adenosylmethionine




## LOW SEROTONIN

Low levels of serotonin may result in behaviors such as impulsivity, impaired social behavior, impaired learning and memory, difficulty resisting short-term gratification, aggression, and lack of altruism[38]. The behaviors associated with low serotonin may be seen in disorders such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, Alzheimer's disease, Parkinson's disease, depression, anxiety, and impulsive behavior disorder[38]. Since serotonin generally has an inverse relationship with catecholamines, lower levels of serotonin may be associated with higher levels of dopamine and other catecholamines. Nutrient deficiencies, such as vitamin B6, which is the cofactor for AAADC that converts 5-HTP to serotonin, can result in decreased levels of serotonin. High activity of SERT can lead to increased serotonin transport into the neuron for degradation. High enzymatic function of the MAOa enzyme, which breaks down serotonin, may also result in lower levels. Medications, such as SSRIs have been shown to increase extracellular serotonin levels, however, chronic SSRI use can reduce serotonin tissue levels demonstrating decreased intraneuronal serotonin concentrations[39]. Animal studies pairing SSRI treatment with slow release 5-HTP prevented decreased serotonin levels, particularly in Tph2 mutation carriers[39]. Upregulation of the kynurenine pathway due to factors such as increased inflammation, infections, and cortisol, can divert tryptophan away from serotonin synthesis and towards the kynurenine pathway.

**Symptoms (LOW)**[29,38]: Poor sleep, flat affect, lack of joy/enjoyment from life, lack of pleasure, aches throughout the body (joint pain), heightened pain response, constipation, poor GI motility, tinnitus, aggressive behavior, anger, poor emotional responses to anger, social phobia, weakened immune serotosystem, impaired memory, decreased dreaming, increased libido, dependence behaviors, cravings, increased appetite, suicidal behavior

**Conditions (LOW)**[38]: ADHD, anxiety, autism spectrum disorder, bipolar disorder, chronic fatigue syndrome, depression, eating disorders, fibromyalgia, insomnia, irritable bowel syndrome, migraines, obsessive compulsive disorder, Parkinson's disease, rheumatoid arthritis, schizophrenia



## HIGH SEROTONIN

High levels of serotonin can result in a life-threatening medical emergency called serotonin syndrome. This often results when medications that increase serotonin levels, such as SSRIs and MAOIs, are paired with supplements that may increase serotonin levels, such as 5-HTP or L-tryptophan. Symptoms associated with serotonin syndrome can range from mild to severe, with common features including hypertension, tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia, hyperthermia, delirium, muscle rigidity, seizures, coma, and deathxl. High serotonin can also occur due to decreased breakdown to 5-HIAA, which can occur with medications, supplements, or nutrient deficiencies from vitamin B2 that decrease the MAO enzyme. Impaired functioning of the phenol sulfotransferase (PST) enzyme, resulting in decreased sulfate conjugation of serotonin, can result in higher levels[37]. Impaired conversion of serotonin to melatonin may also result in higher levels and can be seen with deficiencies in nutrient cofactors including SAMe and acetyl CoA. Extremely elevated serotonin levels can be an indication of carcinoid syndrome, which is usually found with serotonin levels about 100 times above the normal limit and associated with elevated levels of 5-HIAAxli. Since serotonin generally has an inverse relationship with catecholamines, high levels of serotonin may be associated with lower levels of dopamine and other catecholamines. It's important to assess high serotonin in relation to other intermediates along the serotonin pathway; if tryptophan or 5-HTP are also high, follow intervention recommendations to decrease those intermediates.

**Symptoms (HIGH)**[42,43]: Agitation, excitement, restlessness, irritability, confusion, delirium, insomnia, anxiety, low libido, mydriasis (dilated pupils), diaphoresis (sweating), tachycardia (increased heart rate), tachypnea (increased breathing rate), vomiting, diarrhea, arrhythmias, tremor, hyperreflexia, myoclonus, babinski sign, hypertonia

**Conditions (HIGH)**[40,41]: Serotonin syndrome (life-threatening situation caused by high levels of serotonin with symptoms including high fever, seizures, Irregular heartbeat, unconsciousness), carcinoid tumors (release serotonin), Celiac disease, Hypertension

### Clinical Pearl:

If serotonin levels are low, assess whether tryptophan is being shunted towards the kynurenine pathway. Be sure to assess all markers on the kynurenine pathway, kynurenic acid, quinolinic acid and xanthurenic acid. If the markers are on the higher end, be sure to address the root causes that cause the kynurenine pathway to be upregulated, including infections, stress/high cortisol, and inflammation.

# SEROTONIN CONSIDERATIONS

| | LOW SEROTONIN | HIGH SEROTONIN |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for AAADC enzyme *(Converts 5-HTP to serotonin)*<br>  • **Vitamin B6** (Pyridoxal 5-Phosphate): 10-50 mg/d<br>• **5-HTP**[24]: 50-600mg/d<br>  • Typical to dose before bed due to potential melatonin synthesis<br>  Controlled release available<br>• **Vitamin D3**[38]: 10,00IU-5,000IU/ day<br>  • Brain serotonin levels are synthesized from tryptophan via TPH2, which is transcriptionally activated by vitamin D<br>• **Omega 3 fatty acids**[38]:<br>  • EPA & DHA regulate serotonin release in the presynaptic neuron. EPA inhibits prostaglandin E2 (PGE2) series, and PGE2 inhibits serotonin.<br>• **Rhodiola**[44,45]: 200-600mg/day<br>  • Animal studies show rhodiola could increase serotonin in the hippocampus<br>• **Cannabidiol**[46,177]: 5-20mg/kg/day<br>  • Animal models show increased serotonin levels in the brain<br>• **Probiotics**[47,48]**:**<br>  • Animal studies show spore-forming probiotics can induce serotonin synthesis from enterochromaffin cells in the gut[49]<br>  • Animal studies showed certain strains of lactobacillus and Bifidobacterium can increase serotonin[48]<br>  • Lactobacillus plantarum<br>  Lactobacillus helveticus<br>  Lactobacillus rhamnosus<br>• **Melatonin: .5-3mg/d**<br>  • Low levels of serotonin may result in decreased melatonin synthesis<br>• **MAOa enzyme inhibitors**[50,51,52,53,54,55,56,57,58]**:** *MAO inhibitors decrease catabolism of serotonin to 5-HIAA, resulting in increased (In vitro and animal studies)*<br>  • Curcumin, quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African Rue, St. John's Wort, berberine<br>*NOTE: If tryptophan or 5-HTP levels are low, see interventions for low tryptophan or 5-HTP* | • Support nutrient cofactors for MAOa enzyme *(Catabolizes serotonin to 5-HIAA):*<br>  • **Vitamin B2** : 6-30mg/d[59]<br>  • If serotonin is high and 5-HIAA is lower, support/induce MAO enzyme<br>• Support nutrient cofactor for ASMT enzyme: *(Converts serotonin to melatonin)*<br>  • **SAMe:** 400-1600mg/day[60]<br>• *Assess levels of tryptophan and 5-HTP and if levels are high, follow recommendations to lower accordingly so that there are lower levels of precursors for serotonin synthesis* |
| DIETARY CONSIDERATIONS | • Increase tryptophan rich foods if tryptophan levels are low/suboptimal<br>• Increasing carbohydrates and decreasing protein can decrease competition from other large neutral Amino acids (LNAA) for transport into the brain and may increase tryptophan levels in the brain for serotonin synthesis in the CNS | **Decrease intake of serotonin rich foods sources**[61]**:**<br>  • Bananas, chicory, Chinese cabbage, coffee, green onion, hazelnut, kiwi, lettuce, nettle, paprika, passion fruit, pawpaw, pepper, pineapple, plantain, plum, pomegranate, potato, spinach, strawberry, tomato, velvet bean, wild rice<br>  • Since serotonin does not cross the BBB, food sources may only impact periphery |



| | | |
|---|---|---|
| DIETARY CONSIDERATIONS | | **Other Dietary Interventions:**<br>  • Decrease carbohydrates and increase protein for more competitive inhibition of tryptophan (if tryptophan is higher) |
| LIFESTYLE CONSIDERATIONS | • **Exposure to bright light**[62]: May increase serotonin levels based on indirect evidence<br>• **Exercise**[62]: May increase brain serotonin levels<br>• **Meditation**[63]: Focused attention meditation on tanden breathing can result in higher 5-HT levels<br>• **Massage Therapy**[64]: Massage can increase serotonin and decrease cortisol levels | • **Epsom salt baths (magnesium sulfate)**[37]**:**<br>  • Theoretically provides a source of sulfate to assist with sulfate conjugation of serotonin |
| TESTING CONSIDERATIONS | • **Gut Zoomer:** to assess for digestive insufficiency (if tryptophan is also low)<br>• **Micronutrient:** to assess for nutrient deficiencies/ insufficiencies<br>• **Methylation Panel:** to assess for methylation impairments related to BH4<br>• **Infection Panel:** to assess for infections that may shift tryptophan to kynurenine pathway<br>• **Other tests:** Cortisol, CBC, iron panel, CRP, other inflammatory markers | • **Gut Zoomer:** to assess for dysbiosis<br>• **Micronutrient:** to assess for nutrient deficiencies/insufficiencies<br>• **Urinary Hormones:** to assess for hormone imbalances, such as estrogen, cortisol, and melatonin, which may be influencing serotonin levels |

# 5-HIAA

## What is 5-HIAA?

5-HIAA, 5 hydroxyindoleacetic acid, is the primary metabolite of serotonin breakdown. Serotonin is a biogenic monoamine that functions as both a neurotransmitter in the central nervous system and a hormone in the periphery. When serotonin is broken down in the liver, it forms 5-HIAA, which is a common conventionally used marker to assess for serotonin levels.

## 5-HIAA metabolism and pathways:

5-HIAA is formed when monoamine oxidase a (MAOa) enzymatically deactivates serotonin, using vitamin B2 as an essential nutrient cofactor.


## LOW 5-HIAA

Low 5-HIAA is commonly a result of low serotonin levels since it is the primary metabolite of serotonin breakdown. Low levels of 5-HIAA have been correlated with aggressive and violent behavior, depression and obsessive-compulsive disorder. Low levels of 5-HIAA have also been found in patients with multiple sclerosis and were correlated with the severity of symptoms in relapsing-remitting multiple sclerosis patient[65]. Genetic deficiencies, including AADC deficiency and sepiapterin reductase deficiency are associated with low levels of 5-HIAA. If low levels of 5-HIAA are paired with higher serotonin levels, it's important to ensure sufficient vitamin B2 for optimal MAOa enzymatic function. It may also be important to rule out any supplements or medications that are impairing MAOa enzyme function. Specific medications, such as acetaminophen and risperidone may lower 5-HIAA levels[69]. Conditions such as renal insufficiency and small bowel resection can also decrease 5-HIAA levels. While acetaminophen may decrease 5-HIAA, it alternatively increases serotonin levels in the brain by inhibiting tryptophan 2,3-diogxygenase in the liver. It's important to interpret 5-HIAA levels in conjunction with serotonin levels to determine if levels are low due to low serotonin, or whether they are low due to other factors affecting the MAOa enzyme related to genetics, nutrient deficiencies, or medications and supplements.

## HIGH 5-HIAA

High 5-HIAA is a marker for elevated serotonin levels since it is the primary metabolite of serotonin breakdown. High levels of 5-HIAA in the urine can result from the use of medications or supplements that increase serotonin levels, such as SSRI drugs, therefore increasing the amount of 5-HIAA from serotonin catabolism. Elevation in the absence of SSRI may be generated by xenobiotic compounds such as acrylamide that interact with serotonin receptors[66]. Elevated 5-HIAA levels can be an indication of carcinoid tumors or carcinoid syndrome. Carcinoid tumors are neuroendocrine tumors within the gastrointestinal tract or pulmonary system and while not all carcinoid tumors produce serotonin, midgut carcinoid tumors are known to secrete serotonin. Assessing 5-HIAA urine level as a marker for carcinoid tumors, has a specificity of 100% and sensitivity of 73-91%[67]. In carcinoid tumors, excessive use of tryptophan for serotonin synthesis diverts it away from the kynurenine pathway, which can impair vitamin B3 synthesis[68]. High levels of 5-HIAA have been seen in conditions such as autism spectrum disorder, diseases of malabsorption, celiac disease, nontropical sprue, IBS-D, type 2 diabetes patients with microalbuminuria and renal insufficiency and some studies with cystic fibrosis patients[69].

### Clinical Pearl:

Since 5-HIAA is typically a marker of serotonin levels, if there is a discrepancy between serotonin and 5-HIAA levels assess MAO enzyme function. See enzyme chart for other reactions that involve the MAO enzyme, such as dopamine and norepinephrine.



# 5-HIAA CONSIDERATIONS

| | LOW 5-HIAA | HIGH 5-HIAA |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | *If serotonin is high, support/induce MAOa Enzyme:*<br>• **Vitamin B2:** 6-30mg/d[59]<br>  • Nutrient cofactor for MAOa enzyme; converts serotonin to 5-HIAA<br>*If serotonin is low, slow/decrease MAOa Enzyme:*<br>*Slowing the MAOa enzyme may decrease the rate of serotonin catabolism*<br>• MAOa enzyme inhibitors[50,51,52,53,54,55,56,57,58]<br>*Slowing the MAOa enzyme may decrease the rate of serotonin catabolism*<br>*(In vitro and animal studies)*<br>  • Curcumin (10-80mg/kg), quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African rue, St. John's Wort (500mg), berberine<br>*If serotonin is low, follow interventions for low serotonin* | *If serotonin is low, slow/decrease MAOa Enzyme:*<br>• MAOa enzyme inhibitors[50,51,52,53,54,55,56,57,58]<br>*Slowing the MAOa enzyme may decrease the rate of serotonin catabolism*<br>*(In vitro and animal studies)*<br>  • Curcumin, quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African rue, St.John's Wort (500mg), berberine<br>*If serotonin is high, follow interventions for high serotonin* |
| DIETARY CONSIDERATIONS | • Increase tryptophan rich foods if tryptophan is low<br>• Limit alcohol intake | • Decrease carbohydrates and increase protein for more competitive inhibition of tryptophan (if tryptophan is higher)<br>• Limit/avoid caffeine intake[70] |
| LIFESTYLE CONSIDERATIONS | • **Strenuous exercise[71]:**<br>  • If serotonin is low, strenuous exercise may increase serotonin levels in the synaptic cleft and consequently increase 5-HIAA levels | • **Strenuous exercise[72]:**<br>  • Social stress increases the 5-HIAA/5-HT ratios |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies/insufficiencies | • **Environmental Toxins Test:** to assess for toxins that may affect 5-HIAA levels (e.g. acrylamide) |

# KYNURENIC ACID

## What is kynurenic acid?

Kynurenic acid (KYNA) is a neuroprotective metabolite formed from the kynurenine pathway.

## What are the functions of kynurenic acid?

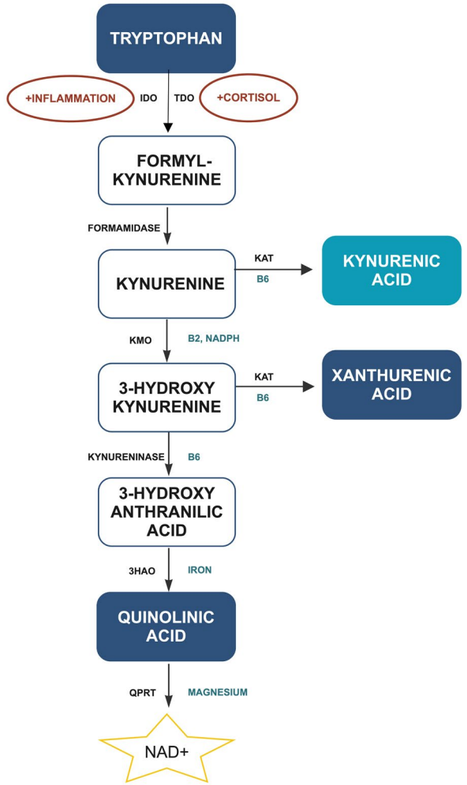
KYNA is known to be neuroprotective and serves many functions in the body. It acts as a glutamate receptor antagonist, with even small concentrations in the brain leading to a 30-40% decrease in glutamate levels[74]. KYNA exerts its blockade activity at the glycine co-agonist site of the NMDA receptor. KYNA also acts as a negative allosteric modulator at the a7-nicotinic acetylcholine receptor, which can result in suppression of local GABAergic transmission. It plays a role in decreasing multiple inflammatory pathways by acting as an agonist at G-protein-coupled receptors (GPR35)[74]. It also has a regulatory effect on the immune system by acting as an agonist on aryl hydrocarbon receptors (AhR), which plays an important role in inhibiting cytokine release in immune cells such as macrophages[74]. KYNA demonstrates antioxidant properties and may have a positive impact on reducing oxidative stress[76]. The immunomodulatory effects of kynurenic acid may depend on whether inflammatory or homeostatic conditions are present. KYNA can also influence other neurotransmitters and has been shown to have inhibitory actions on dopamine release in animal studies[89]. Kynurenic acid is primarily expressed in the astrocytes in the brain, whereas quinolinic acid is predominantly express in the microglia, indicating that location is an important aspect of which branch the kynurenine pathway follows. Animal studies have shown that kynurenic acid reversely regulated dopaminergic tone, where KYNA administration reduces dopamine levels in the brain[73].

## What is the kynurenine pathway?

The kynurenine pathway catabolizes roughly 95% of available tryptophan and plays an important role in the biogenesis of nicotinamide adenine dinucleotide (NAD) as well as acting as a key regulator of the immune system. The pathway begins with two rate limiting enzymes occurring in many bodily tissues, tryptophan dioxygenase (TDO) active particularly in the liver, and indoleamine 2,3-dioxygenease (IDO) in the brain and immune cells[74]. These two enzymes, TDO and IDO are responsible for converting tryptophan to kynurenine and are upregulated in the presence of proinflammatory cytokines, infections, and cortisol from elevated stress responses[74]. Once kynurenine is formed, it can be used to synthesize other intermediates in the pathway.

## Kynurenic acid metabolism and pathways:

KYNA is synthesized from kynurenine by the activity of kynurenine aminotransferase (KAT) enzymes, which requires vitamin B6 as an essential nutrient cofactor. The fate of kynurenine is either to form KYNA or it can be converted to anthranilic acid or 3-hydroxykynurenine (3-HK), which the path to 3-HK usually occurs under more inflammatory conditions. When KYNA acid is formed, there is a shift away from quinolinic acid and NAD+ formation along the kynurenine pathway.






## LOW KYNURENIC ACID

Low levels of KYNA augment dopaminergic, acetylcholinergic, and glutamatergic neurotransmission[75]. Low levels of KYNA may play a role in improving cognitive function, such as seen in schizophrenia patients. Low levels of KYNA have been linked to patients suffering from depression, Alzheimer's disease, Parkinson's disease, chronic migraines, IBS, and specific types of cancer such as prostate, cervical and glioma[78]. Estrogen has been shown to exert an inhibitory effect on KAT enzymes, leading to decreased levels of KYNA, but it typically occurs in a dose-dependent manner[97]. Women taking oral contraceptives showed lower levels of KYNA compared to women who were not taking them. Since vitamin B6 is required for the KAT enzymes, any deficiency or other impairments of the enzymes could lead to decrease KYNA levels. It's important to assess low KYNA levels in conjunction with other intermediates along the kynurenine pathway and serotonin pathway.

## HIGH KYNURENIC ACID

Animal studies have shown that higher levels of KYNA were able to reduce excitotoxic neuronal damage in the rat brain by reducing glutamatergic neurotransmission[76]. There is also evidence that increased levels of KYNA result in decreased dopaminergic neurotransmission as well. Even though most of the research around KYNA has resulted in positive physiological outcomes, KYNA has been under investigation for its underlying role in cognitive deficits associated with schizophrenia. Higher levels of KYNA have been found in inflammatory bowel disease patients, which may have to do with its positive role in the gastrointestinal tract, especially with ulcers, colon obstruction and colitis[77]. Higher levels have also been seen in patients with type 2 Diabetes, multiple sclerosis, and chronic kidney disease[78]. In vitro studies of human macrophages have shown that treatment with physiological doses of progesterone resulted in increased KYNA levels and consequently a decrease in quinolinic acid formation. In animal studies, medications such as COX-1 inhibitors have been shown to lead to increased brain levels of KYNA. Higher levels of kynurenic acid are seen in patients with type 2 diabetes and metabolic syndrome[79]. It is not yet fully understood whether KYNA levels are high in specific disease states as a protective element or as a contributor to the particular disease state. Typically, when KYNA levels are high, there is a shift in the kynurenine pathway away from quinolinic acid and NAD+ production.

## Clinical Pearl:

Increased tryptophan directed towards the kynurenine pathway may impede its precursor availability for serotonin and melatonin synthesis. Therefore, it's important to interpret KYNA levels and other kynurenine pathway intermediates in combination with serotonin and its pathway intermediates. It has been proposed that the ratio of xanthurenic acid: kynurenic acid can be used as a marker of vitamin B3 deficiency. While an exact ratio has not been established, a low ratio correlates with low niacin status, and a higher ratio occurs with a recovering niacin status. A vitamin B3 deficiency manifests as low xanthurenic acid and higher kynurenic acid due to the KMO enzyme requiring NADPH.

# KYNURENIC ACID CONSIDERATIONS

| | LOW KYNURENIC ACID | HIGH KYNURENIC ACID |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for KAT enzyme *(Converts kynurenine to KYN):*<br>  • **Vitamin B6** (pyridoxal 5-phosphate): 10-50mg/d<br>*If kynurenic acid is low but other kynurenine metabolites are high, assess factors that may be upregulating the kynurenine pathway (such as inflammation, cortisol/stress, infections)* | • **Amino acid supplementation[75]:**<br>  • Specific amino acids have been shown to suppress KYNA production by blockade of kynurenine transport (leucine, isoleucine, phenylalanine, methionine, and tyrosine)<br>  • Specific amino acids have been shown to block KYNA synthesis in the brain (alanine, cysteine, glutamine, glutamate, and aspartate)<br>• **Probiotics & choline[80]:**<br>  • Animal study showed supplementation with both choline and probiotics reduced KYNA levels<br>• Support nutrient cofactors for kynurenine 3- monooxygenase (KMO) *(Converts kynurenine to 3-hydroxykynurenine);nutrient cofactor deficiencies lead to kynurenine buildup and shifts to* KYNA<br>  • **Vitamin B2[59,81]**: 6-30mg/d<br>  • **Vitamin B3[82]**: 50-100mg/d |
| DIETARY CONSIDERATIONS | • **Ketogenic diet[83,95]:**<br>  • Human studies and animal studies have shown increased levels of KYNA on a ketogenic diet<br>• **Increase KYNA food sources and herbs[78,84]**:<br>  • Broccoli, honey, propolis, basil, thyme, peppermint, nettle, birch leaf, horsetail herb, breastmilk | • Reduce intake of high kynurenic acid foods (if necessary) |
| LIFESTYLE CONSIDERATIONS | • **Endurance Exercise[85]:**<br>  • Endurance exercise increases KYNA levels | • Lifestyle interventions do not significantly affect high kynurenic acid levels |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies/ insufficiencies | • **Infections Panel:** to assess for infections upregulating the kynurenine pathway<br>• **Urinary or Salivary Hormones:** to assess for hormone imbalances, such as cortisol elevations and estrogen dominance<br>• **Micronutrients:** to assess for nutrient deficiencies/ insufficiencies<br>• **Other tests:** CRP, other inflammatory markers |



# XANTHURENIC ACID

## What is xanthurenic acid?

Xanthurenic acid is a metabolite formed from the kynurenine pathway.

## What are the functions of xanthurenic acid?

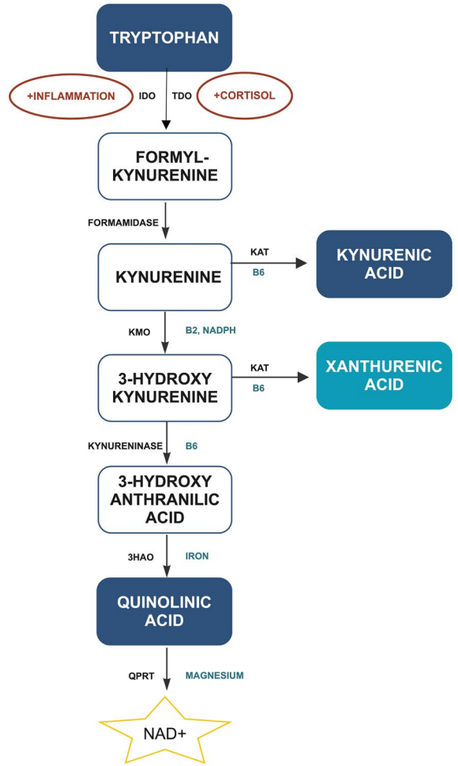
Xanthurenic acid serves many functions in the body, including antioxidant properties in vitro and in vivo, vasorelaxing properties, inhibiting metal ion-induced lipid peroxidation[86], and improving tetrahydrobiopterin biosynthesis[87]. It has been shown to function as an endogenous modulator of glutamatergic neurotransmission resulting in decreased extracellular glutamate levels. In animal studies, xanthurenic acid has been shown to dose -dependently stimulate dopamine release in the prefrontal cortex[88]. Xanthurenicacid also has negative effects, including its diabetogenic activity through binding and inactivating insulin, and inducing mitochondrial damage and cell death[89].

## What is the kynurenine pathway?

The kynurenine pathway catabolizes roughly 95% of available tryptophan and plays an important role in the biogenesis of nicotinamide adenine dinucleotide (NAD) as well as acting as a key regulator of the immune system. The pathway begins with two rate limiting enzymes occurring in many bodily tissues, tryptophan dioxygenase (TDO) active particularly in the liver, and indoleamine 2,3-dioxygenease (IDO) in the brain and immune cells[90]. These two enzymes, TDO and IDO are responsible for converting tryptophan to kynurenine and are upregulated in the presence of proinflammatory cytokines, infections, and cortisol from elevated stress responses[74]. Once kynurenine is formed, it can be used to synthesize other intermediates in the pathway.

## Xanthurenic acid metabolism and pathways:

Kynurenine, formed from the kynurenine pathway, undergoes an enzymatic reaction to form 3-hydroxy-kynurenine (3HK), which can be converted to either 3-hydroxyanthranilic acid by the kynureninase enzyme or xanthurenic acid by the KAT enzyme. Both enzymes require vitamin B6 as a nutrient cofactor, but the kynureninase is more sensitive to a vitamin B6 deficiency and will therefore often shift the pathway towards xanthurenic acid production under those conditions.



## LOW XANTHURENIC ACID

Low levels of xanthurenic acid can occur as a result of decreased activation of the kynurenine pathway. One potential cause could be low levels of tryptophan, which may impair the production of many kynurenine pathway intermediates, including xanthurenic acid. A vitamin B2 deficiency, which is an important nutrient cofactor for the KMO enzyme that converts kynurenine to 3-HK, may decrease precursor availability for xanthurenic acid production[94]. The KMO enzyme also requires nicotinamide adenine dinucleotide phosphate (NADPH), therefore any deficiency in vitamin B3 could impair xanthurenic acid synthesis[82].

## HIGH XANTHURENIC ACID

High levels of xanthurenic acid typically occur when there's a vitamin B6 deficiency, which shunts the 3-HK towards xanthurenic production instead of 3-hydroxyanthranilic acid. Animal studies showed that tryptophan loading paired with a vitamin B6 deficiency, resulted in increased excretion of xanthurenic acid[91]. High xanthurenic acid levels have been associated with high insulin resistance and increased risk of developing diabetes[100]. Research has shown that increased xanthurenic acid excretion may be associated with increased zinc excretion, therefore zinc status should be assessed. In individuals using oral-contraceptives, researchers saw a greater increase in xanthurenic acid levels due to the estrogen metabolites competitively inhibiting the kynureninase enzyme[92]. If there is increased activity in the kynurenine pathway, with a greater influx than the kynurinase enzyme can handle, the pathway may be shifted towards xanthurenic acid to compensate for burdened kynureninase enzyme. Xanthurenic acid has been shown to be a potent inhibitor of sepiapterin reductase, which is the final enzyme in de novo BH4 synthesisxciv. Therefore, high levels of xanthurenic acid may impair endogenous production of BH4.

### Clinical Pearl:

Since xanthurenic acid is a marker of B6 deficiency, assess other enzymatic reactions in neurotransmitter synthesis that use vitamin B6 to determine its global impact. The enzyme, aromatic amino acid decarboxylase, requires vitamin B6, which converts 5-HTP to serotonin and L-DOPA to dopamine. Since high levels of xanthurenic acid can impair BH4 synthesis, it's also important to assess the enzymes that use BH4 as a cofactor, which include tryptophan hydroxylase and tyrosine hydroxylase, among others.



# XANTHURENIC ACID CONSIDERATIONS

| | LOW XANTHURENIC ACID | HIGH XANTHURENIC ACID |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for kynurenine 3- monooxygenase (KMO) (*Converts kynurenine to 3-HK);* any nutrient cofactor deficiencies leads to kynurenine buildup and shifts to KYNA<br>  • **Vitamin B2**[59,94]: 6-30mg/day<br>  • **Vitamin B3**[82]: 50-100mg/day | • Support nutrient cofactor for kynureninase enzyme: *(Converts 3-HK to 3-hydroxyanthranilic acid)*<br>  • **Vitamin B6 (pyridoxal 5-phosphate)**: 10-50mg |
| DIETARY CONSIDERATIONS | If tryptophan levels are low, ensure sufficient intake of tryptophan rich foods | • **Ketogenic Diet**[95]:<br>  • May decrease kynurenine production, which is a non-direct precursor for xanthurenic acid synthesis |
| LIFESTYLE CONSIDERATIONS | Lifestyle interventions do not significantly affect xanthurenic acid levels | Lifestyle interventions do not significantly affect xanthurenic acid levels |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess nutrient levels important for xanthurenic acid pathways | • **Micronutrients:** to assess nutrient levels important for xanthurenic acid pathways<br>• **Infection Panel:** to assess for infections upregulating the kynurenine pathway<br>• **Other tests:** Cortisol, CRP, other inflammatory markers |

# QUINOLINIC ACID

## What is quinolinic acid?

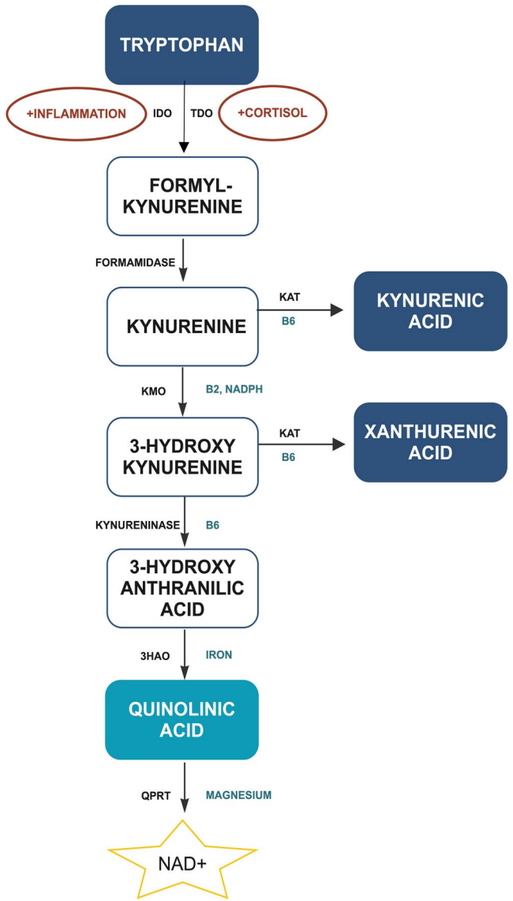
Quinolinic acid is a neurotoxic metabolite formed from the kynurenine pathway.

## What are the functions of quinolinic acid?

Quinolinic acid exhibits many deleterious nervous system effects such as triggering neural damage, increased oxidative stress, increased glutamate levels, and even cell death. Quinolinic acid acts as an NMDA receptor agonist and effectively inhibits reuptake of glutamate by astrocytes, contributing to excitotoxicity[97]. Quinolinic acid has multiple neurotoxic impacts on the body, including production of reactive oxygen species, disruption of the blood brain barrier, destabilization of the cellular cytoskeleton, promotion of tau phosphorylation, impaired autophagy, and enhanced inflammatory response from proinflammatory mediators in astrocytes[97]. When the kynurenine pathway is activated, the production of metabolites, including quinolinic acid, can exert a variety of immunosuppressive effects. These effects include the downregulation of natural killer cell receptors, the death of natural killer cells, lymphocyte cell-cycle arrest and apoptosis, downregulation of T-cell receptor, all of which can suppress the adaptive immune system and allow for tumor escape, vulnerability to infectious disease and deficient vaccine-induced immunogenicity[97]. Since activated immune cells require large amounts of energy to fight infections, quinolinic acid production may act as an important intermediate used to form more NAD+ under these conditions.

## What is the kynurenine pathway?

The kynurenine pathway catabolizes roughly 95% of available tryptophan and plays an important role in the biogenesis of nicotinamide adenine dinucleotide (NAD) as well as acting as a key regulator of the immune system. The pathway begins with two rate limiting enzymes occurring in many bodily tissues, tryptophan dioxygenase (TDO) active particularly in the liver, and indoleamine 2,3-dioxygenease (IDO) in the brain and immune cellsxcviii. These two enzymes, TDO and IDO are responsible for converting tryptophan to kynurenine and are upregulated in the presence of proinflammatory cytokines, infections, and cortisol from elevated stress responses[74]. Once kynurenine is formed, it can be used to synthesize other intermediates in the pathway.






## Quinolinic acid metabolism and pathways:

Kynurenine, formed from the kynurenine pathway, can undergo multiple enzymatic reactions to form quinolinic acid, which is then used to form NAD+. Kynurenine forms 3-hydroxykynurenine (3-HK) by the kynurenine 3-hydroxylase (KMO) enzyme, which requires vitamin B2 and NADPH as cofactors. Kynureninase then cleaves 3-HK to form 3-hydroxyanthranilic acid (3-HA), which requires vitamin B6 as a cofactor. 3-HA is converted to an unstable intermediate, aminocarboxymuconic semialdehyde, by 3-hydroxyanthranilic acid oxygenase (3-HAO), which is an iron dependent enzyme. Aminocarboxymuconic semialdehyde is converted to quinolinic acid by a nonenzymatic cyclisation9[98]. Once quinolinic acid is formed, it can be converted to NAD+ by the quinolinate phosphoribosyltransferase (QPRT) enzyme. QPRT requires magnesium as a cofactor. There are fewer cells that contain QPRT compared to 3-HAO, thus the production of quinolinic acid in the brain generally occurs at a higher rate than NAD+ synthesis98. The location of these two enzymes are also different. Quinolinic acid is produced by microglia but it must leave those cells to be metabolized by QPRT for conversion to NAD+[98]. Kynurenic acid is primarily expressed in the astrocytes in the brain, whereas quinolinic acid is predominantly expressed in the microglia, indicating that location is an important aspect of which branch the kynurenine pathway follows[98].

## LOW QUINOLINIC ACID

Low levels of quinolinic are generally not very concerning. It's important to assess whether low levels are due to nutrient deficiencies that impair the formation of quinolinic acid. This can be seen with deficiencies in vitamin B2, B3, B6 and iron that may shift the path away from quinolinic acid production towards either kynurenic acid or xanthurenic acid. Medications such as corticosteroids may contribute to decreased levels of quinolinic acid due to decreased inflammation, which upregulates the kynurenine pathway. Since quinolinic acid is a precursor for NAD+ formation, low levels may also contribute to low levels of NAD+ for cellular energy and niacin production. If there's evidence of low niacin and low quinolinic acid, supporting increased levels through supplementation may beneficial.

## HIGH QUINOLINIC ACID

High quinolinic acid demonstrates many deleterious nervous system effects as a neurotoxin, triggering neural damage, increased oxidative stress, and cell death[98]. Elevated levels can also stimulate glutamate release. When quinolinic acid levels are high, it's important to assess the major factors that stimulate the kynurenine pathway, which include infections, inflammation and high cortisol levels. High quinolinic acid levels are seen in many conditions and neurodegenerative diseases, including alzheimer's disease, huntington's disease, depression, autism, amyotrophic lateral sclerosis, and suicidal tendencies[98]. Inhibition of nitric oxide synthase results in an exaggerated increase in kynurenine production, potentially leading to elevated quinolinic acid levels. Animal studies have shown that administration of LPS resulted in increased KMO enzyme activity, leading to greater quinolinic acid formation and less formation towards kynurenic acid. Assessing gastrointestinal function would be appropriate to determine if LPS is a contributing risk factor for elevated levels. Neurotoxic levels of quinolinic acid can also result from decreased metabolism to NAD+, which can occur when quinolinic acid is produced at a higher rate than its ability to convert to NAD+ by the QRPT enzyme[98]. Other factors such as elevated environmental toxins, particularly phthalates, have been shown to increase quinolinic acid and decrease conversion to NAD+[99]. A high quinolinic acid/kynurenic acid ratio has been associated with major depression, therefore, when interpreting quinolinic acid, assess levels in relation to KYNA levels. If quinolinic levels are high, then it's important to assess in relation to serotonin levels and its metabolites since tryptophan may be shunted towards the kynurenine pathway and away from serotonin and melatonin production. In addition to addressing the root causes of increased quinolinic acid levels, it may be prudent to incorporate recommendations that offset the negative impacts of high QA levels.

### Clinical Pearl:

Increased quinolinic acid levels may indicate the body's need for synthesizing more NAD+ and niacin. Assess vitamin B3 levels to determine if that's playing a role in quinolinic acid metabolism.

# QUINOLINIC ACID CONSIDERATIONS

| | LOW QUINOLINIC ACID | HIGH QUINOLINIC ACID |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for kynureninase enzyme: *(An enzymatic reaction for precursors to quinolinic acid synthesis)*<br>  • **Vitamin B6**[100]: (pyridoxal 5-phosphate): 10-50mg/d<br>• Support nutrient cofactor for kynurenine 3- monooxygenase (KMO) enzyme:<br>*(An enzymatic reaction for precursors to quinolinic acid synthesis))*<br>  • **Vitamin B6**[59,100]: 6-30mg/d<br>• Support nutrient cofactor for ³-HAO enzyme:<br>  • **Iron**[98]: 15-30mg/d<br>• **Vitamin B3**[101]: 50-100mg/d<br>  • Low quinolinic acid levels may result in decreased endogenous NAD+ and niacin synthesis | • **Curcumin**[102]: 25-50mg/kg/day<br>  • Animal study showed curcumin with piperine had strong antioxidant and protective effects against quinolinic acid-induced behavioral and neurological damage<br>• **L-Theanine**[103,104]: 200-400mg/d<br>  • Animal study showed L-theanine significantly prevented negative quinolinic acid effects by inhibiting nitric oxide production<br>• **Melatonin**[105]: 1-3mg/d<br>  • Study shows treatment exerted a significant protective effect antagonizing quinolinic acid induced neurotoxicity<br>• **Garlic**[106]: 300-450mg/kg of S-allylcysteine<br>  • An animal study showed an active compound in garlic, improved in vivo quinolinate striatal toxicity<br>• **Selenium**[107]: 50-200mcg/day<br>  • Selenium protected against quinolinic acid-induced neurotoxicity that is mediated by oxidative stress<br>• **Probiotics**[108]:<br>  • Lactobacillus reuteri may decrease IDO activity<br>*Assess niacin levels, since the end product of quinolinic acid is NAD+/niacin production, and upregulation of this pathway may be due to a physiological need for more NAD+/niacin* |
| DIETARY CONSIDERATIONS | *There are no dietary recommendations for low quinolinic acid. If tryptophan levels are low, increase intake of tryptophan rich foods.* | • **Anti-inflammatory diet:**<br>  • Inflammation upregulates the kynurenine pathway<br>• **Sulfurophane rich foods**[109]**:**<br>  • Prevents quinolinic acid induced mitochondrial dysfunction in animal study<br>• **Green tea (EGCG)**[110]**:**<br>  • Inhibits quinolinic aid-induced NMDA receptor activation |
| LIFESTYLE CONSIDERATIONS | • **Exercise**[111]: Increase acute endurance exercise | • Avoid products high in phthalates<br>• Caution with acute endurance exercise, which may increase quinolinic acid levels[111] |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrient deficiencies important in the kynurenine pathway | • **Infection Panel:** tto assess for subclinical infections that may upregulate kynurenine path<br>**Gut Zoomer:** to assess for dysbiosis and potential bacteria increasing LPS<br>**Micronutrients:** to assess for micronutrient deficiencies important in pathways<br>**Environmental Toxins:** to assess for toxins that may increase quinolinic acid |



# TRYPTAMINE

## What is tryptamine?

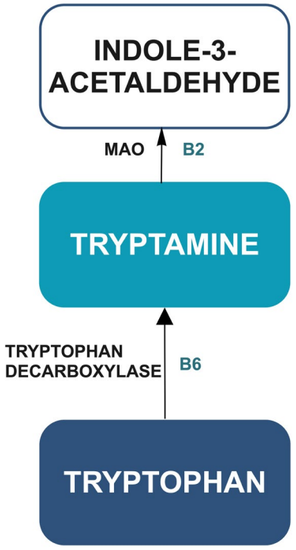
Tryptamine is an indolamine metabolite of tryptophan metabolism. It is popularly known and categorized as a group of psychedelic compounds that induce states of psychosis, hallucinations and altered states of consciousness[112].

## What are the functions of tryptamine?

Tryptamine exerts many physiological functions and has neuromodulatory effects. Altered tryptamine metabolism has been seen in conditions including pellagra, Hartnup's disease, schizophrenia, Parkinson's disease, phenylketonuria, thyrotoxicosis and some cases of carcinoid tumor[113]. It has been shown to weakly activate the trace-amine associated receptor (TAAR1), resulting in beneficial effects with cognition, stress, depression and addiction. Tryptamine exerts a multitude of behavioral effects that tend to be more excitatory in nature. Animal studies have also shown alterations in blood glucose control, hyperinsulinemia and hypoglycemia from tryptamine administration[113]. Hypoxia has been shown to shunt tryptophan metabolism away from the kynurenine pathway and towards increased tryptamine production, contributing to higher levels in the liver, serum, and braincxiii. Since tryptamines also function as hallucinogenics, this may be one mechanism by which higher altitudes contribute to states of hallucinations. Tryptamines also activate the aryl hydrocarbon receptor (AHR), which exhibits immunosuppressive activity. This may explain why hypoxia leads to immunosuppressive activity. Animal studies have shown that tryptamine inhibits the uptake of both serotonin and dopamine in the brain of mammals[113].

## Tryptamine metabolism and pathways:

Tryptamine is produced by decarboxylation of tryptophan by the enzyme aromatic amino acid decarboxylase (AADC). The AADC enzyme requires vitamin B6 as an essential nutrient cofactor. The main route of catabolism occurs via the MAO enzyme as tryptamine is converted to indoleacetaldehyde and then to indole 3-acetic acid via aldehyde dehydrogenas[113].




## LOW TRYPTAMINE

Nutrient deficiencies, particularly vitamin B6 and tryptophan may decrease synthesis of tryptamine due to their critical role in the enzymatic reactions. Any medication or supplement that upregulates the MAO enzyme may increase the catabolism of tryptamine, leading to decreased levels. A diet low in tryptamine rich foods may also contribute to lower levels.

## HIGH TRYPTAMINE

Increased levels of tryptamine excretion have been seen in patients with schizophrenia, Parkinson's disease, and psychosis[114]. Certain medications that block the synthesis of serotonin have been shown to increase tryptamine levels due to increased availability of tryptophan as a precursor. Inhibition of the MAO enzyme with medications or supplements, may contribute to increased levels since it's responsible for the metabolism of tryptamine. High levels of tryptamine have been seen in situations of hypoxia, which shifts tryptophan's use away from the kynurenine pathway and towards tryptamine synthesis[112].

### Clinical Pearl:

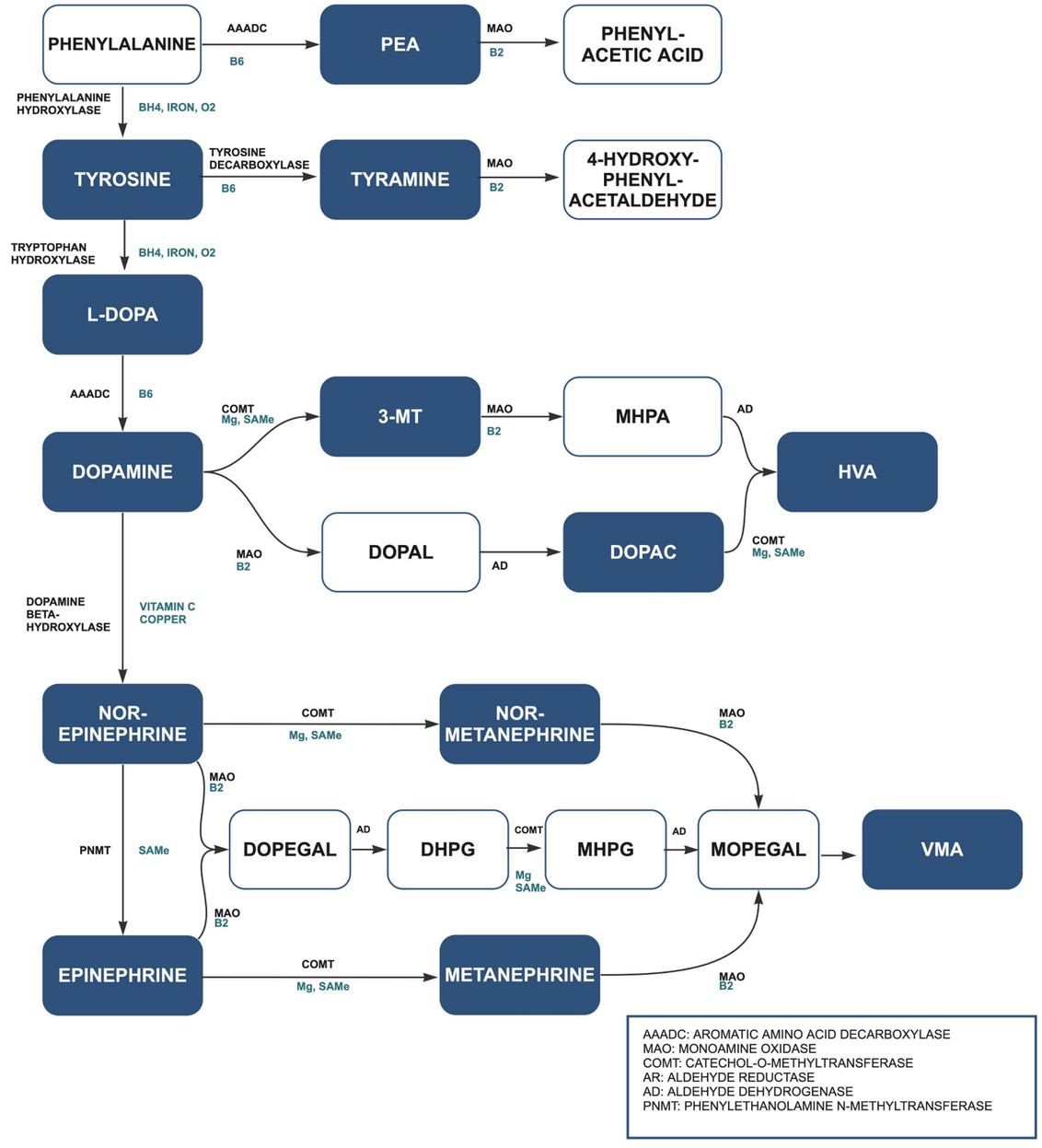
A pattern of high amounts of tryptamine, tyramine and histamine can come from food sources, such as cheeses and other fermented foods as they can be high in all three of these amines.

# TRYPTAMINE CONSIDERATIONS

| | LOW TRYPTAMINE | HIGH TRYPTAMINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for AAADC: *(Converts tryptophan to tryptamine);*<br>  • **Vitamin B6**:(Pyridoxal 5- phosphate): 10-50mg/d | • Support nutrient cofactor for MAO enzyme: *(Responsible for catabolism of tryptamine)*<br>  • **Vitamin B6**[59]: 6-30mg/d<br>• Support nutrient cofactors for tryptophan hydroxylase:<br>  • Ensure nutrient cofactors for the conversion of tryptophan to 5-HTP to ensure pathway is not shifted to tryptamine due to nutrient deficiencies<br>  • **BH4:** Nutrient cofactors for synthesis and regeneration of BH4 listed below[18]<br>  • 5-Methyltetrahydrofolate or folate: 400-800mcg<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>  *Note: Inflammation and oxidative stress may decrease BH4 levels[19]*<br>  • **Iron:** 15-30mg |
| DIETARY CONSIDERATIONS | • Ensure sufficient intake of tryptophan rich food sources | • **Reduce intake of high tryptamine foods**[114]:<br>  • Fermented foods (sauerkraut, fermented tofu), cheese, sausage, fish, wine, beer<br>  Caution is warranted with high tryptamine foods when combined with medications or supplements that act as MAO inhibitors due to risk of hyptertensive crisis |
| LIFESTYLE CONSIDERATIONS | *Lifestyle interventions do not significantly influence low tryptamine levels* | • Limit activities that may induce states of hypoxia, such as climbing at high altitudes[112] |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies impacting pathways | • **Micronutrients:** to assess for nutrient deficiencies impacting pathways |



# CATECHOLAMINE METABOLISM




AAADC: AROMATIC AMINO ACID DECARBOXYLASE
MAO: MONOAMINE OXIDASE
COMT: CATECHOL-O-METHYLTRANSFERASE
AR: ALDEHYDE REDUCTASE
AD: ALDEHYDE DEHYDROGENASE
PNMT: PHENYLETHANOLAMINE N-METHYLTRANSFERASE

# TYROSINE

## What is tyrosine?

Tyrosine is a non-essential amino acid and a precursor to catecholamine neurotransmitters, including dopamine, norepinephrine, and epinephrine. Tyrosine is found in many different food sources, however, it is not considered an essential amino acid because the body is able to synthesize it from phenylalanine. The exception to this are individuals with the disorder phenylketonuria (PKU), who are unable to convert phenylalanine to tyrosine and require a diet low in phenylalanine to prevent buildup of the amino acid.

## What are the functions of tyrosine?

One of tyrosine's most notable roles is acting as a precursor to catecholamine neurotransmitters. It also plays a role in other important physiological functions, such as protein synthesis, production of thyroid hormone, melanin synthesis and formation of tyramine[115]. Tyrosine is transported across the blood brain barrier (BBB) by a carrier that acts competitively with other large neutral amino acids (LNAA)[115]. Therefore, even though tyrosine levels may be robust, the quantity of other LNAA can influence its transport into the brain for synthesizing catecholamine neurotransmitters. Since tyrosine is used as a precursor for dopamine, norepinephrine and epinephrine synthesis, it plays an important role in conditions and symptoms associated with catecholamines.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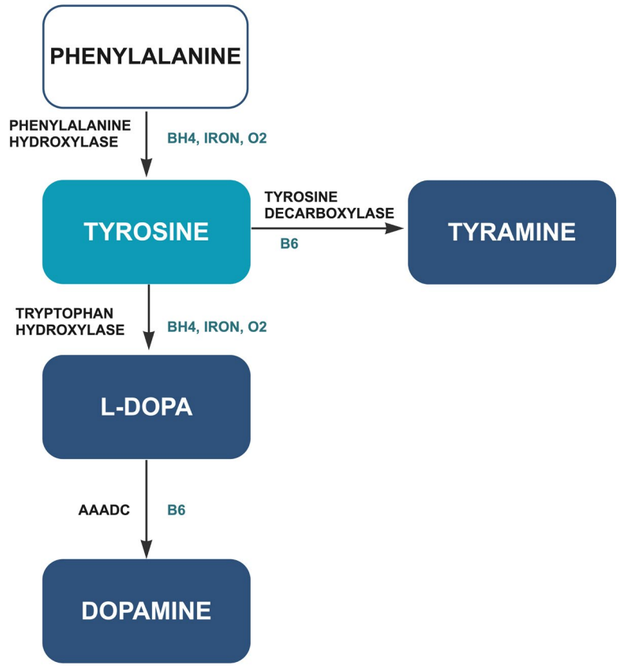



## LOW TYROSINE

Administering a diet low in tyrosine can contribute to low tyrosine levels. Any digestive impairments or gastrointestinal dysfunction can also result in poor digestion and absorption of tyrosine. Since tyrosine competes with other LNAA to cross the BBB, any increase in other LNAA can result in decreased levels of tyrosine in the brain. Tyrosine depletion has shown behavioral and physiological effects consistent with decreased dopamine levels. Physiological effects of low tyrosine include increased prolactin levels, impaired features of spatial recognition memory and performance, decreased manic symptoms in patients with mania, low mood, and increased apathy[cxvi]. Low tyrosine may also be linked with disorders such as hypothyroidism. The disorder PKU is a genetic disorder of phenylalanine hydroxylase, where phenylalanine builds up due to the ability to convert to tyrosine.

## HIGH TYROSINE

Very high levels of tyrosine can be due to genetic disorders that impair the breakdown of tyrosine, leading to its buildup and contributing to significant health problems. These include hereditary tyrosinemia (HT) types 1, 2, 3 and alkaptonuria (AKU)[115]. Nutrient deficiencies can contribute to higher levels of tyrosine due to decreased enzymatic function. Tetrahydrobiopterin (BH4), oxygen, and iron are essential nutrients for tyrosine hydroxylase, that's required to convert tyrosine to L-DOPA[115]. If tyrosine is high and L-DOPA is low, consider nutrient cofactor support. High levels of tyrosine can potentially lead to higher levels of catecholamine synthesis, therefore, it's important to interpret results in conjunction with other intermediates along the catecholamine pathway. High tyrosine levels are commonly due to supplementation or a high protein diet. Caution is warranted with certain medications that increase catecholamines when tyrosine levels are elevated.

### Clinical Pearl:

Even if tyrosine levels are normal, elevated catecholamines can contribute to low availability of tyrosine for other functions, such as thyroid hormone production due to increased demand.

# TYROSINE CONSIDERATIONS

| | LOW TYROSINE | HIGH TYROSINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **L-Tyrosine**[116]: 100-150mg/kg for up to 3 months<br>• **DL/L Phenylalanine**: 200-1000mg/d<br>  • Requires conversion to L-tyrosine and sufficient nutrient cofactors<br>Support nutrient cofactors for phenylalanine hydroxylase (converts phenylalanine to tyrosine)<br>  • **BH4**: Nutrient cofactors for synthesis and regeneration of BH4 listed below18<br>  • 5-Methyltetrahydrofolate or folate: 400-800mcg/d<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>  *Note: Inflammation and oxidative stress may decrease BH4 levels*[19]<br>  • **Iron:** : 15-30mg/d | • Support nutrient cofactors for tyrosine hydroxylase *(converts tyrosine to L-DOPA)*<br>  • If tyrosine is high and L-DOPA is low, focus on cofactor support for tyrosine<br>  • **BH4:** Nutrient cofactors for synthesis and regeneration of BH4 listed below[18]<br>  • 5-Methyltetrahydrofolate or folate: 400-800mcg/d<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>  *Note: Inflammation and oxidative stress may decrease BH4 levels*[19]<br>  • **Iron:** 15-30mg<br>• Avoid/limit supplements that contain tyrosine |
| DIETARY CONSIDERATIONS | • **Increase intake of tyrosine rich foods**[117]<br>  • Cheese, soybeans, beef, lamb, pork, fish, chicken, nuts, eggs, dairy, beans, and whole grains<br>• **Increase intake of phenylalanine rich foods**[118]**:**<br>  • Meat, chicken, fish, eggs, dairy products, nuts, seeds, quinoa, oats, soy, lentils, gelatin | • Limit intake of tyrosine rich foods (may be more important if catecholamines are significantly elevated) |
| LIFESTYLE CONSIDERATIONS | *Lifestyle interventions do not significantly impact tyrosine levels* | *Lifestyle interventions do not significantly impact tyrosine levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies that may impact tyrosine levels<br>• **Gut Zoomer:** to assess for maldigestion/malabsorption contributing to low tyrosine levels<br>• **Thyroid Panel:** to assess thyroid function since tyrosine is a precursor for its synthesis<br>• **Methylation Panel:** to assess for methylation that may impact tyrosine levels | • **Micronutrients:** to assess for nutrient deficiencies that may impact tyrosine levels<br>• **Methylation Panel:** to assess for methylation that may impact tyrosine levels |



# L-DOPA

## What is L-DOPA?

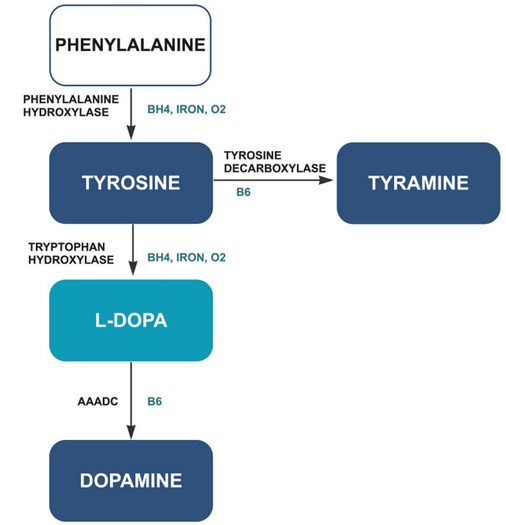
L-DOPA is an amino acid and a precursor for catecholamine synthesis.

## What are the functions of L-DOPA?

While originally thought to just be an intermediate in dopamine synthesis, there is now speculation that L-DOPA might exert some neurotransmitter properties itself, but research is still limited in this area[119]. A significant amount of research revolves around L-DOPA due to its use in the treatment of Parkinson's disease (PD). The pharmaceutical form of L-DOPA is known as Levadopa, which is commonly used as a treatment in PD due to its ability to cross the blood brain barrier and increase dopamine levels[119]. It is also commonly used in combination with another medication, such as Carbidopa, which is used as a peripheral inhibitor for amino acid decarboxylase so that L-DOPA can successfully enter the brain[110].

## L-DOPA metabolism and pathways:

L-DOPA is formed from the hydroxylation of L-tyrosine by tyrosine hydroxylase, which is the rate limiting step in catecholamine synthesis[121]. This enzymatic reaction requires tetrahydrobiopterin (BH4), iron and oxygen. L-DOPA can then be converted to dopamine by the enzyme aromatic amino acid decarboxylase (AADC), which requires vitamin B6 as a nutrient cofactor[121]. L-DOPA also undergoes peripheral metabolism by the COMT enzyme, which is another target for pharmaceutical interventions to inhibit in order to increase dopamine levels




## LOW L-DOPA

Low levels of L-DOPA can occur due to a genetic deficiency of tyrosine hydroxylase. Insufficient levels of tyrosine can also contribute to low levels of L-DOPA. A lack of essential nutrient cofactors, including tetrahydrobiopterin and iron, may lead to decreased enzymatic function of tyrosine hydroxylase. Low levels can lead to low concentrations of catecholamines including dopamine, norepinephrine, epinephrine and their corresponding metabolites.

## HIGH L-DOPA

Most of the research involving L-DOPA is centered around Levadopa, therefore, much of the information that's available regarding high levels is due to medication use. High L-DOPA, leading to high levels of its derivatives, can contribute negative effects when degraded by MAO and COMT enzymes. This includes the formation of free radicals and induction of apoptosis[122]. When individuals take Levadopa, contributing to higher levels of L-DOPA, negative side effects can occur, including nausea, dizziness, headache, somnolence, confusion, hallucinations, delusions, psychosis and agitation[122]. Contraindications are in place with concurrent use of medications, such as MAOIs due to the risk of a hypertensive crisis.

### Clinical Pearl:

If L-DOPA is high due and dopamine is low, consider a vitamin B6 deficiency. Look at other enzymatic reactions that require vitamin B6 to determine if the pattern matches. The enzyme chart at the end of the document may be helpful.

# L-DOPA CONSIDERATIONS

| | LOW L-DOPA | HIGH L-DOPA |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **L-Tyrosine**[116]: 50-150mg/kg for up to 3 months<br>• **Mucuna Pruriens**[123]: 200-500mg/d<br>  • The main phenolic compound of Mucuna seeds is L-DOPA<br>• If tyrosine is on the higher end and L-DOPA is low, support tyrosine hydroxylase enzyme with nutrient cofactor support:<br>  • **BH4:** Nutrient cofactor for conversion of tyrosine to L-DOPA. Nutrient cofactors for synthesis and regeneration of BH4 listed below[19]<br>  • 5-Methyltetrahydrofolate or folate: 400-800mcg/d<br>  • Vitamin B3: 50-100mg<br>  • Zinc: 15-30mg<br>  • Magnesium: 400-800mg<br>  *Note: Inflammation and oxidative stress may decrease BH4 levels*[20]<br>  • **Iron:** : 15-30mg/d<br>  • Nutrient cofactor for convesion of phenylalanine to tyrosine | • If L-DOPA is high and dopamine levels are low, support AAADC enzyme with nutrient cofactor support<br>  • **Vitamin B6** (Pyridoxal 5- phosphate): 10-50mg<br>• If tyrosine is elevated, see recommendations for high tyrosine to limit precursor |
| DIETARY CONSIDERATIONS | • **Increase foods rich in tyrosine (if tyrosine is low)**<br>• **Consume fava beans**[124]**:** a rich source of L-DOPA | • Increase intake of high antioxidant foods due to free radical production from high L-DOPA metabolism<br>• If tyrosine is high, limit high tyrosine rich foods sources and a high protein diet |
| LIFESTYLE CONSIDERATIONS | *Lifestyle interventions do not significantly affect L-DOPA levels* | *Lifestyle interventions do not significantly affect L-DOPA levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies that may impact L-DOPA levels<br>• **Methylation Panel:** to assess for methylation impairments | • **Micronutrients:** to assess for nutrient deficiencies that may impact L-DOPA levels |



# DOPAMINE

## What is dopamine?

Dopamine is a monoamine neurotransmitter that is classified as a catecholamine. It is generally excitatory in nature, but it can also exhibit inhibitory functions depending on multiple factors such as location and target cell receptors. Dopamine is related to the "reward system" of the brain and is also commonly known as the "pleasure" chemical messenger. It is also the most abundant neurotransmitter in the brain.

## What are the functions of dopamine?

Dopamine plays a predominant role in regulating motor neurons, spatial memory, motivation, arousal, reward and pleasure, sleep regulation, attention, cognitive function, feeding, olfaction, lactation, sexual behavior, and nausea[125]. Dopamine plays an important role in pleasure, where activities such as eating, sexual activity, and shopping commonly result in feelings of pleasure from dopamine release. Multiple systems are influenced by dopamine levels, including the endocrine, immune, cardiovascular, gastrointestinal, and renal systems. Dopamine is formed in the central nervous system as well as peripheral organs, including the kidneys and the gut. In the brain, dopaminergic neurons are concentrated in the central tegmental area (VTA), the substantia nigra pars compacta and the arcuate nucleus in the hypothalamus[125]. Dopamine receptors (D1-D5) exhibit different functions in the body, where D1 and D4 play a strong role in the cognitive enhancing effects of dopamine, while D2 is more closely related to motor function and sleep[128]. The most common conditions and disorders associated with dopamine dysfunction include Parkinson's disease, Huntington's disease, Schizophrenia, ADHD, depression, restless leg syndrome and addiction[125,126]. Dopamine affects the endocrine systems in multiple ways, such as inhibiting the release of prolactin by the anterior pituitary gland[128]. Estrogen has been shown to promote dopamine release in the striatum[127]. This may be due to estrogens inhibitory effect on GABA release since a decrease in inhibitory tone may increase dopamine release[127]. There is also often an inverse relationship with serotonin and catecholamines, but not always.

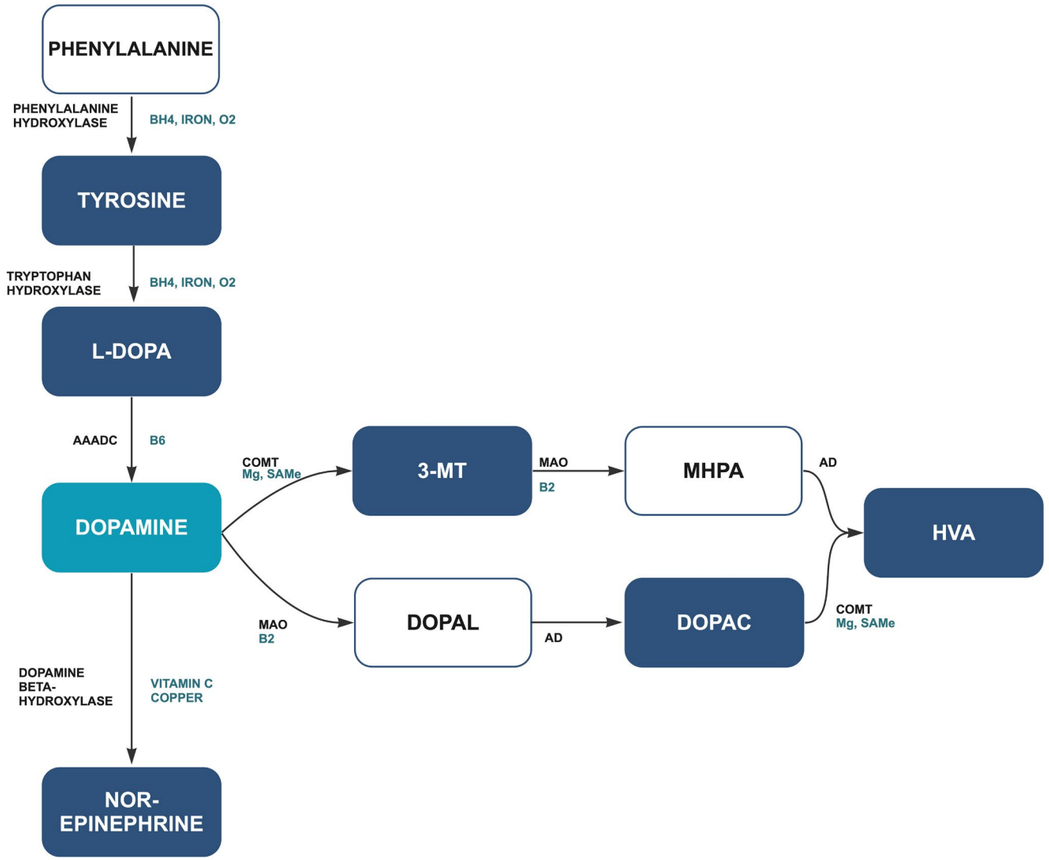
## Dopamine metabolism and pathways:

Dopamine can be synthesized from the amino acids phenylalanine or tyrosine. Tyrosine hydroxylase is the rate limiting enzyme in the pathway, which converts tyrosine to L-DOPA. This reaction requires important cofactors, including tetrahydrobiopterin (BH4), oxygen, and iron[125]. L-DOPA can then be decarboxylated by aromatic L-amino acid decarboxylase to form dopamine. This reaction requires pyridoxal phosphate (vitamin B6) as an essential nutrient cofactor. Dopamine is then transported by a vesicular monoamine transporter (VMAT2), from the cytosol to synaptic vesicles where it is stored until it's ready to be released into the synaptic cleft[125]. The acidic nature of the vesicles where dopamine is stored prevents its oxidation. Dopamine is catabolized by two different pathways. The first requires the MAOa enzyme for conversion to 3,4-Dihydroxyphenlacetaldehyde (DOPAL), which is then converted to 3,4- dihydroxyphenylacetic acid (DOPAC) by the enzyme aldehyde dehydrogenase (ALDH)[125]. Once DOPAC is formed, the COMT enzyme can further metabolize it to homovanillic acid (HVA) with the cofactors SAMe and magnesium. The second path requires the COMT enzyme for conversion to 3-MT, which is then converted to an intermediate, MHPA, by the MAOa enzyme. Aldehyde dehydrogenase rapidly convert MHPA to HVA as one of the main end products of dopamine catabolism. It's important to note that COMT is predominantly expressed in glial cells and is either lacking or found at very low concentrations in neurons[128]. Dopamine and its metabolites can go through two different phase II conjugation reactions before excretion, sulfation and glucuronidation. Sulfation occurs by the phenolsulfotransferase (PST) enzyme, whereas glucuronidation occurs via the uridine diphosphoglucuronosyltranferase (UGT) enzyme. These are alternate pathways that metabolize dopamine to an inactive form, such as dopamine o-sulfate or dopamine o-glucuronide.

Dopamine has been shown to produce damaging reactive oxygen species (ROS) through normal and alternative metabolism. Normal degradation of dopamine via the MAOa enzyme produces hydrogen peroxide as a byproduct, which can increase ROS. Alternatively, dopamine has the ability to spontaneously oxidize into toxic quinones if it's not sequestered into vesicles or metabolized down degradation pathways by MAOa, COMT, and SULT1A3[125]. Dopamine that's in the cytosol spontaneously oxidizes to dopamine o-quinone and then cyclization to aminochrome, which is a precursor to neuromelanin, which all have negative effects. The production of these compounds may explain the role that dopamine plays in inducing neurotoxicity since they have been

associated with oxidative stress, mitochondrial dysfunction, inflammation, and proteasome impairment[130,131]. High amounts of transition metals, such as iron, copper and manganese, may contribute to increased quinone production and subsequent macromolecular damage and cell death[129].

In noradrenergic cells, dopamine can be converted to norepinephrine by the enzyme dopamine beta-hydroxylase (DBH). DBH requires copper and vitamin C as important nutrient cofactors. Various factors have been shown to inhibit DBH, such as overgrowth of Clostridia bacteria[158]. Norepinephrine can then be broken down or converted to epinephrine. While a significant amount of dopamine is produced within the central nervous system, roughly 50% of dopamine in the body is synthesized in the gut[132]. Staphylococcus in the GI tract has the ability to convert L-DOPA to dopamine by staphylococcal aromatic amino acid decarboxylase[132].






## LOW DOPAMINE

Low levels of dopamine can occur due to genetic SNPs, nutrient deficiencies, and other factors that interfere with the enzymatic reactions involved in dopamine metabolism. The most important nutrients for dopamine synthesis include tyrosine, tetrahydrobiopterin (BH4), iron, and vitamin B6. Low levels of dopamine can also impair the synthesis of other catecholamines, norepinephrine and epinephrine, due to its role as a precursor. The most commonly known disorder associated with dopamine is Parkinson's disease, which is caused by a decreased amount of dopamine in the substantia nigra. The low dopamine availability manifests with symptoms such as resting tremor, bradykinesia, shuffling gait, and postural instability[133]. Treatments are aimed at increasing dopamine levels with medications such as Levadopa and often combining them with a DOPA decarboxylase inhibitor, such as Caribdopa, to prevent peripheral conversion to dopamine[133]. Since serotonin and catecholamines exhibit an inverse relationship, it's important to assess serotonin levels as a factor in low dopamine levels. High activity of the MAOa enzyme, increases catabolism of dopamine, leading to lower levels. Supplements that act as MAO inhibitors may help slow the activity of the enzyme to increase dopamine levels.

**Symptoms (LOW)**: Apathy, fatigue, poor motivation, low mood, memory issues, sleep disturbances, lack of stress tolerance/stress response outbursts, poor focus, lack of socialization, lack of pleasure, feeling worthless/hopeless, low libido

**Conditions (LOW)**[126]: Parkinson's disease, pituitary tumors (prolactinomas), restless leg syndrome, movement disorders, Alzheimer's disease, depression, multiple sclerosis, hypothyroidism

## HIGH DOPAMINE

High levels of dopamine can occur due to increased levels of tyrosine and other precursors for dopamine synthesis. Common lifestyle patterns that increase dopamine levels include high amounts of screen time, gambling, thrill-seeking activities, shopping and obsessive hobbying to name a few[134,151]. When there are chronically high levels of dopamine, the brain can be desensitized to dopamine and this may drive increased behaviors to seek that same dopamine response. It may be important to avoid or limit activities associated with increased dopamine surge. High levels of dopamine have the potential to exert toxic effects, particularly when there are high levels of extracellular dopamine. One animal study showed that a high dose of dopamine injected into the striatum resulted in selective dopamine terminal loss[129] while other studies showing high levels of extracellular dopamine contributing to striatal neuron degeneration[129]. Incorporating some protective agents, such as glutathione, when dopamine levels are high may help offset some of the physiological damage incurred. Mercury toxicity can lead to increased dopamine levels due to its inhibitory effect on the COMT enzyme[135]. Elevated dopamine levels can also occur due to impaired catabolism to DOPAC, 3-MT and sulfated conjugation of dopamine. Any impairments in DBH, which can decrease the conversion of dopamine to norepinephrine, can also result in the buildup of dopamine. Slow activity of the MAOa enzyme can impair the breakdown of dopamine and lead to higher levels. It would be contraindicated to incorporate any supplements that act as an MAO inhibitor in this case.

**Symptoms (HIGH)**[126,136,137,138]: Compulsive behaviors (sexual behavior, eating, buying, gambling), increased risk taking, addiction, aggression, psychosis, hypersocialability, ambitious attitude, depression, suicidal ideation, anxiety, paranoia, panic attacks, less empathetic, hiccups, nausea and vomiting, decreased gut motility, excess salivation

**Conditions (HIGH)**[139,140,158]: ADHD, anxiety, autism spectrum disorder, bipolar disorder (mania), Huntington's disease, neuroblastoma, obsessive compulsive disorder, tardive dyskinesia, Tourette syndrome, schizophrenia

### Clinical Pearl:

Dopamine catabolism can contribute to oxidative stress due to byproducts that are produced from enzymatic reactions by aldehyde dehydrogenase, for example. Decreasing the breakdown of dopamine can decrease the production of oxidative stress. Chronic high levels of dopamine may require more antioxidants to counter the oxidative stress.

# DOPAMINE CONSIDERATIONS

| | LOW DOPAMINE | HIGH DOPAMINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • If L-DOPA is high & dopamine is low, support nutrient factors for AAADC:<br>• **Vitamin B6 (Pyridoxal 5-phosphate):** 10-50mg<br>**Green Oat Herb Extract**[141]: 800mg/day<br>• Inhibitory effects on MAO to decrease dopamine catabolism<br>**L-Theanine**[104,142]: 200-400mg/day<br>• Animal models showed increased dopamine levels with L-theanine intake<br>**Mucuna Pruriens**[143]: 200-500mg/daya<br>• The main phenolic compound of *Mucuna* seeds is L-DOPA<br>**Probiotics**[108]: L. plantarum, L. helveticus, L.casei, L. bulgaricus<br>**MAOa enzyme inhibitors** [50,51,52,53,54,55,56,57,58]<br>*Decrease catabolism of dopamine (In vitro and animal studies)*<br>• Curcumin (10-80mg/kg), quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African Rue, St. John's Wort, berberine<br>*If tyrosine or L-DOPA are low, follow recommendations to increase them accordingly* | • **Bacopa Monniera**[144,145]: 300-600mg/day<br>• Animal models showed reduction of the dopamine concentration in the frontal cortex region of the brain<br>• **Glutathione**[146,147]: 250-1000mg/day<br>• Bind dopamine and DOPAC quinones by their thiol group so proteins are spared from damage<br>• If dopamine is higher and norepinephrine/ epinephrine are lower, support DBH with nutrient cofactors<br>• **Vitamin C**: 500-1500mg/day<br>• **Copper:** 1-3mg/day<br>• If dopamine is higher and 3-MT is lower, support MAO enzyme with nutrient cofactors<br>• **Vitamin B2**[59]: 6-30mg/d<br>If higher levels are higher and DOPAC is lower, support COMT enzyme with nutrient cofactors:<br>• **SAMe**[60]: 400-1600mg/day<br>• **Magnesium:** 400-800mg/d<br>**Limit MAOb inhibitors, which may increase dopamine levels*<br>**If tyrosine or L-DOPA are high, follow recommendations to lower them accordingly* |
| DIETARY CONSIDERATIONS | • **Increase intake of tyrosine rich foods:** (particularly important if tyrosine levels are low) | • **Limit tyrosine rich foods** (particularly important when tyrosine levels are also high)<br>• **Limit high dopamine foods**[148]**:**<br>• Banana, plantain, avocado, orange, apple, eggplant, spinach, pea, tomato, common bean, velvet bean<br>• **Limit intake of high mercury seafood**<br>• **Avoid/limit caffeine and high sugar intake**[149]<br>• **Increase high antioxidant foods due to free radicals formed from dopamine metabolism** |
| LIFESTYLE CONSIDERATIONS | • *Increase engagement in activities that are pleasurable* | • **Lemon Oil vapor**[150]: Animal study showed suppressed dopamine activity<br>• **Epsom salt baths (magnesium sulfate):** Theoretically provides a source of sulfate to assist with sulfate conjugation of dopamine<br>• **Limit screen time**[134]: Reduce time in front of television, tablets, and phones<br>• **Limit/avoid behaviors that may increase dopamine surge**[151]**:** Gambling, thrill-seeking activities, shopping, obsessive hobbying |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for deficiencies that may impact dopamine levels<br>• **Methylation Panel:** to assess for methylation impairments<br>• **Neural Zoomer Plus:** to assess for antibodies to dopamine receptors 1 and 2 | • **Micronutrients:** to assess for deficiencies that may impact dopamine levels<br>• **Methylation Panel:** to assess for methylation impairments<br>• **Gut Zoomer:** to assess for dysbiosis, particularly overgrowth of Clostridia levels<br>• **Heavy Metals:** to assess for heavy metals that may interfere with dopamine levels |



# DOPAC

## What is DOPAC?

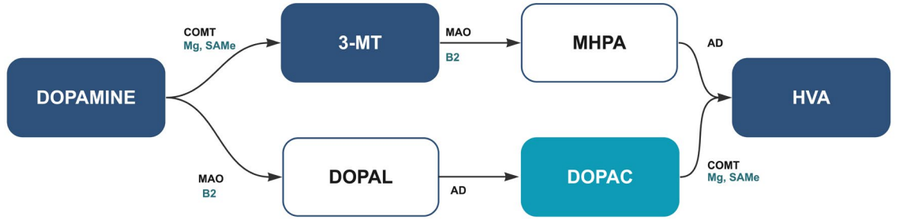
DOPAC is one of the major metabolites of dopamine breakdown. Dopamine is a catecholamine neurotransmitter that is related to the "reward system" of the brain and is also commonly known as the "pleasure" chemical messenger.

## What are the functions of DOPAC?

As a metabolite, DOPAC does not exert any known independent functions in the body.

## DOPAC metabolism and pathways:

Dopamine catabolism occurs by oxidative deamination via the MAOa enzyme in the cytoplasm of neurons to form DOPAL (3,4-dihydroxyphenylacetaldehyde). Even though DOPAL is short-lived, it is a highly reactive intermediate that is toxic to dopaminergic cells, modifies proteins and causes protein aggregation[152]. DOPAL is then converted to DOPAC, which is a less toxic intermediate, by the enzyme aldehyde dehydrogenase (ALDH). DOPAC formation can lead to oxidative stressmediated neurotoxicity due to the ALDH reaction producing hydrogen peroxide and DOPAC's ability to form quinone molecules[153]. Any impairments in aldehyde dehydrogenase may lead to higher DOPAL levels, which can contribute to cellular insult and lower DOPAC levels. To a lesser extent, DOPAL can also breakdown to DOPET by aldehyde/aldose reductase. Since DOPAC is formed from dopamine in the cytoplasm, this may correlate with presynaptic dopamine levels.




## LOW DOPAC

Low levels of DOPAC can occur with low levels of dopamine. Any impairments in the MAOa enzyme can result in lower levels of DOPAL and potentially lower DOPAC. These include genetic SNPs, medications, supplements, and nutrient deficiencies (Vitamin B2). There are many commonly used supplements that act as MAOa inhibitors that should be assessed to see if they are contributing to low DOPAC levels. There are multiple factors that contribute to aldehyde dehydrogenase (ALDH) inhibition, including increased oxidative stress and exposure to pesticides, that may lead to increased levels of DOPAL and decreased conversion to DOPAC[152]. Drugs such as amphetamines have been shown to decrease the concentration of extracellular DOPAC[153].

## HIGH DOPAC

High levels of DOPAC correlate with high levels of dopamine. It's important to assess high levels of DOPAC in combination with dopamine levels and follow recommendations for high dopamine if the pattern fits. If there is any blockade in the DBH enzyme that converts dopamine to norepinephrine, there may be a greater shift in dopamine metabolites, such a DOPAC. This can be due to factors such as genetic influences, clostridia overgrowth, or nutrient deficiencies (vitamin C, copper). Any impairments in the COMT enzyme that converts to DOPAC to HVA, may also lead to higher levels. This can include genetic SNPs, medications, supplements, impaired methylation or nutrient deficiencies (magnesium). Antipsychotic drugs have been shown to increase the levels of extracellular DOPAC[153].

### Clinical Pearl:

DOPAC can be an important marker of MAOa activity. Since the MAOa enzyme also metabolizes serotonin and other catecholamines, norepinephrine and epinephrine, assessing those other neurotransmitters can provide information about the activity of the MAOa enzyme.

# DOPAC CONSIDERATIONS

| | LOW DOPAC | HIGH DOPAC |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for MAO enzyme:<br>  • **Vitamin B2**[59]: 6-30mg/d<br>*If dopamine is low, follow recommendations for low levels* | • Support nutrient cofactors for COMT:<br>  • **SAMe**[60]: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d<br>If dopamine is high, follow recommendations for high levels |
| DIETARY CONSIDERATIONS | • **Choose organic foods to minimize exposure to pesticides**[152]<br>• *If dopamine is low, follow dietary recommendations for low levels* | • **Increase high antioxidant foods due to free radicals formed from dopamine metabolism**<br>• If dopamine is high, follow dietary recommendations for high levels |
| LIFESTYLE CONSIDERATIONS | • **Reduce exposure to environmental pesticides** | • *If dopamine is high, follow lifestyle interventions recommendations for high levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for deficiencies that may impact DOPAC levels<br>• **Environmental Toxins:** to assess for toxins that may be impacting DOPAC levels | • **Micronutrients:** to assess for deficiencies that may impact DOPAC levels<br>• **Methylation Panel:** to assess for methylation impairments that may impact DOPAC levels<br>• **Organic Acids:** to assess for dysbiosis markers that may inhibit DBH |



# 3-MT

## What is 3-MT?

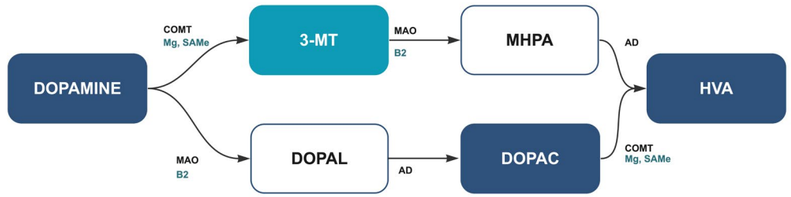
3-methoxytyramine (3-MT) is an extracellular metabolite of dopamine.

## What are the functions of 3-MT?

3-MT was previously thought to be an inert metabolite of dopamine metabolism, but research has shown that it has neuromodulator effects influencing both physiology and behavior independent of dopamine. 3-MT exerts its effects partially by acting on the trace amine associated receptor 1(TAAR1)[154]. Some of the behavioral effects associated with 3-MT include tremor, stereotypies, hyperactivity and hypoactivity[154].

## 3-MT metabolism and pathways:

A major source of 3-MT comes from dopamine that is released in the extracellular space and is then methylated by the COMT enzyme to form 3-MT. COMT is present in glial cells, but it is absent in dopaminergic nigro-striatal neurons. Since 3-MT is formed in the extraneuronal space from dopamine that is released, 3-MT is considered to be a reflection of dopamine activity. 3-MT is then further metabolized by the MAO enzyme to form an intermediate, MHPA. Aldehyde dehydrogenase quickly converts MHPA to homovanillic acid (HVA), the main end product of dopamine catabolism. The enzymatic reaction by MAO can contribute to increased oxidative stress due to the production of hydrogen peroxide, aldehyde, and ammonium as metabolic end productsclvi. Hydrogen peroxide is a known inducer of inflammation by activating NFκB, while biogenic aldehydes can contribute to neuroinflammation and mitochondrial dysfunction[155].




## LOW 3-MT

Low 3-MT often correlates with low dopamine levels and low dopamine release. Any symptoms or conditions associated with low dopamine would also apply to low 3-MT. Any decrease in COMT activity through supplements, medications, genetic SNPs, or nutrient deficiencies may decrease the concentration of 3-MT formed. The nutrient cofactors that are essential for COMT activity include magnesium and SAMe, therefore, any deficiencies in these nutrients can lead to decreased 3-MT formation. Heavy metals, such as mercury are also known to inhibit the COMT enzyme, which can lead to lower 3-MT levels[135].

## HIGH 3-MT

Higher levels of 3-MT have been shown to exert behavioral effects independent of dopamine, including tremors, stereotypies, and hyperactivity and hypoactivity[154]. Any blockade of the enzymes responsible for degradation of 3-MT, including MAO and aldehyde dehydrogenase (ALDH), may result in increased levels. While there are specific medications that are classified as MAO inhibitors, supplements and other environmental factors can also decrease MAO activity. Exposure to cigarette smoke[156] and toxic metals such as mercury may also decrease MAO activity[155], leading to higher levels of 3-MT. MAO enzyme activity is dependent on flavin adenine dinucleotide (FAD), which relies on vitamin B2. Therefore, any deficiency in vitamin B2 may lead to increased 3-MT levels. Since serotonin is also similarly catabolized by MAOa and ALDH, assessing and comparing serotonin and 5-HIAA to dopamine and its metabolites can provide more valuable information about enzyme activity.

### Clinical Pearl:

A major source of 3-MT comes from dopamine that is released into the extracellular space and is formed from metabolism by COMT. Therefore, 3-MT has been considered a marker of dopamine that's released.

# 3-MT CONSIDERATIONS

| | LOW 3-MT | HIGH 3-MT |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for COMT<br>  • **SAMe[60]**: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d | • Support nutrient cofactor for MAO:<br>  • **Vitamin B2[59]**: 6-30mg/d<br>*If dopamine is high, see supplement recommendations to address high levels* |
| DIETARY CONSIDERATIONS | • *If dopamine is low, see dietary recommendations to address low levels* | • *If dopamine is high, see dietary recommendations to address high levels* |
| LIFESTYLE CONSIDERATIONS | • *If dopamine is low, see lifestyle interventions to address low levels* | • *If dopamine is low, see lifestyle interventions to address high levels* |
| TESTING CONSIDERATIONS | • **Methylation:** to assess for impairments in methylation that may impact 3-MT levels<br>• **Heavy Metals:** to assess for heavy metals that may impact COMT activity<br>• **Micronutrients:** to assess for micronutrient that may impact 3-MT levels | • **Micronutrients:** to assess for micronutrient that may impact 3-MT levels |



# HOMOVANILLIC ACID (HVA)

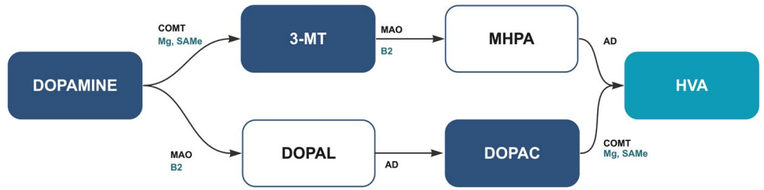
## What is HVA?

Homovanillic acid (HVA) is the major catecholamine metabolite from dopamine breakdown.

## What are the functions of HVA?

HVA is an inert metabolite and does not exert any independent functions in the body.

## HVA metabolism and pathways[206]:




HVA is the end product that's formed via two different pathways of dopamine catabolism. The first pathway involves oxidative deamination of dopamine to DOPAL and then dehydrogenation to DOPAC. From DOPAC, is it methylated by COMT utilizing magnesium and SAMe as cofactors to form HVA. Alternatively, dopamine can be methylated by COMT to form 3-methoxytyramine (3-MT). 3-MT is then deaminated by MAO to an intermediate, 3-methoxy-4-hydroxyphenylacetaldehyde, before undergoing dehydrogenation by aldehyde dehydrogenase to form HVA. Most HVA is formed outside of the liver. Roughly 12% of the HVA levels are contributed from the brain, whereas the rest originates from peripheral tissues.

## LOW HVA

Low levels of HVA generally correlate with lower levels of dopamine in the body. Impaired MAO or COMT activity due to either genetics, medications, or supplement interventions can lead to decreased HVA levels. The most important nutrients for these enzymes are vitamin B2, magnesium and SAMe.

## HIGH HVA

Elevated levels of HVA are a marker of elevated dopamine breakdown in the body. If dopamine levels are also elevated, follow recommendations to decrease dopamine synthesis. Increased enzymatic activity of COMT and MAO can also result in higher levels of HVA. Elevated levels of HVA can occur in individuals with catecholamine-secreting tumors such as neuroblastoma, pheochromocytoma and neural crest tumors. Impaired function of the DBH enzyme that converts dopamine to norepinephrine can lead to increased levels of HVA due to dopamine shifting towards catabolism instead of towards norepinephrine synthesis. Research has demonstrated that an overgrowth of clostridia bacteria may inhibit the DBH enzyme and result in higher levels of HVA[158].

### Clinical Pearl:

If there is a discrepancy between dopamine and HVA levels, consider the activity of both the MAO and COMT enzymes. Another important note is that the more dopamine that is metabolized, the more reactive oxygen species are formed from the by byproducts produced. These include hydrogen peroxide, aldehyde, and ammonium.

# HVA CONSIDERATIONS

| | LOW HVA | HIGH HVA |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for COMT<br>  • **SAMe**[60]: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d<br>• Support nutrient cofactor for MAO<br>  • **Vitamin B2**[59]: 6-30mg/d | *If dopamine is elevated, follow recommendations to lower dopamine accordingly*<br>*There is some evidence that quercetin may increase HVA level159* |
| DIETARY CONSIDERATIONS | • If tyrosine is low, increase food sources of tyrosine, which can increase dopamine levels and the HVA metabolite | • *If tyrosine levels are high, decrease tyrosine rich food sources to decrease dopamine synthesis and the HVA metabolite* |
| LIFESTYLE CONSIDERATIONS | • If dopamine is low, follow lifestyle interventions for low dopamine | • Limit/avoid lifestyle interventions that are associated with high dopamine levels (if applicable) |
| TESTING CONSIDERATIONS | • **Methylation Panel:** to assess for methylation impairments that may impact COMT activity<br>• **Heavy Metals:** to assess for heavy metal toxins that may impair COMT activity<br>• **Micronutrients:** to assess for deficiencies that may impact HVA levels | • **Organic Acids:** to assess for dysbiosis markers and elevated Clostridia that may impact HVA levels |



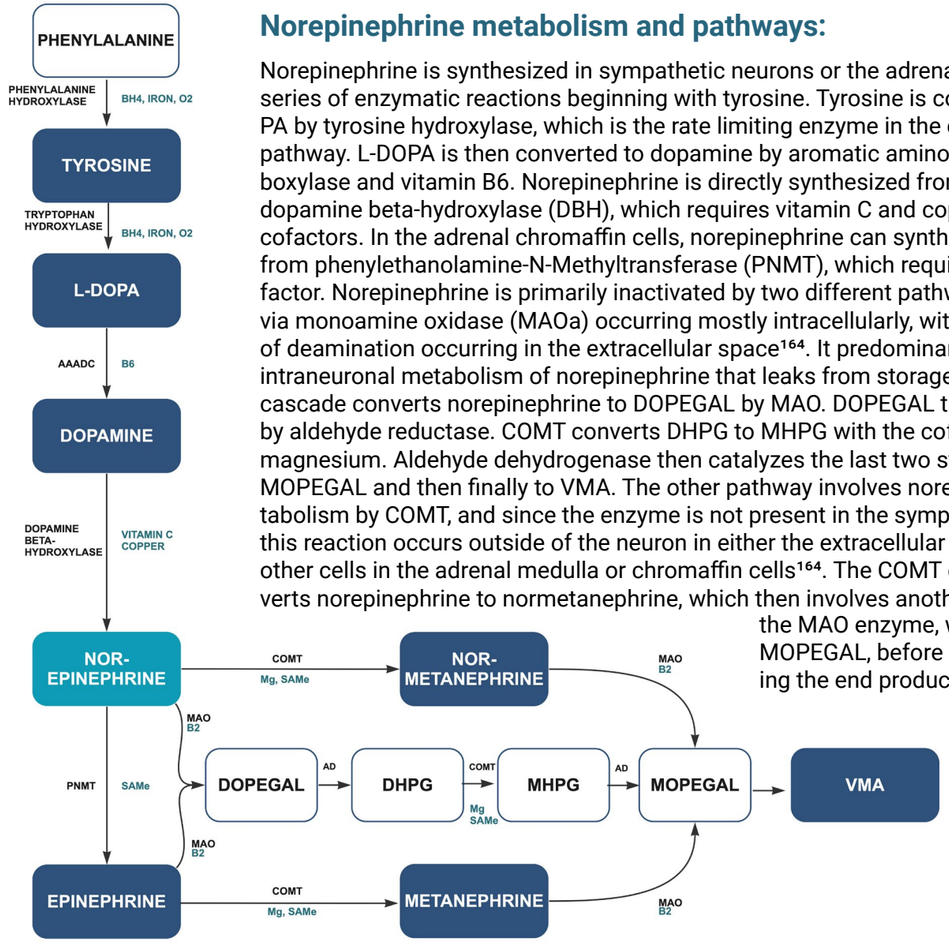
# NOREPINEPHRINE

## What is norepinephrine?

Norepinephrine is a catecholamine neurotransmitter that exerts functions in both the central and peripheral nervous system. It is also commonly known as noradrenaline, and is part of the sympathetic nervous system, which deals with the body's stress response. Norepinephrine is produced in the adrenal medulla and sympathetic nerves. It is mainly produced by neurons in the locus coeruleus in the brain, but it is released all throughout the brain[160].

## What are the functions of norepinephrine?

Norepinephrine functions primarily as an excitatory neurotransmitter. It plays an important role in arousal, alertness, memory, attention, mood, appetite, and triggering the acute stress response also known as the "fight-or-flight" response[161]. One of the most important functions of norepinephrine is as a peripheral vasoconstrictor and it is used as a first line intervention for untreated hypotension[162]. Other peripheral functions of norepinephrine include vasoconstriction in the skin, vasoconstriction in viscera and vasoconstriction in skeletal muscle. Research has also indicated that norepinephrine plays a primary role in early brain development. Norepinephrine is an important neuromodulator that enhances the actions of other neurotransmitters, including GABA and glutamate[163]. Norepinephrine acts primarily on the alpha adrenoreceptors in blood vessels. This differs from the actions of epinephrine, which is able to act on both the alpha and beta adrenoreceptors[191].




## Norepinephrine metabolism and pathways:

Norepinephrine is synthesized in sympathetic neurons or the adrenal medulla from a series of enzymatic reactions beginning with tyrosine. Tyrosine is converted to L-DOPA by tyrosine hydroxylase, which is the rate limiting enzyme in the catecholamine pathway. L-DOPA is then converted to dopamine by aromatic amino acid decarboxylase and vitamin B6. Norepinephrine is directly synthesized from dopamine by dopamine beta-hydroxylase (DBH), which requires vitamin C and copper as nutrient cofactors. In the adrenal chromaffin cells, norepinephrine can synthesize epinephrine from phenylethanolamine-N-Methyltransferase (PNMT), which requires SAMe as a cofactor. Norepinephrine is primarily inactivated by two different pathways. The first is via monoamine oxidase (MAOa) occurring mostly intracellularly, with small amounts of deamination occurring in the extracellular space[164]. It predominantly occurs from intraneuronal metabolism of norepinephrine that leaks from storage vesicles[165]. This cascade converts norepinephrine to DOPEGAL by MAO. DOPEGAL then forms DHPG by aldehyde reductase. COMT converts DHPG to MHPG with the cofactors SAMe and magnesium. Aldehyde dehydrogenase then catalyzes the last two steps, MHPG to MOPEGAL and then finally to VMA. The other pathway involves norepinephrine's catabolism by COMT, and since the enzyme is not present in the sympathetic nerve cell, this reaction occurs outside of the neuron in either the extracellular space or within other cells in the adrenal medulla or chromaffin cells[164]. The COMT enzyme converts norepinephrine to normetanephrine, which then involves another reaction with the MAO enzyme, where it forms MOPEGAL, before eventually forming the end product of VMA.

## LOW NOREPINEPHRINE

Low levels of norepinephrine can occur due to any impairment of the DBH enzyme due to genetics, nutrients deficiencies, and other factors. Nutrient cofactors that are important for DBH activity include vitamin C and copper. Overgrowth of clostridia bacteria has also been shown to decrease activity of the enzyme, leading to impaired conversion of dopamine to norepinephrine[166]. Animal studies have shown that emotionally disturbed children with a history of neglect have lower activity of DBH, resulting in lower norepinephrine levels[167]. Genetic deficiencies of DBH are often diagnosed in childhood and can result in symptoms such as hypotension, muscle hypotonia, eyelid ptosis, nasal stuffiness, vomiting, and reduced ability to exercise[168]. Any factors that impair the catecholamine pathway, beginning from tyrosine to L-DOPA to dopamine can contribute to low norepinephrine. These factors include genetic factors, nutrient deficiencies, digestive dysfunction, methylation impairments, and medications/supplements. It's important to assess other intermediates along the pathway to determine if there are any other reasons why norepinephrine may be low.

**Symptoms (LOW)**[169]: Hypotension, impaired memory, fatigue, migraines

**Conditions (LOW)**[170,171,175]: Depression, ADHD, fibromyalgia, Bipolar disorder, Parkinson's disease, Alzheimer's disease, chronic fatigue syndrome

## HIGH NOREPINEPHRINE

Many factors that activate the sympathetic nervous system can lead to increased release of norepinephrine. These factors include any form of stress (physical, psychological, or environmental), exercise, emotional arousal (anger, fear, excitement), exposure to cold, and low oxygenation[172]. Emotional arousal has been shown to increase levels of norepinephrine and modulate the formation of memories[173]. Mercury, cadmium, and other heavy metal toxicity can lead to increased norepinephrine levels to its inhibitory effect on the COMT enzyme[135]. Any other factor that impairs COMT or MAO enzymes can decrease the degradation of norepinephrine and increase levels. Since norepinephrine is also used to synthesize epinephrine by the PNMT with SAMe as a cofactor, sufficient methylation is another important factor to assess. It's important to assess all intermediates along the catecholamine cascade to assess what is contributing to elevated norepinephrine levels. For example, high tyrosine can increase catecholamine synthesis, therefore, it's important to assess all markers. Since catecholamines and serotonin often have an inverse relationship, assess serotonin levels and if they are low, supporting serotonin may help to reduce norepinephrine levels.

**Symptoms (HIGH)**[174,175]: Anxiety, hypertension, insomnia, tachycardia, hyperglycemia, headaches

**Conditions (HIGH)**[170,175]: PTSD, chronic kidney disease, bipolar disorder, pheochromocytoma, neural crest tumors, neuroblastoma, schizophrenia

### Clinical Pearl:

Since catecholamines are all on the same pathway, supporting one catecholamine can influence all of the others. Catecholamines and serotonin have an inverse relationship, so supporting one may influence the other.



# NOREPINEPHRINE CONSIDERATIONS

| | LOW NOREPINEPHRINE | HIGH NOREPINEPHRINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for dopamine beta hydroxylase *(Enzyme converts dopamine to norepinephrine)*:<br>  • **Vitamin C**: 500-1500mg/d<br>  • **Copper:** 1-3mg/d<br>• **Rhodiola**[44,176]: 200-600mg/day<br>  • Rhodiola may increase norepinephrine by inhibiting the MAO enzyme<br>• **Cannabidiol**[44,177]: 5-20mg/kg/day<br>  • Animal models showed increased norepinephrine levels in the hippocampus<br>• **Probiotics**[109]:<br>  • L. helveticus, L. casei, L. bulgaricus<br>*Assess other intermediates along the catecholamine pathway to determine if there are other imbalances contributing to low norepinephrine levels. If dopamine is also low, follow recommendations for low dopamine.* | • *If dopamine is also elevated, look at recommendations for high dopamine*<br>• Support nutrient cofactor for PNMT *(Enzyme converts norepinephrine to epinephrine)*<br>  • **SAMe**[60]: 400-1600mg/day |
| DIETARY CONSIDERATIONS | • *If tyrosine levels are low, increase intake of tyrosine or phenylalanine rich foods*<br>**Increase foods/drinks containing caffeine**[178]**:**<br>  • Tea, coffee, chocolate | • **Avoid or limit caffeine**[178]:<br>  • Caffeine may increase norepinephrine and activate noradrenergic neurons<br>• **Drink green tea**[179]:<br>  • ECGC inhibited the release of catecholamines and can offset effects of elevated catecholamines from caffeine |
| LIFESTYLE CONSIDERATIONS | • **Cold water immersion**[172]:<br>  • Results in increased norepinephrine levels<br>• **Sauna**[180]:<br>  • Small human trials showed exposure to intense heat increased norepinephrine secretion | • **Meditation**[181]:<br>  • Studies show individuals who meditate had lower levels of norepinephrine levels<br>• **Reduce stress**[172]:<br>  • All forms of stress, emotional, physiological and environmental, can activate the sympathetic nervous system and increase NE release |
| TESTING CONSIDERATIONS | • **Organic Acids:** to assess for clostridia overgrowth impacting DBH enzymatic conversion of dopamine to norepinephrine<br>• **Gut Zoomer:** to assess for dysbiosis and digestive insufficiency impacting norepinephrine levels<br>• **Micronutrients:** to assess whether deficiencies are impacting norepinephrine levels | • **Methylation Panel:** to assess whether methylation impairments could be impacting norepinephrine levels<br>• **Heavy Metals:** to assess for heavy metals that may affect epinephrine levels |

# NORMETANEPHRINE

## What is normetanephrine?

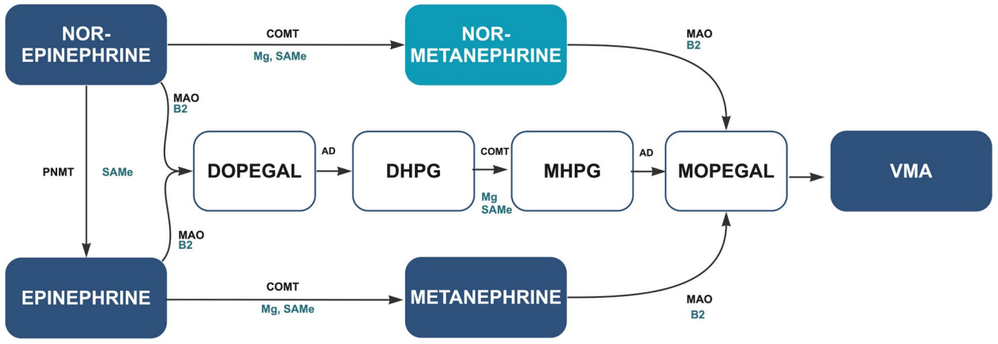
Normetanephrine is a metabolite of norepinephrine, which is an important catecholamine neurotransmitter. It is considered a marker of norepinephrine release, since it is formed extraneurnonally[165]. It is also one of the preferred markers for diagnosis and follow up of pheochromocytoma and paraganglioma[182]. Concentrations of metanephrines (including normetanephrine and metanephrine) have been positively correlated to the tumor size[207].

## What are the functions of normetanephrine?

Normetanephrine does not have direct physiological functions and is not known to be biologically active.

## Normetanephrine metabolism and pathways:

Normetanephrine is formed from o-methylation of norepinephrine by COMT. The COMT enzyme requires nutrient cofactors, magnesium and SAMe. Normetanephrine is derived from non-neuronal sources (extra-neuronal and adrenomedullary pathways) since sympathetic nerves do not have generally express COMT, only MAO[165]. This reaction can occur extraneuronally from norepinephrine that is released by nerves that do not undergo reuptake. Roughly 40% of normetanephrine is derived from metabolism of norepinephrine within the adrenal medulla[165]. The majority (60%), however, is produced from extraneuronal metabolism of norepinephrine once it's released from the neuron, either before (73%) or after (27%) it reaches systemic circulation[165]. Some normetanephrine is metabolized to an intermediate (MOPEGAL) via the MAO enzyme and then converted to VMA by aldehyde dehydrogenase. Areas of the body, such as chromaffin cells in the adrenal medulla, contain both MAO and COMT allowing the complete metabolism from normetanephrine to VMA to occur[164]. Metanephrine can also be conjugated by sulfotransferases (SULT1A3) in extraneuronal tissues before excretion by the kidneys[186].






## LOW NORMETANEPHRINE

Low levels of normetanephrine can occur due to either low level of norepinephrine or poor conversion. Since normetanephrine is formed from the o-methylation of norepinephrine by the COMT enzyme, any impairments of the enzyme may contribute to lower normetanephrine levels. This can include genetic SNPs, supplements, medications, poor methylation, or nutrient deficiencies of magnesium and SAMe, which can all impact COMT activity. If norepinephrine levels are also low, follow the recommendations for low norepinephrine.

## HIGH NORMETANEPHRINE

High normetanephrine is an indication of high norepinephrine levels. It is commonly used as an indicator for the presence of tumors in the chromaffin cells in the adrenal medulla. These include pheochromocytoma and paraganglioma, which result in exponentially elevated normetanephrine levels. High levels of normetanephrine have also been associated with hypertensive cardiomyopathy and metabolic syndrome[183]. Any impairment of the MAO enzyme, which also metabolizes norepinephrine down another pathway, may lead to elevated production of normetanephrine. Since norepinephrine is metabolized to normetanephrine by the COMT enzyme, any upregulation of COMT can also contribute to elevations in normetanephrine. If norepinephrine is also elevated, see interventions to effectively lower levels.

### Clinical Pearl:

Normetanephrine is formed by the COMT enzyme and converted to the next intermediate by the MAO enzyme. Assessing the trends of these reactions and other reactions using the same enzymes (such as in the dopamine degradation pathways), can reveal information about the activity of these enzymes and potential interventions by supporting or inhibiting the enzymes.

# NORMETANEPHRINE CONSIDERATIONS

| | LOW NORMETANEPHRINE | HIGH NORMETANEPHRINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for COMT enzyme *(Converts norepinephrine to normetanephrine)*<br>  • **SAMe**[60]: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d<br>• *If norepinephrine is low, see recommendations to increase levels* | • Support nutrient cofactor for MAO enzyme: *(Converts normetanephrine to MOPEGAL)*<br>  • **Vitamin B2**[59]: 6-30mg/d<br>• *If norepinephrine is also elevated, see recommendations to lower levels* |
| DIETARY CONSIDERATIONS | • *Dietary recommendations do not directly influence normetanephrine levels. If precursors, such as norepinephrine are low, follow recommendations accordingly* | • *Dietary recommendations do not directly influence normetanephrine levels. If precursors, such as norepinephrine are high, follow recommendations accordingly* |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle factors do not directly influence metanephrine levels, but they play a strong role in epinephrine levels. Follow recommendations for low levels of norepinephrine, if relevant.* | • *Lifestyle factors do not directly influence metanephrine levels, but they play a strong role in epinephrine levels. Follow recommendations for high levels of norepinephrine, if relevant.* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrient deficiencies that may affect normetanephrine levels<br>• **Methylation Panel:** to assess for methylation impairments that may impact COMT activity | • **Micronutrients:** to assess for micronutrient deficiencies that may affect normetanephrine levels<br>• *If levels are considerably elevated, consider additional tests for potential adrenal tumors* |



# EPINEPHRINE

## What is epinephrine?

Epinephrine is a catecholamine neurotransmitter and a hormone that is commonly referred to as adrenaline. It is critical to the sympathetic nervous system, where it plays a prominent role in the “fight or flight” stress response. Epinephrine is produced predominantly in the adrenal chromaffin cells located in the adrenal medulla and in smaller amounts in the kidney and other tissues[172]. Epinephrine is different from other neurotransmitters in that it is secreted directly into the bloodstream where it exerts multiple physiological functions[172].

## What are the functions of epinephrine?

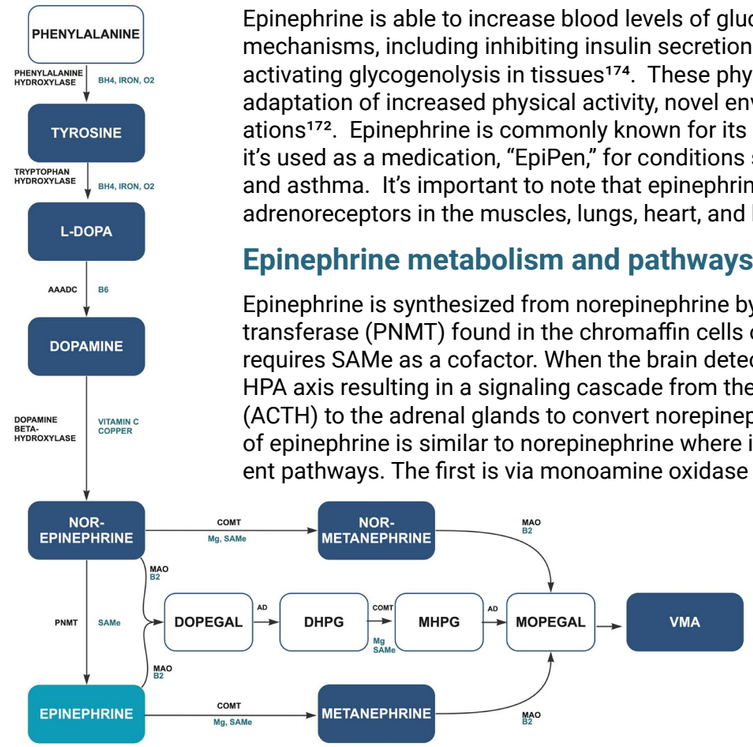
Epinephrine is classified as an excitatory neurotransmitter. Epinephrine is responsible for controlling the adrenal glands, sleep, alertness, and the fight or “flight response”. The physiological effects that occur during the fight or flight response include[172].

- Increased blood pressure
- Shunting blood to skeletal muscles, brain and heart
- Increasing heart rate and contractility
- Relaxing bronchial muscles to improve oxygen delivery to the blood
- Increasing energy availability for muscles by Increasing glycogenolysis and gluconeogenesis in the liver and lipolysis in adipocytes
- Inducing mydriasis for enhanced vision
- Decreasing blood flow to the intestines, and the kidneys
- Relaxing intestinal smooth muscle and the bladder detrusor muscle

Epinephrine is able to increase blood levels of glucose and free fatty acids by multiple mechanisms, including inhibiting insulin secretion, enhancing glucagon secretion, and activating glycogenolysis in tissues[174]. These physiological responses occur to allow adaptation of increased physical activity, novel environment, or anxiety-producing situations[172]. Epinephrine is commonly known for its bronchodilating effects, which is why it’s used as a medication, “EpiPen,” for conditions such as anaphylactic allergic reaction and asthma. It’s important to note that epinephrine can act on both alpha and beta adrenoreceptors in the muscles, lungs, heart, and blood vessels[191].

## Epinephrine metabolism and pathways:

Epinephrine is synthesized from norepinephrine by phenylethanolamine-N-methyltransferase (PNMT) found in the chromaffin cells of the adrenal medulla. This enzyme requires SAMe as a cofactor. When the brain detects a threat or stress, it activates the HPA axis resulting in a signaling cascade from the hypothalamus (CRH) to the pituitary (ACTH) to the adrenal glands to convert norepinephrine to epinephrine. The breakdown of epinephrine is similar to norepinephrine where it is primarily inactivated by two different pathways. The first is via monoamine oxidase (MAOa) occurring mostly intracellu-



larly, with small amounts of deamination occurring in the extracellular space[184]. It predominantly occurs from intraneuronal metabolism of epinephrine that leaks from storage vesicles185. This cascade converts epinephrine toDOPEGAL by MAO. DOPEGAL then forms DHPG by aldehyde reductase. COMT converts DHPG to MHPG with the cofactors SAMe and magnesium. Aldehyde dehydrogenase then catalyzes the last two steps, MHPG to MOPEGAL and then finally to VMA. The other pathway involves epinephrine's catabolism by COMT, and since the enzyme is not present in the sympathetic nerve cell, this reaction occurs outside of the neuron in either the extracellular space or within other cells in the adrenal medulla or chromaffin cells[164]. The COMT enzyme converts epinephrine to metanephrine, which then involves another reaction with the MAO enzyme, where it forms MOPEGAL, before eventually forming the end product of VMA. Metanephrine can also be conjugated by sulfotransferases (SULT1A3) in extraneuronal tissues before excretion bythe kidneys[186].

## LOW EPINEPHRINE

Since epinephrine is located at the end of the catecholamine cascade, any deficiencies or impaired enzyme activity along the pathway may lead to lower epinephrine levels. Therefore, it's important to assess all intermediates along the way to determine the cause of low epinephrine levels. Since the PNMT enzyme, which converts norepinephrine to epinephrine, requires methylation support, any impairments in methylation may also affect the synthesis of epinephrine. Low cortisol levels may correlate with lower epinephrine levels, therefore it's also helpful to assess cortisol levels.

**Symptoms (LOW)**: Depression, headaches, hypotension, hypoglycemia, fatigue

**Conditions (LOW)**[187,188,189,190]: Anxiety, Addison's disease, ACTH deficiency, Depression, Dopamine beta-hydroxylase deficiency, Parkinson's disease, Alzheimer's disease, Metabolic syndrome, obesity

## HIGH EPINEPHRINE

Any stressor that can lead to HPA axis stimulation can also increase levels of catecholamines in the adrenal medulla[172]. These stressors include physical, psychological, or environmental stress, exercise, emotional arousal (anger, fear, excitement), exposure to cold and low oxygenation[172]. Adaptogenic support can help with states of stress. Insulin-induced hypoglycemia can result in an exponential increase in epinephrine levels. Mercury, cadmium and other heavy metal toxicity can lead to increased epinephrine levels to its inhibitory effect on the COMT enzyme[135]. Any genetic SNP, supplement, or medication that slows COMT activity may also result in higher epinephrine levels.

**Symptoms (HIGH)**[172,191]: Tachycardia, bronchodilation, hyperglycemia, dizziness, agitation, headache, palpitations, tremors, weakness, nausea, vomiting, hypertension

**Conditions (HIGH)**[192,193]: PTSD, adrenal gland tumors, cancer, ADHD, depression, sleep apnea, heavy metal toxicity, bipolar disorder, cardiac hypertrophy, heart failure

### Clinical Pearl:

Since epinephrine is produced in response to stress, or activation of the "fight or flight" response, it's important to take a detailed history of what the patient was doing or going through during the time of the test. This may highlight some important considerations to focus on to help modulate epinephrine levels.



## NOREPINEPHRINE CONSIDERATIONS

| | LOW EPINEPHRINE | HIGH EPINEPHRINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for PNMT enzyme: *(Converts norepinephrine to epinephrine)*<br>  • **SAMe**[60]: 400-1600mg/day<br>• *If dopamine and norepinephrine are low, follow recommendations accordingly* | • **Taurine**[194]**:** 6g/day in divided doses<br>  • *Human and animal studies have shown taurine can decrease epinephrine levels*<br>• **Ashwagandha**[195,196]**:** 300-600mg/day<br>  • Animal study showed decreased epinephrine levels with ashwagandha supplementation<br>• **Korean red ginseng**[197,198]**:** 2g/day<br>  • Human, double-blind placebo controlled trial showed 6 weeks of supplementation decreased epinephrine levels indicating this may stabilize the sympathetic nervous system<br>• **Cannabidiol**[46,199]: 5-20mg/kg/day<br>  • Animal study showed cannabinoids inhibited adrenaline secretion in rabbit isolated adrenal glands<br>• *Other adaptogenic herbs may also be supportive*<br>• *May consider reducing methylation support with high epinephrine levels* |
| DIETARY CONSIDERATIONS | • **Increase caffeine intake**[200]**:**<br>  • *If tyrosine is low, increase intake of tyrosine or phenylalanine rich foods* | • **Avoid or limit coffee**[191]:<br>  • Epinephrine showed a strong correlation with coffee consumption<br>• **Drink green tea**[202]:<br>  • ECGC inhibited the release of catecholamines and can offset effects of elevated catecholamines from caffeine<br>• **Balance blood sugar**[203]:<br>  • Implement dietary strategies to prevent episodes of low bloodsugar, which may increase epinephrine levels |
| LIFESTYLE CONSIDERATIONS | • **Increase exercise**[204]:<br>  • Human and animal studies show an increase in epinephrine levels in response to exercise | • **Meditation**[205]:<br>  • Studies show individuals who meditate had lower levels of epinephrine<br>• **Reduce stress**[172]:<br>  • All forms of stress, emotional, physiological, and environmental, can activate the sympathetic nervous system and increase epinephrine release<br>• **Ensure adequate oxygenation during sleep**[172]:<br>  • Poor oxygenation may increase epinephrine levels |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrients that may affect epinephrine levels<br>• **Methylation Panel:** to assess for defects in methylation that may affect epinephrine levels | • **Heavy Metals:** to assess for heavy metals that may affect epinephrine levels<br>• **Other tests:** Cortisol |

# METANEPHRINE

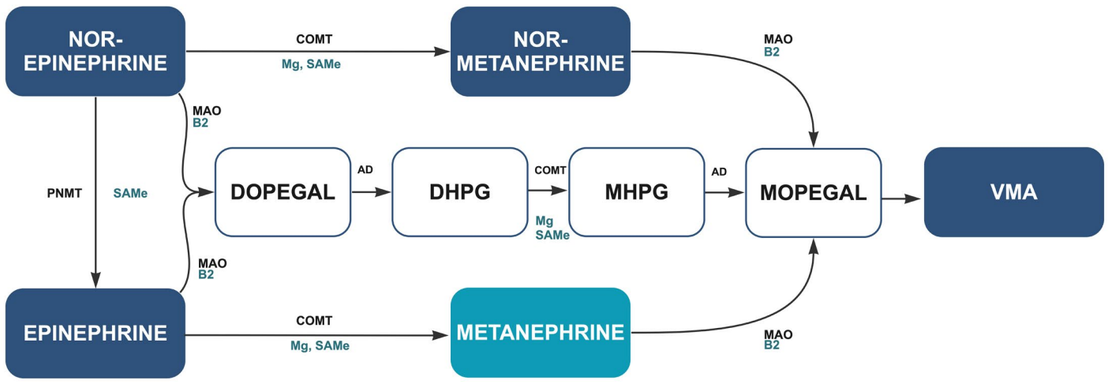
## What is metanephrine?

Metanephrine is a metabolite of epinephrine, which is an important catecholamine neurotransmitter. It is considered a marker of epinephrine release, since it is formed extraneurnonally[165]. It is also one of the preferred markers for diagnosis and follow up of pheochromocytoma and paraganglioma[182]. Concentrations of metanephrines (including normetanephrine and metanephrine) have been positively correlated to the tumor size[207].

## What are the functions of metanephrine?

Metanephrine does not have direct physiological functions and is not known to be biologically active.

## Metanephrine metabolism and pathways:




Metanephrine is formed from o-methylation of epinephrine by COMT. The COMT enzyme requires nutrient cofactors, magnesium and SAMe. Metanephrine is derived from non-neuronal sources (extra-neuronal and adrenomedullatory pathways) since sympathetic nerves generally do not express COMT, only MAO[165]. Some metanephrine is metabolized to an intermediate (MOPEGAL) via the MAO enzyme and then converted to VMA by aldehyde dehydrogenase. Areas of the body, such as chromaffin cells in the adrenal medulla, contain both MAO and COMT allowing the complete metabolism from metanephrine to VMA to occur[165].

## LOW METANEPHRINE

Low levels of normetanephrine can occur due to either low level of epinephrine or poor conversion. Since metanephrine is formed from the o-methylation of epinephrine by the COMT enzyme, any impairments of the enzyme may contribute to lower metanephrine levels. This can include genetic SNPs, supplements, medications, poor methylation, or nutrient deficiencies of magnesium and SAMe, which can all impact COMT activity. If epinephrine levels are also low, follow the recommendations for low epinephrine.



## HIGH METANEPHRINE

High metanephrine is an indication of high epinephrine levels. It is commonly used as an indicator for the presence of tumors in the chromaffin cells in the adrenal medulla. These include pheochromocytoma and paraganglioma, which result in exponentially elevated metanephrine levels. High metanephrine levels have also been associated with hypertensive cardiomyopathy and microalbuminuria[183]. Any impairment of the MAO enzyme, which also metabolizes epinephrine down an alternate pathway, may lead to elevated production of metanephrine. This can include genetic SNPs, vitamin B2 deficiency, and influence from medications or supplements. Since epinephrine is metabolized to metanephrine by the COMT enzyme, any upregulation of COMT can also contribute to elevations in metanephrine. If epinephrine is also elevated, see interventions to effectively lower levels.

### Clinical Pearl:

Metanephrine is formed by the COMT enzyme and converted to the next intermediate by the MAO enzyme. Assessing the trends of these reactions and other reactions using the same enzymes (such as in the dopamine degradation pathways), can reveal information about the activity of these enzymes and potential interventions by supporting or inhibiting the enzymes.

# METANEPHRINE CONSIDERATIONS

| | LOW METANEPHRINE | HIGH METANEPHRINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for the COMT enzyme *(Converts epinephrine to metanephrine)*<br>  • **SAMe**[60]: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d<br>• *If epinephrine is low, see recommendations to increase epinephrine levels accordingly* | • *See recommendations to lower epinephrine levels (especially with evidence of high epinephrine)* |
| DIETARY CONSIDERATIONS | • *Dietary recommendations do not directly influence normetanephrine levels. If precursors, such as epinephrine are low, follow recommendations accordingly* | • *Dietary recommendations do not directly influence metanephrine levels. If precursors, such as epinephrine are high, follow recommendations accordingly* |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle factors do not directly influence metanephrine levels, but they play a strong role in epinephrine levels. Follow recommendations for low levels of epinephrine, if relevant.* | • *Lifestyle factors do not directly influence metanephrine levels, but they play a strong role in epinephrine levels. Follow recommendations for high levels of epinephrine, if relevant.* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrient deficiencies that may affect normetanephrine levels<br>• **Methylation Panel:** to assess for methylation impairments that may impact COMT activity | • *If levels are considerably elevated, consider additional tests for potential adrenal tumors*<br>• |



# VMA

## What is VMA?

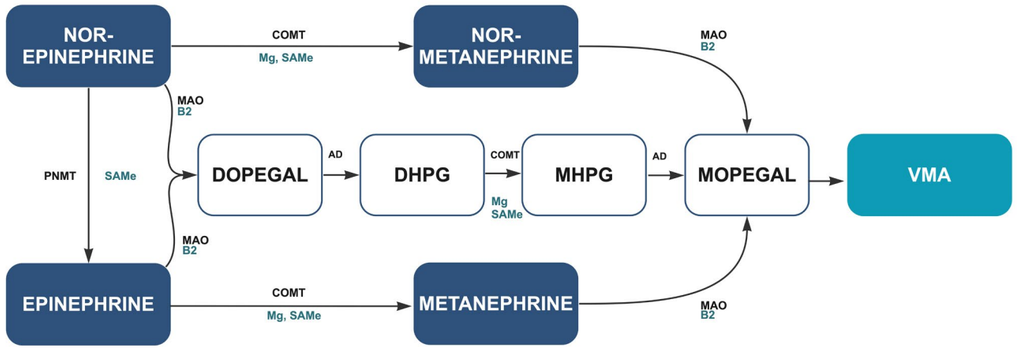
Vanillylmandelic acid (VMA) is the primary end product of norepinephrine and epinephrine metabolism.

## What are the functions of VMA?

VMA is not an active metabolite and does not exert independent functions in the body.

## VMA metabolism and pathways[1206]:

VMA is formed from multiple pathways of norepinephrine and epinephrine metabolism. The main pathway is the same for both norepinephrine and epinephrine and begins with them being deaminated to 3,4-dihydroxyphenylglycolaldehyde (DOPEGAL) by the MAO enzyme. DOPEGAL is a short-lived metabolite that is converted predominantly to DHPG by aldehyde reductase. DHPG is then O-methylated to MHPG by COMT and then alcohol dehydrogenase converts MHPG to another short-lived metabolite, MOPEGAL. MOPEGAL is then finally converted to the product, VMA, by aldehyde dehydrogenase. This pathway involves metabolism of catecholamines leaking from storage granules or recaptured after release by sympathetic nerves[206]. Another important point is that DOPEGAL is considered a highly reactive metabolite, but since it is typically rapidly converted, the toxic effect is generally minimal. A minor pathway also exists to form VMA. The pathway begins with the O-methylation of norepinephrine to normetanephrine and epinephrine to metanephrine by COMT. Normetanephrine and metanephrine are converted to the short-lived metabolite, MOPEGAL, by MAO. MOPEGAL is then metabolized by aldehyde dehydrogenase to the end product, VMA. This minor pathway exists primarily in the adrenal medulla and extraneuronal tissues because COMT is not present in sympathetic nerves, but MAO is present there. Since chromaffin cells in the adrenal medulla contain both MAO and COMT, complete metabolism of norepinephrine and epinephrine to VMA can occur there. It's important to note that over 94% of VMA is produced in the liver[207].



## LOW VMA

Since VMA is a metabolite of norepinephrine and epinephrine metabolism, low levels of these catecholamines can result in low levels of VMA. Any inhibition of the MAO enzyme can result in decreased levels of VMA. Impairments of the COMT enzyme can also decrease VMA levels. Impairments can include genetic SNPs, nutrient deficiencies, or medications or supplements that may affect these enzymes. Particular nutrients of concern include SAMe and magnesium for COMT and vitamin B2 for the MAO enzyme.

## HIGH VMA

High levels of VMA are often an indication of elevated epinephrine and norepinephrine levels. There are multiple factors that can lead to higher catecholamines and consequently higher VMA levels, such as any stressor, including physical, psychological, or environmental stress, exercise, emotional arousal (anger, fear, excitement), exposure to cold and low oxygenation[172]. It' important to assess VMA in conjunction with other catecholamines to determine the source of high levels. Since high catecholamines are often positively correlated with cortisol levels, assessing cortisol may also be useful.

### Clinical Pearl:

VMA is the cumulative end product breakdown of both norepinephrine and epinephrine. If VMA is high, assess all potential stressors, including physical and psychological.

## VMA CONSIDERATIONS

| | LOW VMA | HIGH VMA |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for COMT:<br>  • **SAMe[60]**: 400-1600mg/day<br>  • **Magnesium:** 400-800mg/d<br>• Support nutrient cofactors for MAO:<br>  • **Vitamin B2[59]**: 6-30mg/d | • *Assess norepinephrine and epinephrine levels and follow recommendations for high levels accordingly* |
| DIETARY CONSIDERATIONS | • *Dietary recommendations that decrease norepinephrine and epinephrine may result in lower VMA levels* | • *Dietary recommendations that increase norepinephrine and epinephrine may result in higher VMA levels* |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle factors that decrease norepinephrine and epinephrine may result in lower VMA levels* | • *Lifestyle factors that increase norepinephrine and epinephrine may result in higher VMA levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess nutrient deficiencies that may affect VMA levels<br>• **Other tests:** Cortisol | • **Other tests:** Cortisol |

# TYRAMINE

## What is tyramine?

Tyramine is a trace monoamine that can be found from food or synthesized endogenously. The label of trace monoamine refers to its similarity in structure to other monoamines, but its presence in lower quantities in tissues compared to other monoamines.

## What are the functions of tyramine?

One of the functions of tyramine includes its ability to indirectly release catecholamines. It does that by displacing catecholamines from pre-synaptic storage vesicles. This results in tyramine facilitating the release of presynaptic endogenous neurotransmitters, therefore acting an indirect sympathomimetic[208]. Tyramine is known to activate trace amine-associated receptors (TAARs), a type of G-protein coupled receptor that other biogenic amines also bind to[208]. While the exact functions of TAARs are still being researched, suspected functions include olfaction, modulation of other neurotransmitters, regulation of body weight, and immunologic functions[208]. The TAAR1 in the central nervous system may also play a role in mood, reward circuits, and the limbic system[208]. Since TAAR1 is found in high concentrations in the gut, it may play an important role in the gut-brain axis.

## Tyramine metabolism and pathways:

Tyramine can be synthesized endogenously from tyrosine by aromatic L-amino acid decarboxylase (AADC). This reaction requires vitamin B6 as a cofactor. Tyramine is catabolized by the MAO enzyme (MAOa & MAOb) to form 4-hydroxyphenylacetaldehyde. Since tyramine is metabolized by monoamine oxidase, tyramine can decrease the breakdown of other monoamine neurotransmitters requiring MAO activity[208].


## LOW TYRAMINE

Low levels of tyramine can occur due to low levels of exogenous intake or poor endogenous synthesis. There are many foods that are high in tyramine, mostly in the category of fermented, cured, aged, and spoiled foods, therefore avoidance of these foods can contribute to lower levels. Since the synthesis of tyramine begins with tyrosine and tyrosine hydroxylase enzyme, which requires vitamin B6, any insufficiency in either tyrosine or vitamin B6 can contribute to low tyramine levels. A low level of tyramine is not a significant concern. There is a greater concern for an elevated level of tyramine. Low levels, however, can identify other imbalances or deficiencies in the body.

## HIGH TYRAMINE

High levels of tyramine can occur when foods high in tyramine are consumed. Any impairment in the MAO enzyme, which is responsible for the catabolism of tyramine, can result in higher levels. When consumption of high tyrosine rich foods is paired with an MAO inhibitor, symptoms such as headaches, blurry vision, chest pain, palpitations, hypertension, intracranial hemorrhages, and myocardial injury can occur[208]. The main concern in this scenario is a hypertensive crisis, which can cause severe physiological effects that is considered an emergency[208]. Another name for this is the “cheese effect.” Consuming only 10-25mg of tyramine in combination with MAOIs can result in a severe adrenergic response with symptoms such as hypertension, headaches, and possible intracranial hemorrhage[208]. A common symptom associated with high tyramine levels include migraines. If high tyramine is from endogenous synthesis, this may shift tyrosine away from catecholamine synthesis. It’s important to assess the levels of other neurotransmitters that require tyrosine when tyramine levels are elevated.

### Clinical Pearl:

A pattern of high levels of tyramine, histamine and tryptamine can be from foods, since many share the same sources. When tyramine is elevated, it may decrease MAO availability for other neurotransmitter catabolism.

# TYRAMINE CONSIDERATIONS

| | LOW TYRAMINE | HIGH TYRAMINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for AAADC enzyme: *(Converts tyrosine to tyramine)*<br>  • **Vitamin B6**: (pyridoxal 5-phosphate): 10-50mg | • Support nutrient cofactors for MAO enzyme: *(Responsible for catabolism of tyramine)*<br>  • **Vitamin B2**[59]: 6-30mg/d<br>• **Avoid supplements that act as MAOa inhibitors**[50,51,52,53,54,55,56,57,58]:<br>*MAO inhibitors decrease catabolism of tyramine (In vitro and animal studies)*<br>  • Curcumin (10-80mg/kg), quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African Rue, St. John's Wort, berberine |
| DIETARY CONSIDERATIONS | • *Consider increasing intake of high tyramine rich foods (see to the right)* | • **Limit high tyramine rich foods**[208]<br>  • *Fermented, aged, cured, and spoiled foods*<br>  • Grapes, avocado, beets, cheese, dried meats, cured meats, chocolate, soy sauce, Worcestershire sauce, pickled fish, kimchi, sauerkraut, wine, beer, coffee |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions do not considerably affect tyramine levels* | • *Lifestyle interventions do not considerably affect tyramine levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess any micronutrient deficiencies that may be affecting tyramine levels | • **Micronutrients:** To assess any micronutrient deficiencies that may be affecting tyramine levels |



# PHENETHYLAMINE (PEA)

## What is PEA?

Phenethylamine (PEA) is a trace monoamine neurotransmitter that is commonly known to induce feelings of happiness, pleasure, and emotional wellbeing. The label of trace monoamine refers to its similarity in structure to other monoamines, but its presence in lower quantities in tissues compared to other monoamines. Unlike other neurotransmitters, PEA has the ability to cross the blood brain barrier[210]. PEA is an amphetamine like compound and may exhibit similar physiological effects.

## What are the functions of PEA?

PEA acts as an excitatory neurotransmitter that is a stimulant to the central nervous system. It also acts as a neurohormone that maintains energy, attention, and mood[209]. PEA plays an important role in the modulation of wakefulness, arousal, affect, extrapyramidal movements and other functions relevant to catecholamines[211]. PEA is known to activate trace amine-associated receptors (TAARs), a type of G-protein coupled receptor that other biogenic amines also bind to. When PEA binds to TAAR1 receptors, it affects monoamine transporter functions, specifically inhibiting dopamine, serotonin, and norepinephrine reuptake, contributing to higher levels at the synapses[210]. Studies have demonstrated that TAAR1 receptor activation results in improved symptoms associated with depression and schizophrenia[210]. One study showed a 60% improvement in depressed patients with PEA supplement and another compounds, selegiline, that acts as an MAOb inhibitor[209]. Since phenylacetic acid levels have been found in low concentrations in depressed individuals, researchers have theorized that the phenylalanine-PEA pathway may be hypofunctional in roughly 60% of depressed individuals[209].

## PEA metabolism and pathways:

PEA is synthesized from phenylalanine by aromatic amino acid decarboxylase (AADC). This reaction requires vitamin B6 as a nutrient cofactor. Due to the rapid conversion of PEA to phenylacetic acid by MAOb, high concentrations do not typically develop in the body. The breakdown product of PEA, phenylacetic acid, mimics the activity of naturally occurring endorphins, resulting in the "feel good" or "runner's high" feeling[210].

## LOW PEA

Low levels of urinary PEA were found to be lower in children with ADHD compared to healthy controls[210]. Individuals with depression also demonstrated a PEA deficit, with improved symptoms upon PEA replacement. Patients with Parkinson's disease often demonstrate a deficiency in brain PEA levels[211]. Low levels can be due to reduced endogenous synthesis, as a result of impaired enzyme activity, vitamin B6 deficiency, or low precursor availability from phenylalanine. Additionally, PEA levels can also be low due to excessive breakdown of PEA by the MAOb enzyme. Incorporating supplements that act as an MAOb inhibitor may be helpful to slow the breakdown of PEA.

## HIGH PEA

Commonly used and abused drugs, such as alcohol, marijuana, opioids and amphetamines have been shown to increase levels of PEA in the brain[211]. Elevated levels of PEA may also act as an anxiogen, which is a common symptom associated with amphetamine intoxication and addiction[212]. Animal studies showed that administration of PEA into the brain induced generalized clonic seizures[212]. Individuals with PKU often have excess formation of PEA due to the inability of phenylalanine to convert to tyrosine, therefore more is available to be converted to PEA. Symptoms of excess PEA can also include migraine headaches, hyptertension, anxiety, and seizures[213]. Even though PEA is rapidly converted to phenylacetic acid by MAOb, any impairments in the MAO enzyme can contribute to higher levels of PEA. This can be due to genetic influences, medications, supplements, or nutrient cofactor deficiencies, particularly vitamin B2. Since amino acid decarboxylase activity exists in fermentative bacteria, such as Lactobacillus and enterococcus, increased gut fermentation of phenylalanine can increase PEA levels, and other trace monoamines such as tyramine[213].

### Clinical Pearl:

Supplements that act as MAOb inhibitors may increase PEA levels, but many of those supplements also demonstrate MAOa inhibiting activity, and therefore may also slow the breakdown of other monoamine neurotransmitters, such as serotonin, dopamine and norepinephrine.



## PEA CONSIDERATIONS

| | LOW EPINEPHRINE | HIGH EPINEPHRINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **Phenethylamine HCL or β-phenylethylamine (PEA)[209]**: 10-60 mg/d<br>  • Some studies have combined this with an MAOb inhibitor to inhibit rapid breakdown of PEA<br>• **Wild green oat extract (WGOE)[214]**: 430-1290mg/d<br>  • In vitro and preclinical data show WGOE may have inhibitory effects on MAOb<br>• **DL-phenylalanine[211]**: 200-1000mg/d<br>  • Amino acid precursor for PEA synthesis shown to increase brain levels of PEA<br>• Support nutrient cofactor for AAADC: *(Converts phenylalanine to PEA)*<br>  • **Vitamin B6** (Pyridoxal 5-phosphate): 10-50mg<br>• **MAOb inhibitors[216,216,217,218,219]**<br>  • Fenugreek, pterostilbene, curcumin, Australian willow, kava kava, garlic, propolis | • Support nutrient cofactor for MAOb enzyme: *(Catabolizes MAO to phenylacetic acid)*<br>  • **Vitamin B2[59]**: 6-30mg/d<br>• **Lithium[220,211]**: 450-900mg/day<br>  • Chronic treatment may decrease PEA synthesis<br>• **Avoid supplements that act as an MAOb inhibitor**<br>*Avoid any supplements that may increase PEA levels (see left)* |
| DIETARY CONSIDERATIONS | • **Increase food sources of PEA[210]:**<br>  • Chocolate, eggs, beans, peas, clover, fermented foods (cheese, wine, natto)<br>• **Increase intake of Phenylalanine rich foods[118]:**<br>  • Meat, chicken, fish, eggs, dairy products, nuts, seeds, quinoa, oats, soy, lentils, gelatin | • **Decrease intake of PEA rich food sources**<br>• **Reduce intake of phenylalanine rich foods** |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle considerations do not significantly affect low PEA levels* | • **Avoid use of recreational drugs and excess alcohol intake[211]** |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess any micronutrient deficiencies that may be affecting PEA levels | • **Gut Zoomer:** to assess for GI dysbiosis and whether the microbiome may be contributing to higher PEA levels |

# GLUTAMATE

## What is glutamate?

Glutamate is the most abundant excitatory neurotransmitter in the central nervous system. It is also categorized as a non-essential amino acid, commonly referred to as glutamic acid.

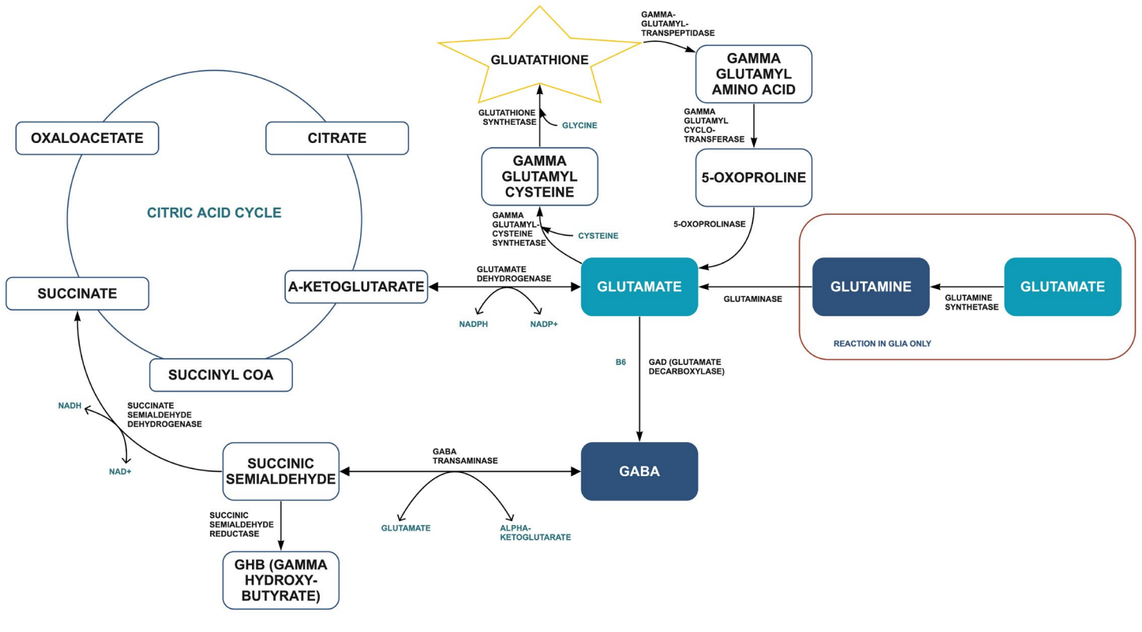
## What are the functions of glutamate?

One of glutamate's main functions includes acting as an excitatory neurotransmitter. Even though glutamate is essential for multiple functions in the body, when the level of excitation by glutamate is excessive or not counterbalanced by inhibitory neurotransmitters, it may lead to destruction and cell death. Prolonged activation of NMDA and AMPA receptors can lead to neuronal degeneration due to the excitotoxic effects associated with increased cytosolic calcium levels[229]. Due to this, glutamate is an important focus in neurogenerative diseases. Glutamate is used to form GABA, which is the main inhibitory neurotransmitter in the CNS. In addition, glutamate also has other functions in the body, including consolidation of memories, optimizing learning, sleep, mood, and libido[221]. Glutamate plays an important role in synaptic plasticity, which is essential for optimal brain function and plays an important role in the developing brain. Glutamate is essential in the synthesis of glutathione, where it is combined with cysteine and glycine to form glutathione.

Glutamate acts as an important signaling molecule, exerting its actions in the CNS by two different receptors, ionotropic glutamate receptors and metabotropic glutamate receptors. Glutamate has been found to stimulate afferent gastric vagal nerves. Glutamate activity can be heavily influenced by different hormones. Progesterone, for example, has been shown to suppress the excitatory glutamate response[127]. Estrogen, on the other hand, facilitates glutamate transmission[127].

## Glutamate metabolism and pathways:

Glutamate can be synthesized by two main mechanisms, the first is from α-ketoglutarate and the second is from amino acids. Glutamate can be synthesized from α-ketoglutarate by two different enzymes, aspartate aminotransferase or GABA-T from the GABA shunt pathway[250]. Within the central nervous system, most of the glutamate produced is from glutamine by the enzyme glutaminase. Glutamate can also be synthesized by other amino acids besides glutamine, including arginine, proline, and histidine by different pathways[222]. Glutamate






is primarily inactivated by uptake from the synapses via excitatory amino acid transporter (EAAT-3) in neurons and (EAAT1/2) in glial cells. Glutamate in glial cells can be converted to glutamine by glutamine synthetase, which can then be transported to neurons and metabolized back to glutamate[249]. Glutamate dehydrogenase catalyzes oxidative deamination of glutamate, resulting in α-ketoglutarate and ammonia. This reaction increases the ATP/ADP ratio and stimulates the release of insulin[222]. Since glutamate is used to synthesize glutathione, this is an important pathway in glutamate metabolism. The enzyme glutamate cysteine ligase forms with cysteine to form gamma-glutamyl-cysteine. Glutathione synthetase then combines gamma-glutamyl-cysteine with glycine to form glutathione. Glutathione can also contribute to glutamate synthesis via an alternate pathway involving the glutathione cycle metabolite 5-oxoproline[250].

## LOW GLUTAMATE

Low levels of glutamate can occur due to decreased exogenous intake or endogenous synthesis. Low glutamate levels can impair the body's ability to synthesize glutathione. Any impairments in the citric acid cycle, leading to decreased levels of α-ketoglutarate can decrease endogenous synthesis. Since the primary route of glutamate synthesis in the CNS is via glutamine conversion, it's important to assess glutamine status. Low levels of glutamine can be due to decreased dietary intake, digestive insufficiency or gastrointestinal imbalanced or an upregulated need for glutamine to be used for other physiological functions. Autommunity, leading to the production of anti-glutamate antibodies, can affect the expression of glutamate in the body, reflecting lower glutamate.

**Symptoms**[223]: Impaired intestinal epithelial renewal, poor memory, cognitive decline

**Conditions**[224,225,226]: ALS, Depression, Schizophrenia

## HIGH EPINEPHRINE

Glutamate is the most abundant excitatory neurotransmitter that can also behave as a neurotoxin. High intake of glutamine, through foods or supplementation can result in high glutamate levelsccxxix. Excess levels of glutamate can result in neuronal death due to significant influx of calcium via inotropic glutamate channels. Any decrease in GAD can result in higher glutamate levels and consequently lower GABA levels. This may be due to autoimmunity, genetic SNPs, nutrient deficiencies, etc. Research has also shown that anti-gliadin antibodies also reacted against glutamic acid decarboxylase (GAD65). Antibodies to GAD are also associated with T1DM. Dendritic cells in the intestinal tract can also release glutamate as part of an immunological reaction in the gut. Research has shown that inflammation is associated with elevated glutamate in the brain, there, assessing total inflammatory load and the source of inflammation may help regulate glutamate levels.

**Symptoms**[228]:Social phobia, PTSD, migraines, poor focus, panic attacks

**Conditions**[229,230,231,232]: ALS, Alzheimer's disease, Anxiety, Autism spectrum disorder (ASD), Dementia, Epilepsy, Motor neuron disease, Huntington's disease, Hyperalgesia, Hyperthyroidism, Multiple sclerosis, Obsessive compulsive disorder, Parkinson's disease, Psychosis, Traumatic brain injury

### Clinical Pearl:

The goal for glutamate is to be below the median level of the reference range. It's also important to take into account the level of other excitatory neurotransmitters to assess overall excitation in the nervous system. Since the excitation of glutamate is balanced by the inhibition of GABA, assess GABA levels to ensure an optimal balance and adequate conversion.

# GLUTAMATE

| | LOW GLUTAMINE | HIGH GLUTAMINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **Glutamine**[233]: *Doses vary*<br>  • Precursor for glutamate synthesis<br>• **Glutathione**[234]: 250-1000mg/day<br>  • Glutathione can be used to synthesize glutamate<br>• **Probiotics**[108]:<br>  • L. rhamnosus, L. retueri, L. plantarum, L. paracsei, L. helveticus, L. casei, L. bulgaricus | • Support nutrient cofactor for GAD enzyme: *(Converts Glutamate to GABA)*<br>  • **Vitamin B2** (pyridoxal 5- phosphate): 10-50mg<br>• **Cysteine or N-acetyl cysteine**[235]: up to 2400mg<br>  • Cysteine is essential for converting glutamate to gamma-glutamyl-cysteine to eventually form glutathione<br>• **Taurine**[236]: 6g per day in divided doses<br>  • Animal studies showed that taurine suppressed glutamate-induced toxicity through multiple pathways<br>• **L-Theanine**[104,237]: 200-400mg/d<br>  • L-theanine has been shown to block the binding of L-glutamic acid to glutamate receptors in the brain<br>• **Pyrroloquinoline quinine (PQQ)**[238,239]: 2-3mg/kg/day<br>  • Animal study showed PQQ protected neural cells from glutamate-induced apoptosis<br>• **Selenium**[240]: 50-200mcg/day<br>  • Selenium deficiency increases susceptibility to glutamate-induced excitotoxicity |
| DIETARY CONSIDERATIONS | • **Increase protein intake:**<br>  • Glutamate can also be synthesized from amino acids such as glutamine, arginine, proline, histidine<br>• **Increase intake of glutamine rich foods** | • **Reduce intake of glutamate rich foods**[148]:<br>  • Caviar, cheese, chips, dried cod, fermented beans, fish sauces, gravies, instant coffee powder, meats, miso, mushrooms, noodle dishes, oyster sauce, parmesan cheese, ready to eat meals, salami, savory snacks, seafood, seaweeds, soups, soy sauces, spinach, stews, tomato products<br>  • Glutamate is responsible for the “umami” 5th taste<br>• **Reduce intake of glutamine rich foods**<br>• **Avoid MSG (monosodium glutamate):**<br>  • Concentrated source of glutamate used as an additive or flavor enhancer, more commonly found in Asian cuisines<br>• **Pu-erh tea**[241]:<br>  • Animal study showed that it inhibits the expression of glutamate receptor 5 |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions do not significantly affect low glutamate levels* | • **Decrease stress**[242]<br>  • Animal studies show stress increases glutamate levels in the brain<br>• **Epsom salt baths**[243]<br>  • Animal study showed that magnesium sulfate protects against metabolic failure caused by excitotoxic glutamate |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess whether deficiencies are affecting glutamate levels<br>• **Neural Zoomer Plus:** to assess for anti-glutamate receptor antibodies | • **Micronutrients:** to assess whether high levels of glutamine may be affecting glutamate levels |



# GABA

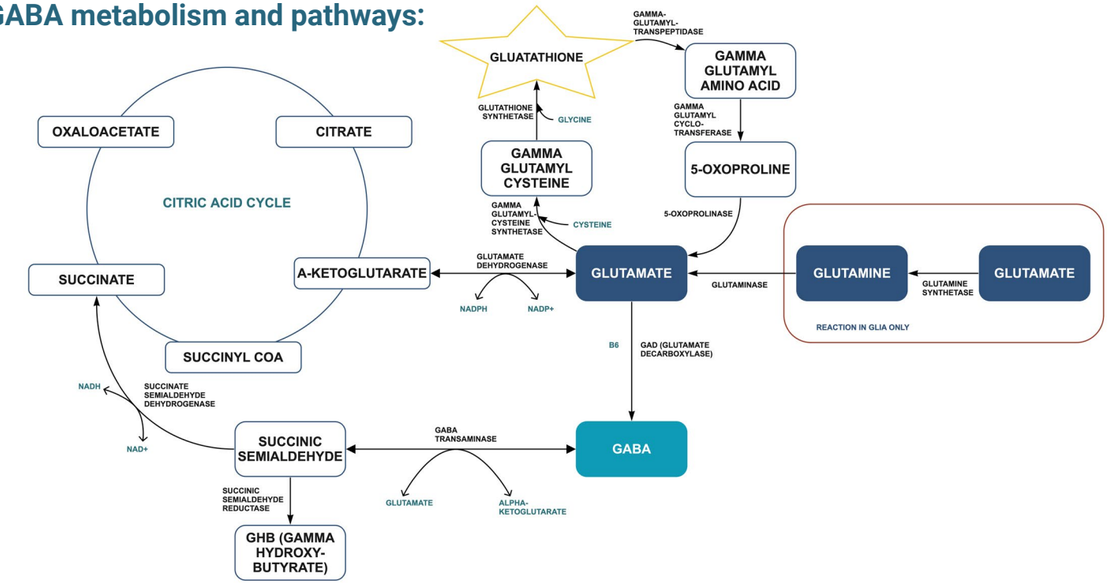
## What is GABA?

GABA (Gamma-amino butyric acid) is the major inhibitory neurotransmitter in the central nervous system. It is considered to be the “brakes” or the “off switch” in the CNS due to its inhibitory effects. GABAergic neurons are found in the hippocampus, thalamus, basal ganglia, hypothalamus and brainstem[244]. GABA can be found in concentrations 1,000 times higher than other monoamine neurotransmitters in certain regions of the brain. Even though GABA is unable to cross the blood brain barrier (BBB), there are reports of therapeutic effects of exogenous GABA, which are not fully understood.

## What are the functions of GABA?

One of the main functions of GABA includes reducing neuronal excitability by inhibiting nerve transmission. It plays an important role in regulating overall inhibition in the nervous system to counter excitatory neurotransmitters, such as glutamate. GABA plays an important role in many functions in the body, including regulating sleep, facilitating neurodevelopment, acting as a neurohormone and immunomodulator, regulating muscle tone/movements, and regulating digestive and cardiovascular functions[245]. GABA can function as a neurohormone where it has been shown to inhibit the release of gonadotropin releasing hormone (GnRH) and prolactin[245]. Estrogen levels can influence GABA levels via an inverse relationship, where estrogen can contribute to decreased GABA levels and suppress GABA’s inhibitory inputs[245]. Progesterone, on the other hand, acts to increase GABA(A) expression and act as a GABA receptor agonis[246]. GABAergic systems can also be regulated by thyroid hormones, with evidence showing hypothyroidism increases enzyme activities and GABA levels[247]. The beta-cells of the pancreas are also able to produce GABA, where it seems to have a cytoprotective effect by reducing apoptosis of beta cells and allowing for their proliferation[248]. GABA acts as an immunomodulator, where GABA has been shown to be synthesized, stored, and released by the immune system. It is able to inhibit and activate cytokine secretion, decrease the proliferation of T-cells and modify defense cells release[245]. It plays an important role in cardiovascular regulation, where it’s able to decrease sympathetic tone, resulting in effects such as decreased heart rate and blood pressure. Within the GI tract, GABA may improve intestinal motility, increase gastric emptying, and decrease gastric acid secretion[245]. There are two different GABA receptors that exert varying function, GABAa, which is a ligand-gated ion channel receptor and GABAb, which is a g-coupled protein receptor. There are multiple medications that have been developed to target different GABA receptors for use in various disorders.

## GABA metabolism and pathways:



The GABA shunt is the metabolic, closed-loop process to both produce and conserve GABA supply. The GABA shunt begins with the transamination of α-ketoglutarate by GABA transaminase (GABA-T) to form L-glutamic acid. A-ketoglutarate is formed from glucose and alternate metabolism in the Kreb's cycle. L-glutamic acid is then decarboxylated by glutamic acid decarboxylase (GAD) to form GABA. The GAD enzyme has two isoforms, $GAD_{65}$ and $GAD_{67}$, which are each expressed differently. The GAD enzyme requires vitamin B6 as a nutrient cofactor. GABA can then be metabolized by GABA-T, which is dependent on vitamin B6 and α-ketoglutarate to form succinic semialdehyde and glutamic acid. An enzyme called succinic semialdehyde dehydrogenase (SSADH) then oxidizes succinic semialdehyde to form succinic acid, which can re-enter the Kreb's cycle. Succinic semialdehyde can also be metabolized into gamma-hydroxybutyric acid (GHB), which affects GABA(B) receptors. The origination of precursors from the Kreb's cycle and formation of end products re-entering the Kreb's cycle is the closed loop process, allowing for excellent efficiency of GABA metabolism.

## LOW GABA

Low levels of GABA can lead to excess excitation in the body. Any impairments in the GAD enzyme, due to genetics, nutrient deficiencies, antibody production, or other factors can lead to decreased synthesis. Since vitamin B6 is a nutrient cofactor for GAD, any deficiency can impair GABA synthesis. Autoimmunity can also result in low levels of GABA with positive antibodies to the GAD enzyme. There has also been an association between gluten sensitivity and the production of GAD antibodies, therefore it may be beneficial to assess for immune reactions to gluten and antibody levels to GAD. With low GABA levels, it's important to assess in relation to glutamate. If glutamate is high and GABA is low, then there may be decreased activity of the GAD enzyme. If both glutamate and GABA are low, then it may be important to focus on increasing glutamate production and ensuring adequate conversion to GABA. The balance between both glutamate, the main excitatory neurotransmitter, and GABA, the main inhibitory neurotransmitter, is important for the overall balance of excitation and inhibition in the nervous system.

**Symptoms**: Chronic stress, spasticity, insomnia, difficulty concentrating, panic attacks

**Conditions**[245,251,252]: ADHD, Anxiety, Insomnia, Autism spectrum disorder, Depression, Dystonia, Epilepsy, Huntington's disease, Multiple sclerosis, Premenstrual dysphoric disorder, Stiff-person syndrome, Schizophrenia, Tourette syndrome

## HIGH GABA

High levels of GABA can be due to higher levels of glutamate that are converted to GABA. If glutamate is also elevated, it may be important to follow the recommendations to decrease glutamate levels. High levels of GABA can also be due to impaired conversion to succinic acid, leading to the buildup of GABA. Since vitamin B6 is a required cofactor for the GABA-T enzyme, a deficiency can lead to impaired breakdown. Alpha-ketoglutarate is also required for that same reaction, therefore any impairments in energy production can decrease breakdown of GABA. Most of the impairments that lead to decreased breakdown of GABA are genetic. It's also important to assess for supplements or medications that may result in higher levels of GABA and make changes or adjust them accordingly. Since GABA is influenced by many different hormones, such as thyroid, estrogen and progesterone, it's important to assess how the endocrine system may be impacting elevated GABA levels.

**Symptoms**[253]:Expressive language impairment, hypotonia, absence seizures, decreased addictive behaviors, coma, excessive sleepiness, fatigue, overproduction of mucus, anxiety

**Conditions**[245,253]: SSADH deficiency, GABA transaminase deficiency, homocarnosinosis

### Clinical Pearl:

Low levels of GABA may be due to a deficiency in vitamin B6. Since many other reactions in neurotransmitter pathways require vitamin B6, it may be helpful to assess whether they follow the same pattern. The enzyme chart at the end of the document may provide helpful information to identify these patterns.



# GABA CONSIDERATIONS

| | LOW GABA | HIGH GABA |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for GAD: *(Converts glutamate to GABA)*<br>  • **Vitamin B6** ((pyrixodal 5-phoshate): 10-50mg<br>• **GABA/PharmaGABA**: 100-200mg 1-3x/day<br>  • Exogenous sources of GABA<br>• **L-Theanine**[104,254]: 200-400mg/d<br>  • Animal studies show increased GABA levels with L-theanine<br>• **Baicalin (Skullcap)**[255]:<br>  • In vivo studies show activation of GABAa receptors<br>• **Taurine**[256]: 6g per day in divided doses<br>  • Animal studies show taurine is a potent activator of extrasynaptic GABAa eceptors<br>• **Probiotics**[257]:<br>  • L. brevis, L. rhamnosus, L. retueri, L. paracasei, L. plantarum, L.bulgaricus, L.helveticus, L.casei<br>• **Nigella sativa**[258]: 20mg/kg<br>  • Animal study showed thymoquinone increased GABA levels and had anxiolytic effects<br>• **Valerian**[259]: 300-600 mg/day<br>  • Animal study showed valerian allosterically modulates GABAa receptors and has anxiolytic effects<br>• *If glutamate is also low, follow recommendations to increase glutamate, which can be converted to GABA* | • Support nutrient cofactor for GABA-T enzyme: *(Converts GABA to succinic semialdehyde)*<br>  • **Vitamin B6** (pyrixodal 5-phoshate): 10-50mg<br>• **Wormwood**[260]: 500-1000mg/day (divided doses)<br>  • Blocks GABAa receptors<br>• **Ginkgo biloba**[261,262]: 80-720mg/day<br>  • GABAa receptor antagonist<br>• *If glutamate is also elevated, follow recommendations to decrease glutamate levels, since glutamate is converted to GABA*<br>• *Limit/avoid any supplements that may increase GABA (see to the left)* |
| DIETARY CONSIDERATIONS | • **Increase intake of GABA rich foods**[263]:<br>  • Tea, tomatoes, rice, fermented foods, adzuki beans<br>• **Increase intake of fermented foods:**<br>  • may increase GABA levels<br>• **Consider a gluten free diet**[264]:<br>  • Research has identified a link between gluten sensitivity & GAD antibodies | • Decrease intake of GABA rich foods<br>• Decreasing intake of high glutamate foods may also help decrease conversion to GABA<br>• Decrease intake of alcohol, which can increase GABA levels |
| LIFESTYLE CONSIDERATIONS | • **Neurofeedback**[265]<br>• **Meditation**[266]<br>  • Transcendental meditation can increase GABA-inergic tone and increase GABA levels<br>• **Vagus nerve stimulation**[267]<br>  • Normalized GABA receptor density in human study compared to control | • *Lifestyle interventions do not significantly affect high GABA levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for deficiencies affecting GABA levels<br>• **Neural Zoomer Plus:** to assess for anti-GABA antibodies<br>• **Wheat Zoomer:** to assess for immune reactivity to gluten<br>• **Hormones:** Thyroid hormones, estrogen, progesterone | • **Micronutrients:** to assess for deficiencies affecting GABA levels<br>• **Hormones:** Thyroid hormones, estrogen, progesterone<br>• **Cytokines:** to assess cytokines, since Gaba inhibits and activates cytokine secretion |

# TAURINE

## What is taurine?

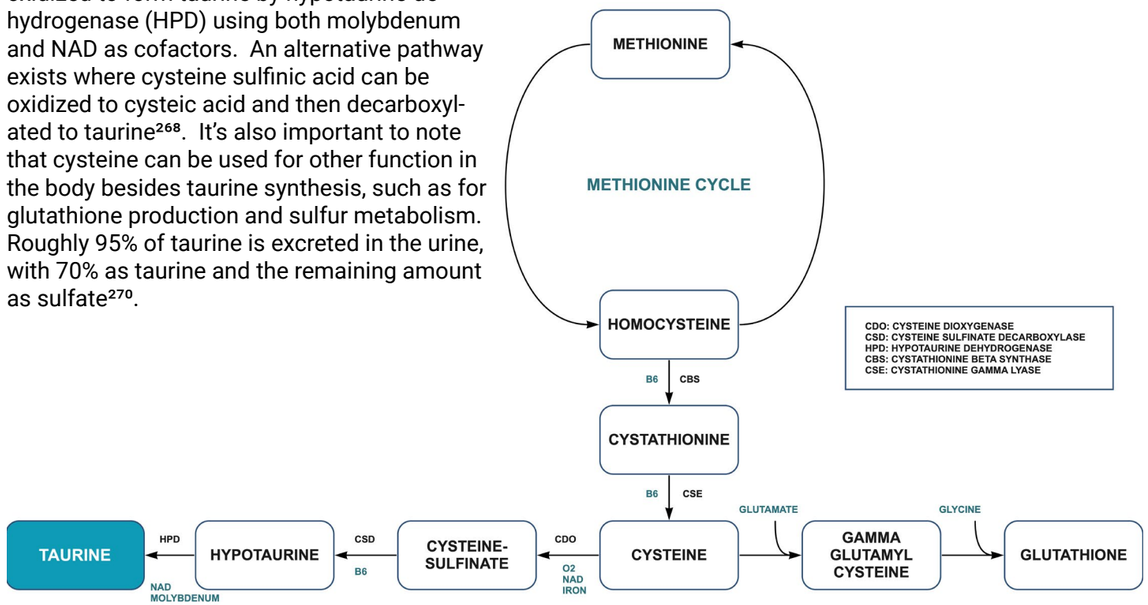
Taurine is a conditionally essential amino acid that contains a sulfonic acid group and has important roles in the nervous system and in the periphery. It is found most abundantly in the heart, retina, developing brain and in the blood[268]. Taurine is found predominantly in animal foods, therefore individuals following a vegan or vegetarian diet may have lower circulating levels and have to rely mainly on endogenous production of taurine.

## What are the functions of taurine?

Taurine is involved in a multitude of physiological processes, including bile salt synthesis, osmoregulation, cellular proliferation, modulation of calcium flux, stimulation of glycolysis and glycogenesis, modulation of neuronal excitability, detoxification, and membrane stabilization[269]. Within the CNS, taurine functions as an inhibitory neurotransmitter to modulate neuronal excitability. It also maintains cerebellar function, modulates hormone release, and has anti-convulsant properties. In the heart, taurine has been shown to be protective against the harmful effects of calcium ion deprivation and excess, essentially offsetting calcium paradox[269]. Additional cardiovascular functions of taurine include antiarrhythmic effects and hypotensive effects. In the liver, taurine conjugates bile acids to form bile salts, which is critical for the emulsification and absorption of fats. Taurine functions as an antioxidant, scavenging reactive oxygen species and protecting against oxidative stress[270]. Taurine plays an important role in platelet function, with taurine exhibiting the highest concentration compared to any other amino acid in platelets[269]. Taurine may play a role in fetal brain development due to the higher concentrations found in the human fetal brain compared to adults, which gradually declines during postnatal development. Taurine is also structurally similar to GABA and can bind to GABA receptors acting as an agonist, contributing to neuronal hyperpolarization and inhibition[270]. Taurine may also influence hormones, with some evidence indicating increased levels of prolactin and growth hormone[270].

## Taurine metabolism and pathways:

Taurine is synthesized from the precursor cysteine, which is formed from methionine. Optimal function of the methylation and transsulfuration pathways are important for cysteine production. Cysteine is converted to cysteinesulfinate by cysteine dioxygenase (CSD), requiring oxygen, NAD and iron. It is then decarboxylated to hypotaurine by cysteinesulfinate decarboxylase (CSAD), which requires vitamin B6[269]. Hypotaurine is then oxidized to form taurine by hypotaurine dehydrogenase (HPD) using both molybdenum and NAD as cofactors. An alternative pathway exists where cysteine sulfinic acid can be oxidized to cysteic acid and then decarboxylated to taurine[268]. It's also important to note that cysteine can be used for other function in the body besides taurine synthesis, such as for glutathione production and sulfur metabolism. Roughly 95% of taurine is excreted in the urine, with 70% as taurine and the remaining amount as sulfate[270].






## LOW TAURINE

Nutrient deficiencies can impair endogenous taurine synthesis, including vitamin B6, vitamin B3, iron and molybdenum. Vitamin B6 is a required cofactor for multiple pathways, including the formation of cysteine in addition to the formation of taurine. Individuals on a vegan diet or even a vegetarian diet may be at risk of taurine deficiency since it is not significantly found in plant-based foods. Cases of protein deficiency or impaired gastrointestinal digestion/absorption may also contribute to taurine deficiency. Reduced taurine levels have been associated with multiple disorders, including degenerative progressive myoclonus epilepsy, Down's syndrome, hypothyroidism, migraines, bone disorders, cancer, schizophrenia, hypertension and atherosclerosis[269,270].

## HIGH TAURINE

High levels of taurine can be due to excess dietary or supplement intake. Shellfish is one of the highest sources of naturally occurring taurine in food, while high amounts of added taurine can be found in different kinds of energy drinks. While taurine can be produced endogenously, high levels are usually from exogenous sources. An upper limit of taurine intake has not been established and concerns for toxicity are generally low. At high levels, taurine may interfere with certain substances, such as alcohol and acetaminophen, since it is a known inhibitor of the cytochrome P450 2E1 enzyme[270]. In general, taurine excess is less of a concern compared to taurine deficiency.

### Clinical Pearl:

Since taurine is formed from cysteine, which is formed from the transulfuration, it's important to assess for methylation issues. If cysteine is required for other functions, such as glutathione synthesis, endogenous taurine synthesis may be compromised. Assess cysteine, glutathione, and vitamin B6 levels on a micronutrient test if taurine levels are low.

# TAURINE CONSIDERATIONS

| | LOW TAURINE | HIGH TAURINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **Taurine**[268]: 6g per day in divided doses for up to 3 months<br>• **N-acetyl cysteine:** up to 2400mg/day<br>  • Cysteine is a precursor for endogenous synthesis of taurine<br>• Support nutrient cofactors:<br>  • **Vitamin B6** (pyridoxal 5-phosphate) (CSAD enzyme): 10-50mg/d<br>  • **Vitamin B3** (CSD, HPD): 50-100mg/d<br>  • **Iron** (CSD): 15-30mg/d<br>  • **Molybdenum**: HPD | • **Limit supplements containing taurine** |
| DIETARY CONSIDERATIONS | • **Increase taurine-rich food sources**[268]**:**<br>  • Shellfish (scallops, mussels, clams), dark meat of turkey and chicken<br>  • Certain energy drinks can contain high amounts of added taurine | • **Limit intake of high taurine foods:**<br>  • Look for hidden sources of taurine, such as energy drinks |
| LIFESTYLE CONSIDERATIONS | • **Limit exposure to environmental toxins:**<br>  • May shift endogenous cysteine towards glutathione synthesis instead of taurine | • *Lifestyle interventions do not significantly affect high taurine levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies important for enzymatic reactions<br>• **Gut Zoomer:** to assess digestive function and bile acids<br>• **Environmental Toxins:** to assess total toxic burden | • *No test recommendations for high taurine levels* |



# GLYCINE

## What is glycine?

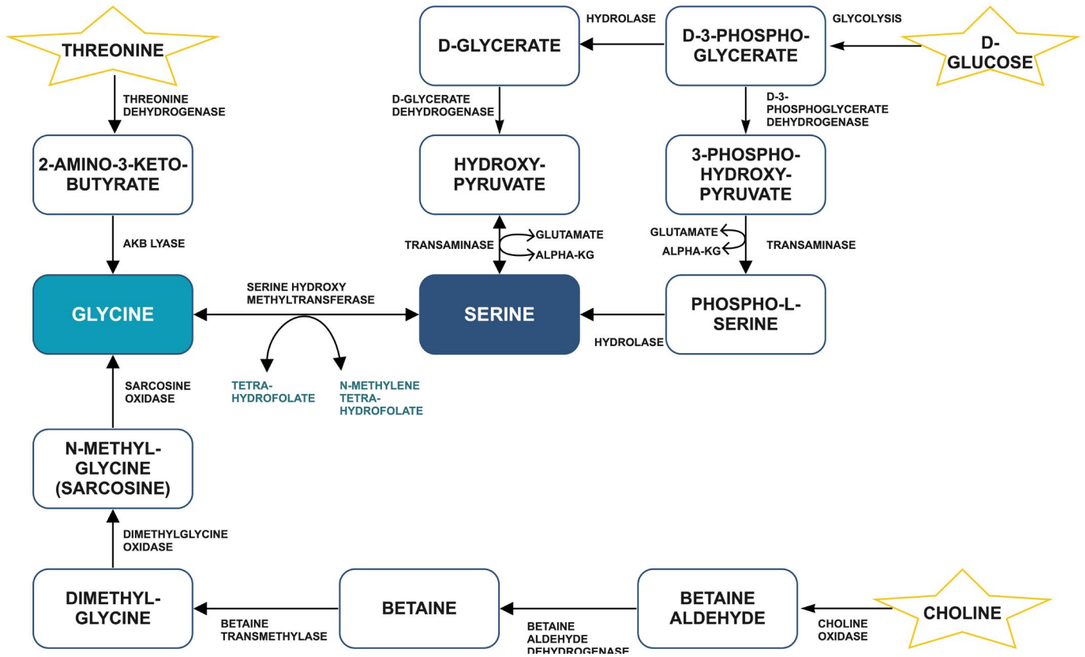
Glycine is an amino acid that serves many functions in the body, including acting as a neurotransmitter. Even though it is considered a non-essential amino acid because the body is able to produce it, the body may require greater quantities to meet physiological demands[271].

## What are the functions of glycine?

Roughly 80% of glycine in the body is used for protein synthesis[274]. Glycine is used in the synthesis of important compounds including glutathione, porphyrins, purines, heme, RNA, DNA, serine, and creatine[274]. It is also a major component of extracellular structural proteins, such as collagen and elastin[274]. Other properties include actions as an antioxidant, anti-inflammatory, cryoprotective, and immunomodulatory agent in the peripheral and nervous tissues[271]. Inhibition of tumor necrosis factor, inflammation, and activation of macrophages all occur by glycine. Glycine also plays an important role in the biliary system and digestion due its role in conjugating bile acids[271]. Through modulating intracellular calcium levels with glycine-gated chloride channels in leukocytes and macrophages, glycine can regulate the production of cytokines, formation of superoxide, and immune function[278]. In the CNS, glycine also acts as a neurotransmitter, influencing behavior, food intake and whole-body homeostasis[275]. It acts as an inhibitory neurotransmitter, however, it can also potentiate the effects of NMDA receptors, also acting as an excitatory neurotransmitter.

## Glycine metabolism and pathways:

Glycine can be synthesized via three main routes. The first is from choline, which gets oxidized and dehydrogenated to betaine, then transfers a methyl group to form dimethylglycine, and is oxidized to form sarcosine before ultimately forming glycine[275]. The next path involves threonine, which undergoes two different reactions, one of which require NAD+, to form glycine. And the other main route is a reversible reaction by serine hydroxymethyltransferase (SHMT)[274], which requires vitamin B6 and tetrahydrofolate as nutrient cofactors[275]. An additional path does exist where glyoxylate can be used to form glycine and glycine can be converted to glyoxylate via a vitamin B6 dependent reaction by alanine glycolate amino transferase[275]. Degradation of glycine occurs through three main pathways, conversion to glyoxylate, conversion to serine by SHMT or through the glycine cleavage system (GCS)[274]. While the GCS is the major route of glycine degradation prevalent in the mitochondria, but this enzyme system is absent in neurons[275]. Research has shown the herbal pesticide, glyphosate, might impair glycine homeostasis by binding to its receptors and disrupt the enzymes that metabolize glycine[276]. While more research needs to be done, there is speculation that glycine supplementation may be helpful in cases of elevated glyphosate levels in the body[276].




## LOW GLYCINE

Low levels of glycine can contribute to suboptimal growth, impaired immune responses, fat malabsorption, and other adverse effects. Research has correlated low levels of glycine with major depression[277]. The same study also showed that a higher ratio of serine to glycine was another finding in major depression[277]. Increased degradation of glycine may contribute to lower levels, which occurs with glucagon, high protein diets and metabolic acidosis[275]. Insufficient glycine levels can impair glutathione synthesis, which has a pertinent role in immunity, antioxidant status, and detoxification[282]. Reduced levels of glycine are found in individuals with insulin resistance, particularly with comorbid obesity[276]. Since glycine is important for conjugation of bile acids, low levels of glycine can contribute to fat malabsorption and poor digestion. Often, the likely reason for low levels of glycine is insufficient dietary intake. Even though the body is able to synthesize glycine endogenously, it is usually not in high enough amounts to meet physiological demands.

## HIGH GLYCINE

High glycine levels can be caused by an inborn error of glycine metabolism that is deficient in the glycine cleavage system called glycine encephalopathy, resulting in nonketotic hyperglycinemia[278]. This disorder leads to an abnormally high levels of glycine buildup in the body and is usually diagnosed early in life. Symptoms of high glycine associated with this disorder can include progressive lethargy, hypotonia, impaired development, epilepsy and even coma[278]. Glycine can metabolize to glyoxylate, which is the precursor for oxalates[279]. Individuals with high levels of glycine may need to assess oxalate levels and symptoms. Impairments in degradation pathways, such as the glycine cleavage system can lead to the buildup of glycine. This can happen with deficiencies in nutrient cofactors, such as alpha lipoic acid and can result in neurological disorders such as neurodegeneration, encephalopathy, and neonatal-onset epilepsy[280]. Elevated glycine can also occur in situations of propionic acidemia, methylmalonic acidemia, isovaleric acidemia and beta-ketothiolase deficiency. Intake of supplements containing glycine or food sources rich in glycine can increase levels.

### Clinical Pearl:

Glycine and serine undergo a bidirectional reaction. Assess serine levels in conjunction with glycine to assess whether cofactors and methylation may be playing a role in glycine levels.



## GLYCINE CONSIDERATIONS

| | LOW GLYCINE | HIGH GLYCINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **Glycine**: 1-6g per day in divided doses for up to 3 months<br>• **Magnesium glycinate**[281]: 400-800mg/d<br>  • Provides two glycine molecules per one magnesium molecule<br>• **Glutathione or N-acetyl cysteine**[282]: *doses vary*<br>  • Low levels of glycine may contribute to low glutathione levels due its role in synthesis<br>• **L-Serine**[291]: 200-700mg/kg/day up to 3 months<br>  • Serine can be used to synthesize glycine<br>• Support nutrient cofactor for SHMT: *(Converts serine to glycine in a bidirectional eaction)*<br>  • **Tetrahydrofolate**[275]**:** 400-800mcg/d<br>  • **Vitamin B6**[275]**:** 10-50mg/d<br>• Support nutrient cofactors/substrates for choline pathway: *(Converts choline to glycine)*<br>  • **Tetrahydrofolate**[274]**:** 50-100mg/d<br>  • **Choline:** substrate for pathway | • Support nutrient cofactor for SHMT: *(Converts serine to glycine in a bidirectional eaction)*<br>  • **Tetrahydrofolate**[275]**:** 400-800mcg/d<br>  • **Vitamin B6**[275]**:** 10-50mg/d<br>• **Alpha lipoic acid**[283,280]: 400-1200mg/d<br>  • Important for the glycine cleavage system for degradation of glycine<br>• **Ginkgo Biloba**[261]: 80-720mg/day<br>  • Acts as a glycine receptor antagonist<br>• **Discontinue supplements that may contain glycine or glycinate compounds** |
| DIETARY CONSIDERATIONS | • **Increase food sources rich in glycine**[284]:<br>  • Collagen, gelatin, meat, poultry, bone broth, seafood, fish, dairy<br>  • Vegan and vegetarian diets may be lower in glycine, however, they can still produce some endogenously<br>  • *Note: a typical diet consists of about 2g glycine daily*<br>• **Increase food sources of choline**<br>  • Choline can be used to synthesize glycine; Egg yolks, liver | • Decrease intake of high glycine rich foods |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions do not significantly impact glycine levels* | • *Lifestyle interventions do not significantly impact glycine levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for nutrient deficiencies important for enzymatic reactions<br>• **Environmental Toxins:** Assess for toxins such as glyphosate<br>• **Gut Zoomer:** to assess for impaired digestion and absorption that may lead to low glycine and for the impact of low glycine on conjugation of bile acids<br>• **Neural Zoomer Plus:** to assess for anti-glycine and anti-NMDA antibodies | • **Micronutrients:** to assess for nutrient deficiencies important for enzymatic reactions<br>• **Environmental Toxins:** Assess for toxins such as glyphosate<br>• **Organic Acids:** to assess for oxalate levels that may be associated with high glycine<br>• **Cytokines:** Glycine plays an important role in cytokine regulation |

# SERINE

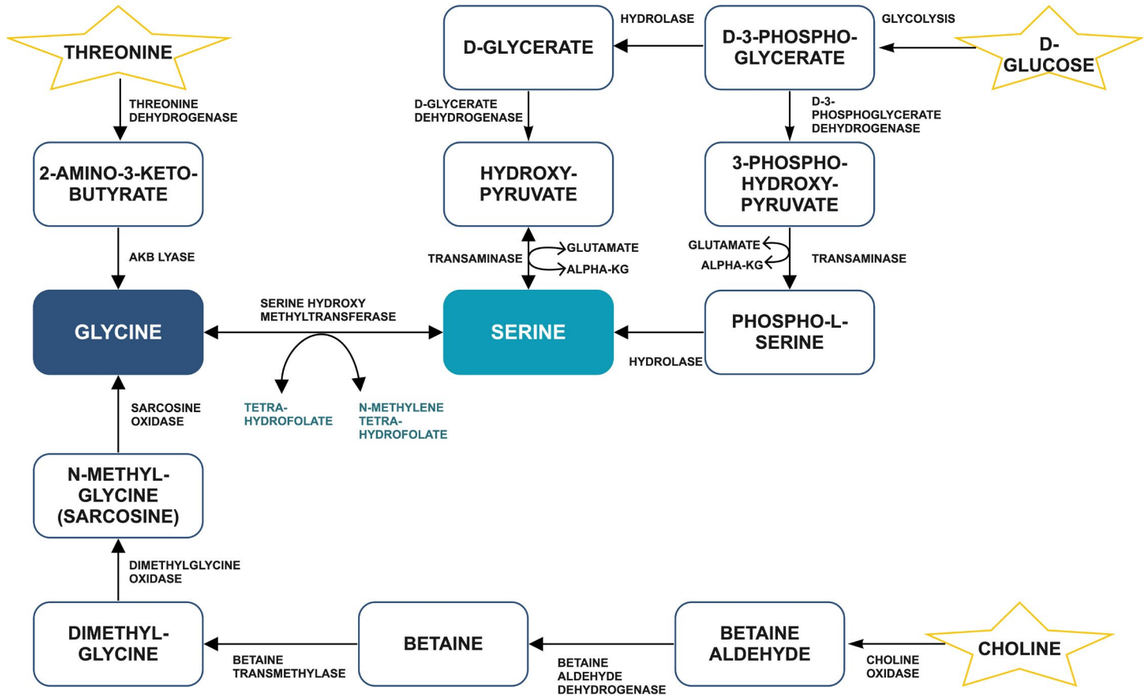
## What is serine?

Serine is a non-essential amino acid that serves many important functions in the body.  Even though the body can synthesize it, physiological demands can outweigh dietary intake, and therefore it is better classified as a conditionally essential amino acid.  Serine exists in two different forms, L-serine and D-serine, which both have different functions in the body.  L-serine can be converted to D-serine by the enzyme serine-racemase[286].

## What are the functions of serine?

As an amino acid, serine plays a role in the synthesis of proteins and nucleotides. Serine is required for the synthesis of three classes of lipids, phosphatidylserine, sphingolipids, and N-acylserines, which impact neuronal membranes and the brain[285]. It acts as a carbon source for methylation, which is critical for controlling cellular processes, synthesizing compounds such as creatine and phosphatidylcholine, forming neurotransmitters, and methylating proteins like DNA and RNA[295]. Other amino acids are formed from serine, including glycine and cysteine, which have other important physiological functions, such as glutathione synthesis. Serine plays an important role in the transulfuration pathway, where it's needed in the cystathionine B-synthase reaction that uses homocysteine to form cystathionine, which is then converted to cysteine[295]. L-serine acts as a neuronal tropic factor that plays a role in growth, differentiation, and elongation of neurons[286]. D-serine, which is an enantiomer of L-serine, functions as a ligand for the N-methyl-Daspartate (NMDA) receptor, mediating neuronal excitation[286]. Serine may also have properties of neuronal protection, which is currently under further investigation with human trials for Alzheimer's disease and amyotrophic lateral sclerosis (ALS)[286]. Evidence does exist for L-serine's role in cell proliferation, with restricted levels of serine having beneficial effects on tumor growth[286]. Evidence also exists for L-serine's role in diabetes, where concentrations of L-serine have been positively correlated with insulin secretion and sensitivity[286].

## Serine metabolism and pathways:






Serine is synthesized predominantly in the kidney, with some synthesis also occurring in the liver. Serine is derived from four main methods. Serine can come from direct intake of dietary food sources. It can be formed from the synthesis of glycolysis intermediate, 3-phosphoglycerate[286]. A common pathway of serine formation occurs from glycine via a reversible reaction by serine hydroxymethyltransferase (SHMT), which requires $^{5,10}$-methylene tetrahydrofolate and vitamin B6 as cofactors[275]. Roughly 50% of the 5-methylene tetrahydrofolate produced from the glycine cleavage system is contributed to form serine from glycine[275]. Serine can also come from the turnover of proteins and phospholipids[286].

## LOW SERINE

Levels of L-serine have been found to decrease with age. The concentrations of L-serine have been found to be low in certain conditions, such as in individuals with diabetes. One study looking at children with type 1 diabetes, found that Lserine levels were decreased by 42% compared to controls[286]. Individuals with low levels of serine have increased levels of deoxysphingolipids, which have been shown to induce apoptosis in beta-cells and impair neuronal function[286]. Low levels of L-serine have been found to increase mitochondrial dysfunction, increase fatty acid oxidation and reduce glucose catabolism[286]. Impaired L-serine biosynthesis, such as seen in genetic disorders like Neu-Laxova syndrome, can result in developmental disorders with symptoms ranging from microcephaly, intellectual disabilities, and epileptic seizures[288]. Homocysteinuria has shown decreased levels of serine, likely due to serine being used to lower plasma homocysteine levels[289]. Low levels of serine can be due to limited dietary intake or impaired endogenous synthesis. It can also be a result of impaired digestion or malabsorption. Decreased levels of serine can occur with Vitamin B6 and 5- methylenetetrahydrofolate deficiency due to their role as cofactors. Impaired methylation can also decrease serine synthesis.

**Conditions**[286,290,291]: Aging, Depression, Diabetes, Encephalopathy, Fibromyalgia, Homocysteinuria, Peripheral neuropathy, Schizophrenia, Seizures, Neu-Laxova syndrome, Phosphoserine aminotransferase deficiency, phosphoserine phosphatase deficiency

## HIGH SERINE

High levels of serine can come from high serine foods or supplements.  Serine may play a role in cell proliferation and therefore elevated levels may be a concern with cancer. High levels of d-serine in the glia can induce glutamate toxicity due to its role as an NMDA receptor co-agonist[292]. Since serine can be formed from glycine, it's important to assess levels in relation to glycine levels as well.

**Conditions**[293,290]: Alzheimer's disease (high d-serine), Bipolar disorder

### Clinical Pearl:

Serine is used in the transsulfuration pathway to convert homocysteine to cystathionine, which then forms cysteine.  Low serine levels may impair cysteine synthesis and consequently other compounds formed from cysteine, such as glutathione and taurine.  An upregulated need for endogenous synthesis of these compounds may deplete serine levels that may be needed for other functions in the body.

# SERINE CONSIDERATIONS

| | LOW SERINE | HIGH SERINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **L-serine**[291]: 200-700mg/kg/day for up to 3 months<br>• **Glycine**[21]: 200-300mg/kg/d<br>• **Phosphatidylserine**[294]: 50-300mg/kg<br>• Support nutrient cofactor for SHMT: *(Converts glycine to serine (assess glycine levels)*<br>  • **5-MTHF** (5-methylene tetrahydrofolate): 400-800mcg/d<br>  • **Vitamin B6 (pyrixodal 5-phosphate):** 10-50mg/d | • Support nutrient cofactors for SHMT: *(Converts glycine to serine; also assess glycine levels)*<br>  • **5-MTHF** (5-methylene tetrahydrofolate): 400-800mcg/d<br>  • **Vitamin B6 (pyrixodal 5-phosphate):** 10-50mg/d<br>• **Reducing serine supplements**<br>• **Reducing glycine or glycinate containing supplements** |
| DIETARY CONSIDERATIONS | • **Increase food sources of serine**[286]:<br>  • Eggs, soy, cheese, nuts, meat, seafood<br>• **Consider increasing glycine rich foods:**<br>  • serine can be synthesized from glycine<br>• **Protein restricted diets:** may increase endogenous synthesis of serine[295]<br>• **Ketogenic diets:** may induce endogenous serine synthesis[296] | • **Reduce intake of high serine food sources**<br>• Consider decreasing high glycine rich foods due to endogenous synthesis of serine from glycine |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions do not significantly impact serine levels* | • *Lifestyle interventions do not significantly impact serine levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrient deficiencies that may affect serine levels<br>• **Neural Zoomer Plus:** to assess anti-NMDA antibodies due to the role of serine as an NMDA co-agonist<br>• **Gut Zoomer:** to assess for protein maldigestion or malabsorption<br>• **Diabetes Panel:** to assess multiple blood sugar parameters due to the association of low serine with diabetes | • **Micronutrients:** to assess for micronutrient deficiencies that may affect serine levels |



# HISTAMINE

## What is histamine?

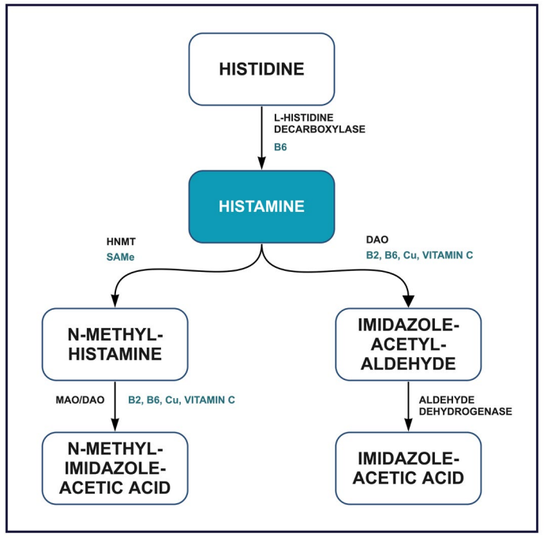
Histamine is a biogenic amine that plays a prominent role in the immune system as well as a neurotransmitter. It is synthesized by mast cells, basophils, platelets, histaminergic neurons and enterochromaffin cells[297]. Histamine is probably best known for its association with allergies, where it is released by mast cells upon encountering an allergen. Other factors may also stimulate the release of histamine from mast cells, including neuropeptides, complement factors, cytokines, hyperosmolarity, lipoproteins, adenosine, superoxidases, hypoxia, chemical and physical factors, alcohol, and certain foods and medications[297]. A common term used is histamine intolerance, which refers to increased availability of histamine and the impaired breakdown of histamine leading to an 'overflowing bucket' of histamines[297].

## What are the functions of histamine?

Histamine exerts many physiological functions across many systems in the body. There are four types of histamine receptors that are all G-protein coupled receptors and exert different functions accordingly. H1 receptors are found in multiple areas of the body including neurons, smooth muscle cells of the airways and blood vessels[298]. $H^1$ receptors regulate sleep-wake cycles, food intake, thermal regulation, emotions/aggressive behavior, locomotion, memory, and learning[298]. When H1 receptors are activated, they result in the typical allergy symptoms, including vasodilation, hypotension, flushing, tachycardia, bronchoconstriction, pruritus and even anaphylaxis[298]. H2 receptors are found predominantly in gastric mucosa parietal cells, smooth muscle cells and the heart[298]. When H2 receptors are activated, they are involved in increasing gastric acid secretion, vascular permeability, hypotension, flushing, headache, tachycardia, and bronchoconstriction[298]. H3 receptors are found in histaminergic neurons and play an important role in modulating other neurotransmitters in the central nervous system. They also regulate the release of histamine from mast cells and cerebral neurons[298]. H4 receptors are found in the bone marrow and peripheral hematopoietic cells and play a fundamental role in differentiation of myeloblasts, promyelobalsts, and chemotaxis. H4 receptors are generally known as the histaminic immune receptor and plays a critical role in different autoimmune and inflammatory disorders[298]. Histamine has also been shown to affect hormones, such as the ability to stimulate the production of estradiol in a dose dependent manner[297].

## Histamine metabolism and pathways:

Histamine is formed from the amino acid histidine by L-histidine decarboxylase, which requires vitamin B6 as a cofactor. Histamine is either metabolized by diamine oxidase (DAO) via oxidative deamination or histamine-N-methyltransferase (HNMT) by ring methylation, depending on the localization of histamine. DAO is used to catabolize histamine to imidazoleacetyl-aldehyde. DAO is stored in plasma membrane vesicles in epithelial cells and is secreted into circulation, demonstrating that its activity may function extracellularly[297]. The highest concentrations of DAO are found in the intestines, placenta, and kidney. Lower levels of DAO can be found in cases of intestinal mucosal damage and inflammatory or neoplastic diseases[297]. Nutrient cofactors for DAO include vitamin B6, copper and vitamin C, which may impact DAO activity. HNMT is used to catabolize histamine to N-methylhistamine, which is further catabolized by either the MAOb or DAO enzyme to N-methylimidazole-acetic acid. The HNMT reaction requires SAMe as a cofactor. HNMT functions in the cytosolic space of cells, therefore converting histamine intracellularly[297].



## LOW HISTAMINE

Low histamine levels can occur with a diet low in histamine-rich foods. Consuming medications or supplements that lower histamine levels can also result in lower levels. A deficiency in vitamin B6, which is needed to convert histidine to histamine by the enzyme L-histidine decarboxylase, may impair its synthesis. Histamine demonstrates anti-convulsant properties and therefore low levels may increase the risk of seizures in certain populations[302]. Increasing histamine rich foods can help increase histamine levels.

**Symptoms**[299,300,301]: Hypersomnolence, low mood, poor motivation, decreased arousal, apathy, poor learning, poor memory, decreased gastric acid secretion, increased appetite

**Conditions**[302,303]: Anxiety, Alzheimer's disease, depression, Seizures, Tourette's syndrome, obsessive-compulsive disorder

## HIGH HISTAMINE

Factors that may increase endogenous production of histamine include allergies, mastocytosis, bacteria, gastrointestinal bleeding, or increased exogenous intake of histidine or histamine from food[297]. Impaired histamine degradation due to genetic or acquired impairment of DAO or HNMT may lead to higher levels of histamine in the body. Gastrointestinal dysfunction may lead to lower DAO activity, such as in cases of intestinal mucosal damage, or inflammatory bowel disorders. This can occur in cases of food allergy, gluten-sensitive enteropathy, Crohn's disease, ulcerative colitis and colon adenoma[297]. Scrombroid poisoning also leads to high histamine levels. Exogenous sources of histamine from the diet may lead to increased levels. Alcohol may have a significant elevation on histamine levels due to its inhibiting effect on DAO.

**Symptoms**[297]: Diarrhea, stomachache, nausea, vomiting, flatulence, increased gastric acid secretion, postprandial fullness, poor appetite, headache, congestion of the nose, sneezing, bronchoconstriction, dyspnea, increased mucus secretion, hypotension, hypotonia, arrhythmia, tachycardia, urticaria, pruritus, flushing, dysmenorrhea, vertigo, addictive behaviors

**Conditions**[297,300]: Mast cell activation syndrome (MCAS), mastocytosis, eosinophilic gastroenteritis, Celiac disease, allergies, asthma, eczema, anorexia

### Clinical Pearl:

Histamine intolerance is an elevated level of histamine and usually an impaired ability to breakdown/catabolize histamine. If histamine intolerance symptoms are present, focus on reducing overall histamine intake, eliminating triggers leading to histamine release, and supporting both DAO and HNMT enzymes to facilitate proper catabolism.



# HISTAMINE CONSIDERATIONS

| | LOW GLYCINE | HIGH GLYCINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for HDC: *(Converts histidine to histamine)*<br>  • **Vitamin B6 (Pyridoxal 5-phosphate):** 10-50mg/d<br>• **Probiotics**[304]**:**<br>  • Certain strains of probiotics may increase histamine levels, such as (but not limited to) lactobacillus reuteri, which contains histidine decarboxylase that converts L-histidine to histamine | • Support nutrient cofactor for HNMT:<br>  • **SAMe**[46]**:** 400-1600mg/d<br>• Support nutrient cofactors for DAO:<br>  • **Vitamin B6 (Pyridoxal 5-phosphate):** 10-50mg/d<br>  • **Vitamin C:** 500-1500mg/day<br>  • **Copper:** 1-3mg/day<br>• **DAO Enzyme**[305]: 4mg up to 3x per day with meals<br>• **Magnesium**[306]: 400-800mg/d<br>  • Animal studies showed magnesium deficiency decreases DAO activity in the duodenum<br>• **Vitamin B1 (Thiamine)**[307]: 10-50mg/d<br>  • Animal studies showed thiamine deficiency is associated with increased histamine levels<br>• **Limit probiotics that increase histamine** |
| DIETARY CONSIDERATIONS | • Increase intake of high histamine foods (see foods to the right) | • **Limit foods high in histamines**[297]**:**<br>  • Fermented foods (sauerkraut), aged cheese, processed meat (sausage), spinach, eggplant, tomatoes, alcohol (wine, beer), leftovers due to bacterial synthesis<br>• **Limit foods with histamine-releasing capacities**[297]**:**<br>  • Citrus, papaya, strawberries, pineapple, nuts, peanuts, tomatoes, chocolate, fish, crustaceans, pork, egg whites, certain additives, and spices<br>• **Avoid alcohol**[297]<br>• **Avoid all food allergens**<br>• **Consume beef kidney for a food source of DAO** |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions do not significantly affect low histamine levels* | • Avoid activities that increase exposure to environmental allergens |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess nutrient deficiencies that may affect histamine levels<br>• **Hormone Panel:** to assess for hormones that may be influenced by low histamine levels, such as estradiol. | • **IgE Foods & Inhalants:** to assess for allergenic foods or environmental allergens that may increase histamine levels<br>• **Food Sensitivity with IgG4/C3D:** to assess for foods that activate the complement system that may trigger histamine release from mast cells<br>• **Gut Zoomer:** to assess for dysbiosis, GI infections and inflammation that may impair DAO and increase histamine levels<br>• **Wheat Zoomer:** to assess for celiac disease or non-celiac gluten sensitivity associated with lower DAO levels<br>• **Micronutrients:** to assess for nutrient deficiencies that may increase histamine |

# ASPARTATE

## What is aspartate?

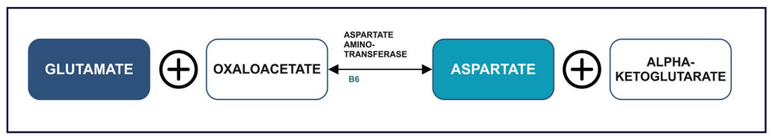
Aspartate is a nonessential amino acid that functions as an excitatory neurotransmitter in the central nervous system. Aspartic acid comes in two forms, D-aspartic acid and L-aspartic acid, where L-aspartic acid plays a role with synthesis of body proteins and D-aspartic acid plays more of a role in hormone regulation.

## What are the functions of aspartate?

Aspartate acts as a specific agonist for NMDAR-type glutamate receptors (but not AMPA-type glutamate receptors) and is very closely related to glutamate as they are often found together at axon terminals[308]. Aspartate acts as the excitatory messenger in the central spinal cord, while glycine exhibits inhibitory function, therefore aspartate and glycine acts as a balancing pair of neurotransmitters within the CNS[309]. Aspartate has many other functions in the body, including an important role in the urea cycle (ammonia removal), role in the malate-aspartate shuttle of gluconeogenesis, immune function, energy production, cognitive function, reproduction, and a building block protein synthesis (aspartic acid). Aspartate is also used to synthesize other amino acids and compounds including asparagine, arginine, threonine, methionine, isoleucine, lysine, pantothenate, NAD, purines, and pyrimidines[310]. D-aspartate is also involved in the regulation of hormones. Animal studies have shown aspartate stimulates the release of various hormones, including gonadotropin-releasing hormone, oxytocin, vasopressin, prolactin, luteinizing hormone, growth hormone, testosterone and progesterone[311]. D-aspartate levels have been shown to significantly increase during postnatal development, while stabilizing upon organ maturation[312]. Another interesting function of L-aspartic acid is as a competitive inhibitor of βglucuronidase activity[313].

## Aspartate metabolism and pathways:

Aspartate can be synthesized endogenously from the transamination of oxaloacetate from the citric acid cycle. This is a reversible reaction by aspartate aminotransferase (AST), which transfers an amino group from glutamate to oxaloacetate to form alpha-ketoglutarate and aspartate. This is a vitamin $B^6$ dependent reaction. AST is found in high concentrations in the liver, as well as in the muscle, heart, kidney, red blood cells, brain and small bowel[314]. This is a common marker tested on liver function tests. The AST reaction is reversible, and the level of enzyme activity can affect both aspartate and glutamate levels. One study found that elevated levels of plasma transaminase could lead to elevated glutamate levels with the reversible reaction[315]. Aspartate can then quickly synthesize asparagine and glutamate by asparagine synthetase, which uses glutamine and ATP to catalyze the reaction.




## LOW ASPARTATE

Low levels of aspartate can be due to low exogenous intake or poor endogenous synthesis. Any impairments in the citric acid cycle, resulting in lower levels of oxaloacetate, can decrease synthesis of aspartate. Any gut-related imbalances, digestive impairments or protein deficiency can also contribute to lower levels of aspartate. A vitamin B6 deficiency can impair the aspartate aminotransferase enzyme, resulting in decreased endogenous synthesis.

**Conditions**: Schizophrenia

## HIGH ASPARTATE

High levels of aspartate can come from exogenous sources in the diet, such as artificial sweeteners containing aspartame. High levels are more of a concern than low levels due to its ability to act as an agonist for NMDAR-type glutamate receptors, contributing to excess excitation in the CNS.

**Conditions**[312]: Anxiety, Alzheimer's disease, Parkinson's disease, seizure



# ASPARTATE CONSIDERATIONS

| | LOW ASPARTATE | HIGH ASPARTATE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • **Aspartic acid**[316]: up to 8g/d for up to 3 months<br>• **Magnesium aspartate**: 400-800mg/d<br>• Support nutrient cofactor for AST: *(Converts oxaloacetate + glutamate to aspartate and alpha-ketoglutarate;reversible reaction)*<br>  • **Vitamin B6 (pyrixodal 5-phosphate):** 10-50mg/d | • Avoid supplements containing aspartic acid or aspartate compounds (magnesium aspartate)<br>• Support nutrient cofactor for AST: *(Converts oxaloacetate + glutamate to aspartate and alpha-ketoglutarate; reversible reaction)*<br>  • **Vitamin B6 (pyrixodal 5-phosphate):** 10-50mg/d |
| DIETARY CONSIDERATIONS | • Increase intake of aspartic acid rich foods (see to the right)<br>• Increase intake of protein rich foods | • **Avoid the artificial sweetener aspartame,** which contains aspartic acid[317]<br>• **Decrease food sources of aspartic acid:**<br>  • **Vitamin B6 (pyrixodal 5-phosphate):** 10-50mg/d |
| LIFESTYLE CONSIDERATIONS | • *Lifestyle interventions to not significantly impact aspartate levels* | • *Lifestyle interventions to not significantly impact aspartate levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for micronutrient levels that may impair aspartate synthesis<br>• **Neural Zoomer Plus:** to assess anti-NMDA antibodies due to the role of aspartate as an NMDA co-agonist<br>• **Gut Zoomer:** to assess for digestive insufficiencies that may impair aspartate levels and to assess beta-glucuronidase levels<br>**Organic Acids Test:** to assess for Kreb cycle intermediates<br>**Hormone Panel:** to assess for hormones that may be influenced by low aspartate levels | • **Micronutrients:** to assess for micronutrient levels that may impair aspartate synthesis |

# ACETYLCHOLINE

## What is acetylcholine?

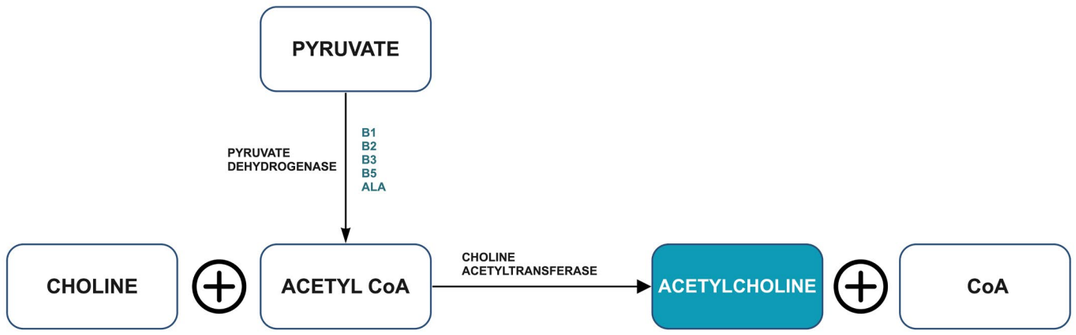
Acetylcholine is an excitatory neurotransmitter and a neuromodulator that has effects both in the CNS and the periphery. Tissues that use acetylcholine or are responsive to it are considered 'cholinergic.' Acetylcholine is produced by cholinergic nerves and non-neuronal cells, including T cells, other immune cells, lung epithelial cells, and pancreatic a-cells[318]. The mechanism of acetylcholine release from immune cells occurs differently from neuronal cells. Stimulated neurons produce norepinephrine, which binds to B2 adrenergic receptors on CD4+T cells in the spleen and stimulates acetylcholine release[318]. This demonstrates the relationship between acetylcholine and the immune system.

## What are the functions of acetylcholine?

Acetylcholine is a ubiquitous signaling molecule[318]. In the brain, acetylcholine has been shown to alter neuronal excitability, influence synaptic transmission, induce synaptic plasticity, and coordinate the firing of groups of neurons[319]. It is involved in memory, motivation, arousal, and attention[320]. Acetylcholine signaling occurs with two different types of receptors, muscarinic receptors, which are G-coupled receptors and nicotinic receptors, which are ion gated cation channels[318]. Both branches of the autonomic nervous system, sympathetic and parasympathetic, use acetylcholine as an important messenger. The vagus nerve, representing the parasympathetic nervous system, relies on acetylcholine as the main messenger, heavily influencing systems such as the gastrointestinal and cardiovascular systems. Acetylcholine has a wide impact on multiple physiological functions, including regulating cardiac contractions, vasodilation, movement, digestion, intestinal peristalsis, glandular secretion, and other autonomic functions[318,320]. In addition, acetylcholine exerts anti-inflammatory and proinflammatory effects depending on the situation, which underlies an important mechanism in dealing with infections.

## Acetylcholine metabolism and pathways:

Acetylcholine is synthesized from acetyl coenzyme A and choline by the enzyme choline acetyltransferase (ChAT)[321].Acetyl CoA is formed from pyruvate, which is derived from glucose, by pyruvate dehydrogenase. This reaction requires multiple nutrients as cofactors, including vitamins B1, B2, B3, B5 and alpha lipoic acid. The postsynaptic action of acetylcholine is dependent upon acetylcholinesterase (AChE), which rapidly breaks it down to acetate and choline. Environmental toxins can impair the function of AChE, leading to higher levels of acetylcholine and potentially causing neuromuscular paralysis. This occurs with compounds such as diphenyl trichloroethane (DTT), the herbicide 2,4- dichlorophenoxyacetic acid (2,4-D) and some chemical warfare agents[321].






## LOW ACETYLCHOLINE

Low levels of acetylcholine can occur when there are deficiencies in nutrient cofactors or precursors essential for its synthesis. Pyruvate dehydrogenase, which converts pyruvate to acetyl CoA, requires vitamins B1, B2, B3 and alpha lipoic acid. Vitamin B5 is also required for the synthesis of coenzyme A, which is needed to form acetyl CoA. A deficiency in choline, often due to insufficient dietary intake of choline rich foods such as eggs and liver. This can occur due to allergies, food intolerances, or vegan and vegetarian diets, which can impair acetylcholine synthesis. Heavy metals, such as mercury, have been shown to inhibit neuronal uptake of choline, activity of ChAT, and reduced concentrations of acetylcholine[323]. Low levels of acetylcholine can induce forgetfulness and impair learning of new information[320].

**Symptoms**[320]: Impaired memory, impaired learning of new information, slowed GI motility, gastroparesis, constipation, large pupils, dry eyes, flushing, elevated inflammation, tachycardia

**Conditions**[320,324,325]: Autism spectrum disorder, Alzheimer's disease, Dementia, Myasthenia gravis, Parkinson's disease, Schizophrenia

## HIGH ACETYLCHOLINE

A high amount of acetylcholine can contribute to a cholinergic crisis. This can occur as a result of overstimulation of nicotinic and muscarinic receptors at the neuromuscular junctions due to inhibition of acetylcholinesterase (AChE) or excessive amounts of acetylcholine. Individuals taking medications or supplements that inhibit the AChE enzyme, which breaks down acetylcholine, may result in higher levels. Environmental toxins can also impair the AChE enzyme, such as pesticides, insecticides, and other agents such as nerve gas can also lead to excessive acetylcholine levels. During infections, acetylcholine levels may be increased in response, particularly at the peak point of infection[326].

**Symptoms**: Cramps, increased salivation, lacrimation, muscular weakness, paralysis, muscular fasciculation, diarrhea, blurry vision.

**Conditions**[327,328]: Depression, Seizures

### Clinical Pearl:

Since many nutrients are involved in the synthesis of acetylcholine, poor nutrition status may impair the ability to synthesize acetylcholine levels. A. micronutrient test is extremely helpful alongside a neurotransmitter test to interpret markers that require multiple nutrients, such as acetylcholine.

# ACETYLCHOLINE CONSIDERATIONS

| | LOW ACETYLCHOLINE | HIGH ACETYLCHOLINE |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactors for pyruvate dehydrogenase: *(Converts pyruvate to acetyl CoA)*<br>  • **Vitamin B1, B2, B3, B5, alpha lipoic acid**<br>• Incorporate sources of choline to synthesize acetylcholine:<br>  • **Choline**[329]: 1-3g/d<br>  • **Phosphatidylcholine**[330]: 1-3g/d<br>  • **Alpha-GPC (glycerylphosphorylcholine)**[331,332]: 400-1200mg/d<br>• **Acetyl L-carnitine**[333,334]: 1.5-3g/d<br>  • Provides an acetyl group to increase acetylcholine synthesis<br>• Incorporate acetylcholinesterase inhibitors *(Animal studies & in vitro studies)*<br>  • **Huperzine A**[335]: 50-200mcg twice daily<br>  • **Bacopa Monnieri**[336,337]: 300-600mg/d<br>  • **Fenugreek**[338]: 500-1000mg/d<br>  • **Ginkgo biloba**[339,340]: 80-720mg/day<br>  • **Curcumin**[341]: 25-50mg/kg/day<br>• **Alpha lipoic acid**[283,342]: 400-1200mg/d<br>  • Animal studies show ALA increases acetylcholine, ChAT activity and decreases acetylcholinesterase<br>• **Magnesium**[343]: 400-800mg/d<br>  • Magnesium deficiency results decreased acetylcholine in the brain<br>• **Probiotics**[257]:<br>  • Lactobacillus plantarum | • **Avoid any supplements that may increase acetylcholine levels**<br>• *If acetylcholine levels are extremely elevated, anticholinergic medication interventions may be considered* |
| DIETARY CONSIDERATIONS | • **Increase intake of choline rich foods sources:**<br>  • Egg yolks and liver<br>• **Fasting**[344]:<br>  • In animal studies, fasting for 24 hrs reduced AChE activity<br>• **Increase dietary fat**[350]:<br>  • Consumption of dietary fat can activate the cholinergic anti-inflammatory pathway, increasing acetylcholine<br>• **Limit high mercury seafood**<br>**Incorporate foods that demonstrate acetylcholinesterase properties:**<br>  • Green tea (EGCG) [345], ginger[346], rosemary[347], cinnamon[348] | • **Reduce intake of caffeine**[349]:<br>  • Animal studies have shown caffeine increases extracellular levels of acetylcholine<br>• **Reduce intake of acetylcholine rich foods**[148]:<br>  • Eggplant, bitter orange, common bean, mung bean, nettles, pea, radish, spinach, squash, wild strawberry |
| LIFESTYLE CONSIDERATIONS | • **Vagal nerve stimulation**[350]:<br>  • Activation of the vagus nerve leads to the release of acetylcholine | • **Reduce stress**[351]:<br>  • Acute stress increases acetylcholine release and enhances neuronal excitability<br>• **Avoid exposure to environmental toxins**[321]:<br>  • Pesticides and insecticides may inhibit acetylcholinesterase and contribute to higher acetylcholine levels. |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess nutrient deficiencies that may impact acetylcholine levels<br>• **Heavy Metals:** to assess for heavy metals<br>• **Neural Zoomer Plus:** to assess for anti-acetylcholine antibodies | • **Environmental Toxins:** to assess for toxins that may impact acetylcholine levels<br>• **Infections Panel:** to assess whether infections may be contributing to elevated acetylcholine |

# OXYTOCIN

## What is oxytocin?

Oxytocin is a pleiotropic peptide hormone and a neuropeptide. It is produced by the parventricular and supra-optic nuclei of the hypothalamus. It has a relatively short half-life of only a few minutes.  Oxytocin is commonly referred to as the "love hormone," because levels of oxytocin increase during hugging, bonding, and orgasm.

## What are the functions of oxytocin?

Oxytocin is best known for its physiological role in lactation and childbirth. Oxytocin also plays an important role in many behaviors, including learning, anxiety, feeding, pain perception, social memory, social bonding and attachment, sexual reproduction, maternal behavior, and aggression[352]. Oxytocin administration has been found to promote prosocial behavior, trust, and a sense of overall wellbeing. Synthetic oxytocin, commonly known as Pitocin, is used to induce labor and stimulate breastmilk production[352]. Oxytocin may be beneficial in the treatment of many conditions, including depression, anxiety, and intestinal problems. For example, oxytocin may prevent chemo-radiotherapy induced intestinal injury as well show beneficial effects in the treatment of IBD[353]. Altered oxytocin levels have been identified in many conditions, including mood disorders, pain conditions, some cancers, benign prostatic disease, autism, schizophrenia, and osteoporosis[354]. Oxytocin is structurally and functionally similar to vasopressin, with overlapping functions in the body. Concentrations of oxytocin are roughly 1000-fold higher in the CNS than periphery, but important functions in the periphery have been noted due to its presence in diverse tissues such as the placenta, adrenal medulla, thymus, pancreas, corpus luteum and interstitial cells of Leydig[355]. The oxytocin receptor gene (OXTR) encodes for the oxytocin receptor. Oxytocin is involved in a positive feedback loop, where the release of oxytocin results in the stimulation of more release, therefore potentiating its effects. Estrogen is a well-known inducer of oxytocin, while progesterone has the opposite effect. Oxytocin and cortisol also have an inverse relationship.

## Oxytocin metabolism and pathways:

Oxytocin is composed of nine amino acids with one disulphide bond[356]. It is synthesized as a large molecule, a prohormone system called oxytocin-neurophysin I complex[356]. It's packaged into membrane bound secretory granules in the endoplasmic reticulum and Golgi apparatus found in the paraventricular and supraoptic nuclei[356]. It's then transported to the axon terminals in the posterior pituitary where it's stored until there's a stimulus, signaling oxytocin to be released into the blood. Just before oxytocin is released, it is cleaved from neurophysin I by the enzyme peptidylglycine α-amidating monooxygenase (PAM)., which requires vitamin C as a nutrient cofactor[356].

## LOW OXYTOCIN

Low levels of oxytocin can be seen in multiple disorders and can be a result of factors such as nutrient deficiencies, hormonal imbalances, and genetic SNPs.  Since cortisol and oxytocin have an inverse relationship, higher levels of stress may result in lower levels of oxytocin.

**Symptoms**: Hyperphagia, heightened levels of pain, disconnected from others, fear, low empathy, feeling lonely, high stress

**Conditions**[357,358,359,360]: Anxiety, autism, depression, borderline personality disorder, bipolar disorder, fibromyalgia, hypothyroidism, multiple sclerosis, Parkinson's disease

## HIGH OXYTOCIN

High levels of oxytocin can occur with medication use, drug use and other life events.  Estrogen has been shown to increase the release of oxytocin, therefore assessing hormone levels may be important.

**Symptoms**: Increased satiety

**Conditions**: Schizophrenia, obsessive-compulsive disorder





| | LOW OXYTOCIN | HIGH OXYTOCIN |
|---|---|---|
| SUPPLEMENT CONSIDERATIONS | • Support nutrient cofactor for PAM:<br>  • **Vitamin C**: 500-1500mg/day<br>• **Vitamin D**[361]: 1000-5000IU/d<br>  • Genes and receptors for oxytocin contain vitamin D responsive elements (VDREs)<br>• **Magnesium**[362]: 400-800mg/d<br>  • Magnesium enhanced effect of oxytocin<br>• **Fenugreek**[363]: 500mg-1000mg/d<br>  • Fenugreek has an oxytocic effect | • *Supplements are not generally used to lower* oxytocin levels |
| DIETARY CONSIDERATIONS | • **Increase intake of dietary fat**[364]:<br>  • Dietary fat intake leads to release of oleoylethanolamide, which activates central oxytocin transmission, and leads to suppressed feeding | • **Reduce intake of caffeine**[365]<br>  • Animal study showed that caffeine excites oxytocin expressing neurons |
| LIFESTYLE CONSIDERATIONS | • **Massage Therapy**[366]:<br>  • Human studies show massage therapy Increases oxytocin levels<br>• **Soothing Music**[367]:<br>  • Randomized control trials showed soothing music increased oxytocin levels in postoperative heart patients<br>• **Reduce stress:**<br>  • Cortisol has an inverse relationship with oxytocin | • *Lifestyle interventions are more relevant for increasing oxytocin levels* |
| TESTING CONSIDERATIONS | • **Micronutrients:** to assess for deficiencies that may affect oxytocin levels<br>• **Other tests:** Cortisol | • **Salivary or Urinary Hormones:** to assess the interrelationship between oxytocin and sex hormones<br>• **Other tests:** Cortisol |

# DIURNAL RHYTHMS

| | DIURNAL RHYTHMS |
|---|---|
| EPINEPHRINE | Epinephrine is a catecholamine neurotransmitter produced in the adrenal glands. Epinephrine is involved in sympathetic nervous system activation in response to stress. The baseline pattern of diurnal epinephrine follows an inverted U-shape. Levels are typically low in the morning, peak by the afternoon and fall by evening. Even if pooled levels of epinephrine are normal, assess each time individually. Understanding the exact abnormal diurnal patterns can allow for better personalized treatments by supporting low and high levels at the appropriate times. Assess all factors that may influence epinephrine levels throughout the day, including dietary impact, supplements, medications, sleeping habits, napping, exercise, illness, stress, and any other relevant factors.<br>**For any dysregulated patterns, follow the recommendations for low or high epinephrine accordingly.*|
| NOREPINEPHRINE | Norepinephrine is a catecholamine neurotransmitter, commonly known as noradrenaline, that is part of the sympathetic nervous system, which deals with the body's stress response. Norepinephrine is produced in the adrenal medulla and sympathetic nerves. The baseline diurnal rhythm of norepinephrine follows a pattern where levels are typically low in the morning, peak by the afternoon and slightly decrease in the evening. Even if pooled levels of norepinephrine are normal, assess each time individually. Understanding the exact abnormal diurnal patterns can allow for better personalized treatments by supporting low and high levels at the appropriate times. Assess all factors that may influence norepinephrine levels throughout the day, including dietary impact, supplements, medications, sleeping habits, napping, posture (standing or sitting), exercise, stress, and any other relevant factors.<br>**For any dysregulated patterns, follow the recommendations for low or high norepinephrine accordingly.*|
| CREATININE | Urine creatinine concentrations are used to determine whether urine samples are valid. Creatinine is excreted at a relatively constant rate, allowing it to be used to normalize analyte concentrations in spot samples[368]. The unit of measurement used is Creatinine mg/ml.<br>**Low Creatinine:** Urine samples with low creatinine concentrations can indicate dilute samples, overhydration, kidney disease, diabetes, old age, or low muscle mass[368,369].<br>**High Creatinine:** Urine samples with high creatinine concentrations can indicate dehydration, strenuous exercise, high muscle mass, a diet high in protein or red meat[368]. It can also be high in various disease states, such as high blood pressure, obesity, and kidney disease.<br>Due to Vibrants' use of advanced technology for measuring neurotransmitter levels, the limit of detection is very low, allowing detection of analytes even in very dilute urine sample. Even though creatinine levels can vary significantly throughout the day, it can be used to standardize measurements for neurotransmitter analytes.<br>Vibrant uses a creatinine adjustment calculation to compensate for any low or high values. This ensures that the results are adjusted based on the creatinine levels so that the interpretation does not need to factor that in.|



# RATIOS

| | LOW RATIO | HIGH RATIO |
|---|---|---|
| NOREPINEPHRINE / EPINEPHRINE | A low ratio indicates a higher level of epinephrine compared to norepinephrine. Research has shown that a low norepinephrine to epinephrine ratio is a risk factor for suicidal behavior[370]. A high epinephrine level indicates greater adrenal output. Follow recommendations for any high epinephrine levels accordingly. | A high ratio indicates a higher level of norepinephrine compared to epinephrine. Norepinephrine is converted to epinephrine by PNMT, which requires SAMe as a cofactor. Impaired methylation can decrease the conversion of norepinephrine to epinephrine, contributing to a higher ratio. If epinephrine is on the higher end, it's also important to assess factors that may be contributing to higher epinephrine levels. |
| HVA/VMA | A low ratio indicates a higher level of VMA compared to HVA. This occurs when there's greater production and metabolism of norepinephrine and epinephrine compared to dopamine. Various factors for a low ratio include high cortisol levels, medication influences (Amphetamines, etc) and tumors. If either HVA or VMA are low or high, follow recommendations accordingly. | A high ratio indicates a higher level of HVA compared to VMA. This occurs when there's greater production and metabolism of dopamine compared to norepinephrine and epinephrine. Any impairments of the DBH enzyme, which converts dopamine to norepinephrine, can increase the ratio. This can be due to genetic disorders (Menkes disease), neuroblastomas, nutrient cofactor deficiencies (vitamin C and copper), or other factors such as overgrowth of clostridia, which may inhibit the DBH enzyme. Other factors include low cortisol levels and presence of tumors. |
| HVA/DOPAC | A low ratio indicates a higher level of DOPAC compared to HVA. DOPAC is converted to HVA by COMT, which requires SAMe. Impaired methylation can reduce COMT activity, resulting in a lower ratio. Since COMT also requires magnesium as a cofactor, a deficiency can also contribute to lower levels of enzyme activity and decreased HVA formation. Any other factors that inhibit COMT activity, such as genetic SNPs, medications, supplements, or heavy metal toxins, can also result in a lower ratio. | A high ratio indicates a higher level of HVA compared to DOPAC. DOPAC is converted to HVA by COMT, which requires SAMe. Increased methylation can induce COMT, resulting in a lower ratio. Any other factors that may induce COMT activity, such as genetic SNPs, medications, supplements, can also result in a higher ratio.<br>If DOPAC levels are low due to decreased MAO activity, which would decrease the conversion of dopamine to DOPAC, it may contribute to a higher ratio. Any factors that may inhibit MAO activity, including genetic SNPs, medications, or supplements, may also affect this ratio. |

| | | |
|---|---|---|
| QUINOLINIC ACID/5-HIAA | A low ratio indicates a higher level of 5-HIAA compared to quinolinic acid. A low ratio is not generally a concern. It indicates that tryptophan is adequately metabolized towards the serotonin pathway. It's important to assess other metabolites in the kynurenine pathway because if there are other metabolites that are elevated, it could indicate an upregulation of the kynurenine pathway without elevated quinolinic acid formation. This can occur, for example, if there is a vitamin B6 deficiency contributing to elevated xanthurenic acid, therefore preventing quinolinic acid formation. Since 5-HIAA is the breakdown metabolite of serotonin, a high MAOa activity leading to greater 5-HIAA formation can also contribute to a lower ratio. | A high ratio indicates a higher level of quinolinic acid compared to 5-HIAA. A high ratio is a concern because it indicates that the kynurenine pathway is upregulated, shifting tryptophan use away from the serotonin pathway and towards the kynurenine pathway. Since quinolinic acid acts as a neurotoxin, greater levels can lead to deleterious health effects. Since 5-HIAA is the breakdown metabolite of serotonin, slowed MAOa activity leading to lower 5-HIAA formation could also contribute to a higher ratio, even with sufficient serotonin levels. When the ratio is high, it's important to address factors that may upregulate the kynurenine pathway, such as inflammation, stress/high cortisol, and infections.<br>**See recommendations for high quinolinic acid* |



# MEDICATIONS & NEUROTRANSMITTERS

*This is not intended to be a comprehensive list of medications that influence neurotransmitters, but it provides some insight into some of the most commonly used medications that may affect neurotransmitters.*

| | Drugs that increase or mimic | Drugs that decrease or block |
|---|---|---|
| Serotonin | **SSRIs:** Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil), Fluvoxamine (Luvox), Citalopram (Celexa), Escitalopram (Lexapro)<br>**Tricyclic antidepressants:** Amitriptyline, Clomipramine, Imipramine<br>**MAOIs (MAOa):** Isocarboxazid, Linezolid, Methylene blue, Phenelzine, Selegiline, Tranylcypromine<br>**Triptans:** Sumatriptan (Imitrex), Almotriptan, Naratriptan<br>**SNRIs:** Duloxetine (Cymbalta), Desvenlafaxine (Pristiq), Venlafaxine (Effexor)<br>**Other:** Buspirone, Carbamazepine, cyclobenzaprine, Dextromethorphan (Robitussin DM), Lithium, Meperidine (Demerol), Methadone, Methamphetamine, Tramadol, Valproic acid | **Serotonin receptor antagonists:** Ondanestron (Zofran), cyproheptadine, risperidone, clozapine, trazadone, propranolol, mirtazapine<br>**Other:** TPH inhibitors, Reserpine |
| Dopamine | **Dopamine agonists:** Apomorphine, Ropinirole, Pramipexole, Rotigotine,<br>**MAOIs (MAOa & MAOb):** Selegiline, Rasagiline, Safinamide, Isocarboxazid, Linezolid, Methylene blue, Phenelzine, Selegiline, Tranylcypromine<br>**NDRIs:** Bupropion (Wellbutrin), methylphenidate (Ritalin, Concerta)<br>**Other:** Levadpopa | **Dopamine antagonists:** Metoclopramide (Reglan), Clomperidone, Clozapine, Risperidone, Haloperidol |
| Norepinephrine | **SNRIs:** Duloxetine (Cymbalta), desvenlafaxine (Pristiq), venlafaxine (Effexor)<br>**Tricyclic antidepressants:** amitriptyline, clomipramine, imipramine<br>**NDRIs:** Bupropion (Wellbutrin), methylphenidate (Ritalin, Concerta)<br>**MAOIs (MAOa):** Isocarboxazid, Linezolid, Methylene blue, Phenelzine, Selegiline, Tranylcypromine<br>**Other:** Pseudoephedrine (Sudafed), Albuterol, Vasopressors (Levophed) | **Beta blockers:** Propranolol, Atenolol, Metoprolol (Lopressor)<br>**Alpha blockers:** Doxazosin, Prazosin<br>**Alpha-2 agonists:** Clonidine, Xylazine |

| | | |
|---|---|---|
| Glutamate | **NMDA glutamate receptor agonist:** D-cycloserine | **Glutamate release inhibitors:** Lamotrigine, Riluzole<br>**NMDA glutamate receptor antagonists:,** Dextromethorphan (Robitussin), Dizocilpine, Memantine (Namenda), Nitrous oxide, Phencyclidine (PCP), Ketamine, Methoxetamine |
| GABA | **GABA agonist:** Baclofen, Propofol, GHB, Barbiturates (Phenobarbital), Benzodiazepines (Valium)<br>**GABA analogs:** Valproic acid, Gabapentin | **GABA antagonists:** Bisculline, Gabazine |
| Histamine | **Histamine agonist:** Impromidine, Betazole<br>**Other:** Opiates | **Antihistamines:** Diphenhydramine (Benadryl), Cetirizine (Zyrtec), Fexofenadine (Allegra), Loratadine (Clartitin), Antipsychotics, Tagamet, Hydroxyzine, Carbinoxamine, Ketotifen, Cyproheptadine |
| Acetylcholine | **Acetylcholinesterase inhibitors:** Donepezil, Rivastigmine, Galantamine<br>**Cholinergic agonist** (Carbachol)<br>**Other:** Nicotine, Chantix | **Anticholinergic:** Atropine, Scopolamine, Botox, Cyproheptadine |

Medications[371,372]



# ENZYME REACTIONS

| | REACTIONS | COFACTORS | INHIBITORS (-) | INDUCERS (+) |
|---|---|---|---|---|
| COMT: O-methylation | Dopamine —> 3-MT<br>DOPAC —> HVA<br>Norepinephrine —> Normetanephrine<br>Epinephrine —> Metanephrine | Magnesium<br>SAMe | **Supplements/Dietary:** Flavonoids, EGCG, quercetin, fisetin, luteolin, oleacein (olive oil)[363,374] | SAMe<br>Methylfolate<br>Methylcobalamin<br>Trimethylglycine |
| MAOa | Serotonin —> 5-HIAA<br>Norepinephrine —> DOPEGAL<br>Epinephrine —> DOPEGAL<br>Normetanephrine —> MOPEGAL<br>Metanephrine —> MOPEGAL<br>Dopamine —> DOPAL<br>3-MT —> MHPA | Vitamin B2 | **Supplements/Dietary:** Curcumin, quercetin, apigenin, luteolin, scutellarein, fenugreek, resveratrol, garlic, eugenol, propolis, African Rue, St. John's Wort, berberine[50,51,52,53,54,55,56,57,58]<br>**Hormones:** Estrogen<br>**Other:** Excess dietary or biogenic amines (due to competitive inhibition), cigarette smoking | **Supplements:** Forskolin[376]<br>**Medications/ Hormones:** Glucocorticoids[375], Progesterone[376]<br>**Other:** Inflammation |
| MAOb | PEA —> Phenylacetic acid | Vitamin B2 | **Supplements/Dietary:** Fenugreek, Pterostilbene, Curcumin, Australian willow, Kava kava, Garlic, Propo is[215,216,217,218,219] | **Supplements:** Retinoic acid[3777] |
| Hydroxylase | **Tryptophan Hydroxylase:** Tryptophan —> 5-HTP<br>**Phenylalanine Hydroxylase** Phenylalanine —> tyrosine<br>**Tyrosine Hydroxylase:** Tyrosine —> L-DOPA | Vitamin B2 | **Inhibitors of GTP cyclohydrolase enzyme used to synthesize BH4:** Glucocorticoids, melatonin, IL-4, IL-10, TGF-ß, Nitric oxide donors[378]<br>**Other:** Hypoxia | **Inducers of GTP cyclohydrolase enzyme used to synthesize BH4:-** Insulin, statins, TNF-α, Interferon-y, IL-1ß, follicle stimulating hormone[378] |

| | | | | |
|---|---|---|---|---|
| Decarboxylase | **AADC**<br>L-DOPA —> Dopamine<br>5-HTP —> Serotonin<br>**Tyrosine Decarboxylase:**<br>Tyrosine —> Tyramine<br>**Tryptophan Decarboxylase**<br>Tryptophan —> Tryptamine<br>**L-Histidine Decarboxylase**<br>Histidine —> Histamine | Vitamin B6 (P5P) | | |
| KAT | Kynurenine —> Kynurenic acid<br>3-HK—> Xanthurenic acid | Vitamin B2 | | |



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