



Neurotransmitter Testing in Dried Urine

Neurotransmitter Testing – Giving a Clinical Edge in Individualizing Therapy for Mood Disorders

Mental health disorders affect millions of people in the U.S. and profoundly contribute to the burden of disease in society. The National Alliance of Mental Illness reports that about 21 million U.S. adults (8.4%) had at least one major depressive episode in 2020 and over 40 million adults in the U.S. (19.1%) have an anxiety disorder such as panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and phobias¹. Mood disorders are the third most common cause of hospitalization in the U.S. for individuals aged 18 to 44¹. The top-prescribed and top-selling prescription drugs in the U.S. in 2020 included antipsychotics, antidepressants, and attention-deficit disorder (ADHD) drugs².

The current mental health treatment paradigm relies on subjective evaluation of clinical signs and symptoms as there is a lack of testable biomarkers. Although subjectively based treatments can work for patients, many have frequent relapse episodes. Furthermore, a large number of patients suffer from treatment-resistant depression³. The selection of the best therapeutic regimen for each patient remains a challenge and is often discovered through a time-consuming process of trial and error. There is a clinical need to augment questionnaire-based diagnostics with objective clinical testing to create a highly individualized therapeutic intervention.

Targeted neurotransmitter testing can help health care practitioners achieve a diagnostic edge beyond the traditional psychological inventory by identifying specific imbalances in neurotransmitter levels. Based on neurotransmitter test results, practitioners can identify specific patterns of neurotransmitter metabolism for each patient, and objectively monitor therapeutic responses during and after intervention. Neurotransmitter testing objectively enhances medical assessment and represents a major advance in the personalization of the treatment of mood disorders.

Available Tests

Neurotransmitters

Tests: GABA, Glu, Gly, DA, Epi, NE, HIST, 5-HT, PEA, DOPAC, HVA, 5-HIAA, NMN, VMA, Trp, Kyn, 3-OHKyn, Tau, Gln, His, N-MeHist, Tyra, KynAc, Xanth, Tyr, Crtn (dried urine)

Neurotransmitters + Saliva Steroids

E2, Pg, T, DS, C

Neurotransmitters + Urine Diurnal Hormones (UDH) I

Free Cortisol x 4, Free Cortisone x 4

Neurotransmitters + UDH II

Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4

Neurotransmitters + UDH III

Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4, NE x 4, Epi x 4

Neurotransmitters + Saliva + UDH III

Testing neurotransmitters in patients with a suspected neurochemical imbalance can help assess individual biochemistry and get to the root of persistent issues such as mood/affective disorders, adrenal dysfunction, addictive behaviors, ADHD, OCD, or PMS/PMDD.

How Neurotransmitters Relay Information Within the Body

The brain orchestrates the delicate interplay between the body and the mind through structural brain units, the neurons, and discharge neurotransmitters. These neurotransmitters provide a communication platform for the brain to fuel internal systems with information. Anything the body senses, feels, hears, smells, touches, or ingests serves as an input that prompts an astoundingly fast response. In the central and peripheral nervous system, neurotransmitters operate as chemical messengers that relay the signal and receive feedback via electrochemical impulses to regulate cognition, memory, emotions, respiration, heart rate and contractility, digestion, metabolism, blood flow and pressure, and hormonal responses. When released from peripheral organs, neurotransmitters can also act as hormones by diffusing to distant sites via the circulation.

Clinical Utility of Urinary Neurotransmitter Analysis

The etiology of mood disorders is profoundly complex and likely encompasses many different types of neurotransmitters, how they achieve balance in the brain and in the gut axis, and how they each interplay with other hormone systems throughout the body. Appropriate balancing of neurotransmitter signals allows the body to maintain equilibrium. When brain and peripheral neurochemistry become unbalanced, the body will struggle to reestablish physiological integrity, which may present in the form of suboptimal psychological well-being. Excessive or deficient levels of certain neurotransmitters in both the brain and in the periphery are associated with a spectrum of neurobiological disorders such as depression, anxiety, insomnia, fatigue, and other unwelcome symptoms. The measurement of specific imbalances may be a very effective neurobiological tool in guiding targeted intervention, aimed at addressing the individual excess or deficiency in question.

Neurotransmitter Functions & Imbalance Profiles

Inhibitory neurotransmitters, at optimal levels, improve mood, promote sleep, and exert overall calming effects on the brain and the body. Research shows that at levels outside of the normal range, inhibitory neurotransmitters are associated with anxiety, depression, irritability, and fatigue.

| Neurotransmitter/Amino Acid | High Levels | Low Levels |
|--|--|---|
| Tryptophan is an amino acid that generates serotonin, melatonin, and kynurenine derivatives. | Tryptophan is high with tryptophan supplementation ⁴ and in some individuals with a high protein diet ⁵ . Clinically, high tryptophan is associated with headaches ⁶ and selective serotonin reuptake inhibitor treatment ⁷ . | Tryptophan excretion is low in patients with autism spectrum disorder ⁸ , and in some individuals with a low protein diet ⁵ . Clinically, low tryptophan is associated with aggression ⁹ , depression ^{10, 11} , impulsivity ¹² , with fructose malabsorption ¹³ , Alzheimer's disease ¹⁴ , Crohn's disease ¹⁵ , multiple sclerosis ¹⁶ , pain disorders like fibromyalgia ¹⁷ , and diabetes ¹⁸ . |
| Serotonin is the "housekeeping" molecule and promotes healthy sleep, regulates appetite, improves mood, supports healthy digestive function and so much more. 5-HIAA is a metabolite. | Serotonin is high in depression ^{19, 20} and with 5-HTP use ²¹ , and is implicated in anxiety, dysbiosis, irritability, and low libido. | Serotonin is decreased in autism spectrum disorder ²² , depression ²³ , with oral contraceptives ^{24, 25} and may be associated with anxiety, low mood, irritability, and sleep disturbances. |
| GABA functions as the major inhibitory neurotransmitter, induces relaxation, and reduces anxiety. | GABA is elevated in sleep apnea ²⁶ , ovarian cancer ²⁷ , and is suspected in anxiety, foggy thinking, and lethargy. | Low GABA is implicated in anxiety, sleep difficulties, adrenal distress, and hypothalamic pituitary adrenal axis feedback dysfunction. Low GABA levels are associated with disorders like ADHD and Tourette syndrome ²⁸ . |
| Glycine plays a dual role as a neurotransmitter and an amino acid that serves as a building block to proteins. | Clinically, high glycine levels are suspected in anxiety and may be associated with insufficient vitamin B status and/or methylation events. | Glycine levels are low in diabetes ²⁹ , hypothyroidism ³⁰ , obesity ³¹ , and after intense exercise ³² . Clinically, low glycine levels are suspected in depression. |
| Taurine improves sleep, relieves anxiety, and has neuroprotective properties. | Taurine excretion is high with taurine supplementation (taurine is an ingredient in many "energy drinks") ³³ , with a high protein diet ³⁴ , after intense exercise ³⁵ , in alcoholism ³⁴ , with adrenal steroid therapy ³⁴ , and in noninvasive bladder cancer ³⁶ . High taurine levels are implicated in autism spectrum disorder ³⁷ , depression ³⁸ , and HIV ³⁹ . | Taurine excretion is low specifically with vegetarian or vegan diets ⁴⁰ and with low protein diets in general ³⁴ . Low taurine levels are implicated in diabetes ⁴¹ , hypertension ⁴¹ , and breast cancer ⁴² . |

Excitatory neurotransmitters, at optimal levels, decrease fatigue, improve energy levels, and promote mental clarity. Research shows that at levels outside of the normal range, excitatory neurotransmitters are implicated in oxidative stress and sleep disturbances, and can contribute to feelings of stress and overwhelm.

| Neurotransmitter/Amino Acid | High Levels | Low Levels |
|--|--|--|
| <p>Glutamine improves immune function, balances ammonia in the body, contributes to biosynthesis of proteins, amino acids, nucleic acids, glutathione, glutamate, and GABA.</p> | <p>Research on urinary high glutamine levels is scarce; however, high circulating levels of glutamine are associated with bipolar depression⁴³.</p> | <p>Low circulating glutamine levels are reported after intense exercise⁴⁴, in overtraining syndrome⁴⁵, in diabetes⁴⁶, depression⁴⁷, and in autism spectrum disorder^{37,48}. Low glutamine levels are associated with high oxidative stress⁴⁹.</p> |
| <p>Glutamate functions as the major excitatory neurotransmitter and metabolic fuel throughout the body.</p> | <p>Glutamate is high in celiac disease⁵⁰ and hyperthyroidism⁵¹. Clinically, high glutamate is suspected in anxiety, autism spectrum disorder, depression, and sleep issues.</p> | <p>Glutamate is low in patients with migraines⁵². Clinically, low glutamate is implicated in depression, chronic fatigue, lack of concentration, low energy levels, and sleep disturbances.</p> |
| <p>Histidine ameliorates fatigue, promotes clear thinking and concentration, reduces appetite, decreases anxiety, improves sleep and glucose homeostasis, and gives rise to histamine.</p> | <p>Histidine excretion is high with histidine administration⁵³, in histidinemia⁵⁴, and in diabetic nephropathy⁵⁵.</p> | <p>Urinary histidine is low in folate deficiency⁵⁶. Low histidine is also implicated in obesity⁵⁷, fatigue with multiple sclerosis⁵⁸, rheumatoid arthritis⁵⁹, obstructive pulmonary disease⁶⁰, and chronic kidney disease⁶¹.</p> |
| <p>Histamine is a neurotransmitter and immunomodulator.</p> | <p>Histamine is high in cystitis⁶², flushing disorder⁶³, food allergies⁶⁴, polycythemia⁶⁵, and pregnancy⁶⁶. High histamine may implicate allergies, depression, headaches, migraines, OCD, and sleep difficulties.</p> | <p>Low histamine is associated with fatigue, low productivity, mild depression, tension headaches, and weight gain.</p> |
| <p>N-methylhistamine is a major metabolite of the neurotransmitter histamine.</p> | <p>N-methylhistamine excretion is elevated with a high protein diet⁶⁷, in gastrointestinal food allergies⁶⁴, in irritable bowel disease⁶⁸, in colitis⁶⁹, in histidinemia⁷⁰, in chronic urticaria⁷¹, in angioedema⁷¹, and with interstitial cystitis⁶².</p> | <p>N-methylhistamine is low in depression⁷², in lupus⁷³, in focal segmental glomerulosclerosis⁷³, and in idiopathic nephrotic syndrome⁷³. Additionally, N-methylhistamine levels can be low in individuals with an alteration in the histamine N-methyltransferase gene.</p> |
| <p>PEA serves as a biomarker for ADHD.</p> | <p>PEA is elevated in individuals with bipolar major affective disorder⁷⁴, anxiety and insomnia⁷⁵, phenylketonuria⁷⁶ and with methylphenidate treatment⁷⁷.</p> | <p>PEA is low in patients with autism spectrum disorder⁷⁸, ADHD^{77, 79, 80}, depression⁸¹, and inattentiveness^{82, 83}.</p> |
| <p>Tyrosine enhances cognitive performance, energy, and alertness, and improves memory after sleep deprivation.</p> | <p>Urinary tyrosine is high in hyperthyroidism⁵¹ and in diabetes⁸⁴.</p> | <p>Tyrosine excretion is low in depression⁸⁵, in post-stroke depression⁸⁶, and in chronic kidney disease⁸⁴.</p> |
| <p>Tyramine is a trace amine derived from tyrosine, found naturally in food. Tyramine has vasoconstrictive properties and can increase blood pressure and trigger migraines.</p> | <p>High tyramine ingestion from food that has been aged, cured, smoked or fermented, can trigger migraines⁸⁷.</p> | <p>Clinical utility has not been established at this time.</p> |
| <p>Dopamine serves as the reward and pleasure center in the brain, and messenger of the sympathetic nervous system in the periphery. DOPAC and HVA are metabolites.</p> | <p>High dopamine is reported in patients with high anxiety⁸⁸, stress⁸⁹, paroxysmal hypertension⁹⁰, primary aldosteronism⁹¹, PTSD⁹², and mercury toxicity⁹³.</p> | <p>Dopamine is low in Alzheimer's disease⁹⁴, anorexia nervosa⁹⁵, fibromyalgia⁹⁶, hypertension⁹⁷, periodic limb movement disorder⁹⁸, sleep disturbances⁹⁹, hypoadrenergic orthostatic hypotension¹⁰⁰.</p> |
| <p>Epinephrine and norepinephrine regulate the "fight or flight" response. Normetanephrine is a norepinephrine metabolite. VMA is a norepinephrine and epinephrine metabolite.</p> | <p>Epinephrine and norepinephrine levels are high in patients with anxiety^{101, 102}, ADHD^{82, 83}, bipolar disorder¹⁰³, depression¹⁰⁴, hyperglycemia¹⁰⁵, sleep apnea²⁶, PTSD⁹², and stress^{106, 107}.</p> | <p>Epinephrine and norepinephrine levels are low in Alzheimer's disease⁹⁴, metabolic syndrome¹⁰⁸, and obesity¹⁰⁹.</p> |

Inflammation is a risk factor contributing to the development of a wide range of mental health conditions. Inflammatory processes in the brain and the body can exacerbate existing issues or give rise to new ones. Assaying the levels of inflammatory neuromodulators can help develop new personalized treatment strategies aimed at reducing inflammation and easing the burden of unwanted symptoms for a given patient.

| Neurotransmitter/Amino Acid | High Levels | Low Levels |
|---|---|---|
| Kynurenine is a central metabolite of the amino acid tryptophan with vasodilatory properties. | Kynurenine is high with tryptophan administration ⁴ , hydrocortisone treatment ¹¹⁰ , metabolic syndrome ¹¹¹ , with major coronary events ¹¹² , and in women in pregnancy ¹¹⁰ . High kynurenine levels have been implicated in disorders like irritable bowel syndrome ¹¹³ , lupus ¹¹⁴ , Crohn's disease ¹⁵ , and Alzheimer's Disease ¹¹⁵ . Additionally, caffeine ¹¹⁶ and regular black tea ¹¹⁷ consumption can elevate kynurenine levels as well. | Urinary kynurenine levels are low in autism spectrum disorder ²² . Low kynurenine levels have been implicated in aggression ⁹ , depression ⁴⁷ , and headaches ⁶ . |
| Kynurenic acid , a neuroactive metabolite produced from kynurenine, is regarded to be neuroprotective unless in excess amounts. | Kynurenic acid levels are high with tryptophan administration ⁴ and metabolic syndrome ¹¹¹ . High kynurenic acid levels are implicated in schizophrenia ¹¹⁸ . | Research shows that kynurenic acid is low with a low protein diet ⁵ and in autism spectrum disorder ²² . Low kynurenic acid is implicated in depression ¹¹⁹ , headaches ⁶ , bipolar disorder ¹²⁰ , and Alzheimer's disease ¹⁴ . |
| 3-Hydroxykynurenine is a metabolic intermediate of the kynurenine pathway that elicits neurotoxic effects. | Urinary levels of 3-Hydroxykynurenine are high with hydrocortisone treatment and in women in pregnancy ¹¹⁰ . High 3-Hydroxykynurenine is implicated in vitamin B6 deficiency ¹²¹ and Alzheimer's disease ¹²² . | Low 3-Hydroxykynurenine levels are implicated in headaches ⁶ , in males in Alzheimer's disease ¹¹⁵ , and schizophrenia ¹¹⁸ . |
| Xanthurenic acid is a metabolite of the kynurenine pathway, formed from 3-Hydroxykynurenine and serves as an indirect marker of vitamin B6 status. | Research shows that xanthurenic acid is high with vitamin B6 deficiency ¹²³ , with hydrocortisone treatment ¹¹⁰ , rheumatoid arthritis ¹²³ , metabolic syndrome ¹¹¹ , autism spectrum disorder ²² , and in women in pregnancy ¹¹⁰ . | Clinical utility has not been established at this time. |

Clinical Validity of Urinary Neurotransmitter Assessment

The importance of effectively assessing and treating mood disorders cannot be overstated. Objectivity is a key element to the therapeutic approach to mood disorders. Currently, the standard of care dictates a trial-and-error pharmaceutical approach is taken with each patient based on both self and clinician assessments. However, without information yielded from objective clinical testing, selection of the most effective treatment for each particular patient with a mood disorder continues to be a challenge. While this may prove effective for some patients, the potential for harm during those interim treatment failures is a real concern for clinicians and patients alike.

Urinary neurotransmitter testing is performed with the goal that therapeutic interventions may be introduced to address, alleviate, and improve a patient's well-being and has a breadth of data to support the efficacy of the test in clinical practice (see above). Evaluation of neurotransmitter levels in urine provides valuable information about the heterogeneity of patient biochemistry, epigenetics, and how the body functions as a whole.

Although the urine test is not a direct measure of brain neurotransmitter levels, it provides relevant information with respect to neurotransmitter regulation in the brain, which can be altered by treatment. The levels in urine often parallel levels in the central and peripheral nervous systems, and the test may therefore assist in the selection of patients with mood issues who might respond to specific pharmaceutical or over-the-counter treatment interventions^{124, 125}. In other words, the test provides a means to glean a functional systemic perspective regarding each neurotransmitter in the periphery, which ultimately operates under the control of the brain.

How do neurotransmitters end up in urine? Some neurotransmitters are produced in the brain and transported across the blood-brain barrier into blood, and others are produced in the periphery (e.g., norepinephrine and epinephrine). Nephrons, the functional units

of the kidney, filter circulating neurotransmitters or their precursors from the blood into urine³⁶. For some neurotransmitters, urinary measurements correlate with levels in the central nervous system (e.g., glutamate, PEA), and for others, what ends up in urine is only reflective of peripheral biosynthesis (e.g., serotonin, GABA, dopamine, norepinephrine, epinephrine). Regardless of production origin, neurotransmitter excretion reflects the overall systemic neurotransmitter tone, dysregulation of which may contribute to disease states. The ability to identify abnormality across specific areas of the catecholamine and PEA, GABA/glutamate, serotonin, histamine, and glycine pathways allows health care providers to develop a tailored treatment plan to the specific areas associated with imbalance.

Dried Urine - A Convenient Testing Option

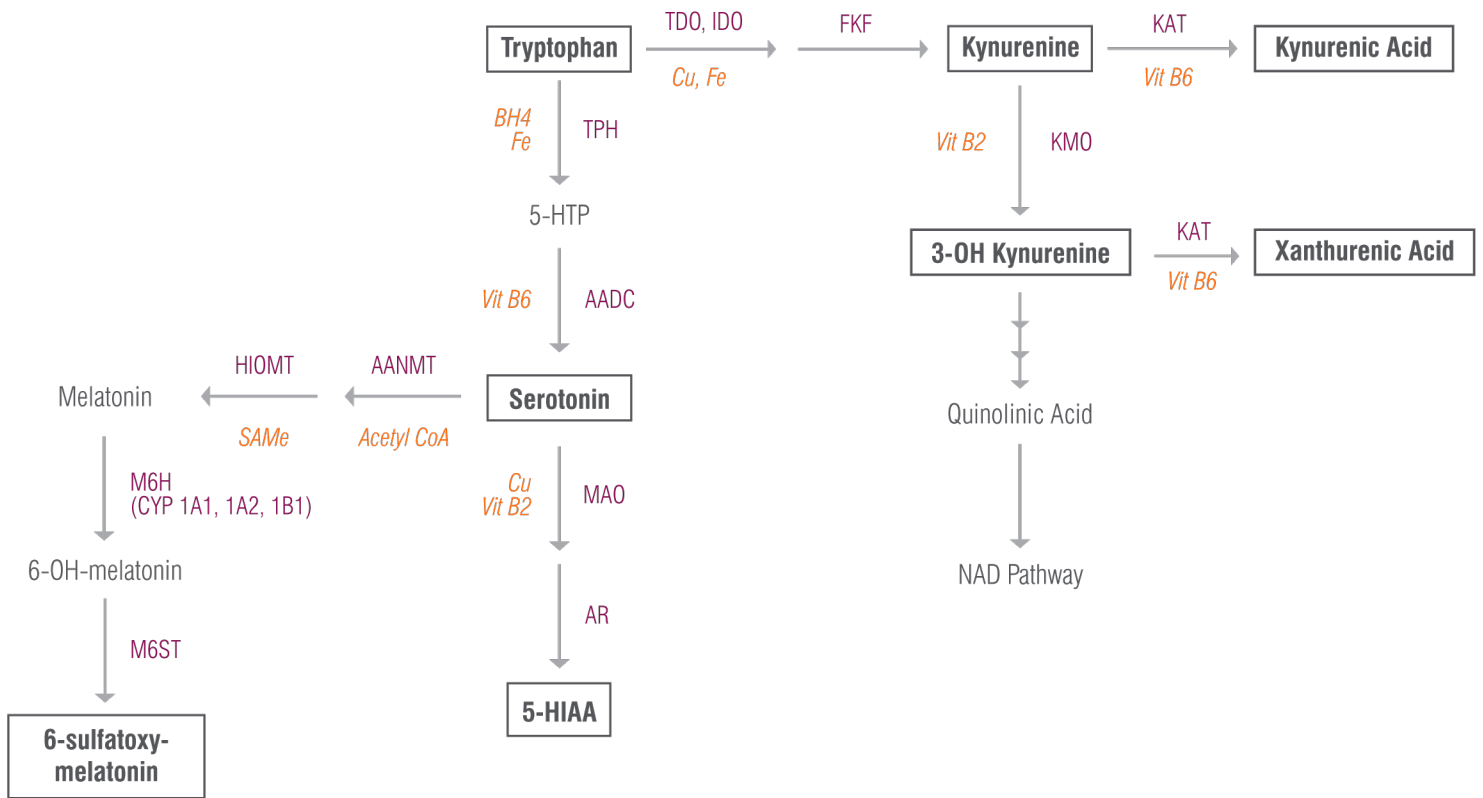
The nature of urine collection is noninvasive and preferable over the traditional invasive collection approaches such as measurement of cerebrospinal fluid. Even with liquid urine collection the patient experiences the enormous hassle of collecting all urine voids over a 24-hour period into a large jug. To circumvent this inconvenience some labs have settled for collecting only the 2nd void, limiting neurotransmitter results to a single morning time point snapshot. ZRT Laboratory offers an alternative to the liquid urine collection method by offering a simple and convenient collection of four separate urine samples at specific time points throughout the day – 1st morning, 2nd morning (approximately two hours after the first collection), early evening, and bedtime. Urine is collected onto filter strips by urinating directly on the strip or by dipping the filter card in a cup containing the collected urine. The urine cards are then allowed to dry overnight and sent to ZRT for testing. The convenience of the collection method warrants patient compliance and ease of incorporation into clinical practice.

Considerations

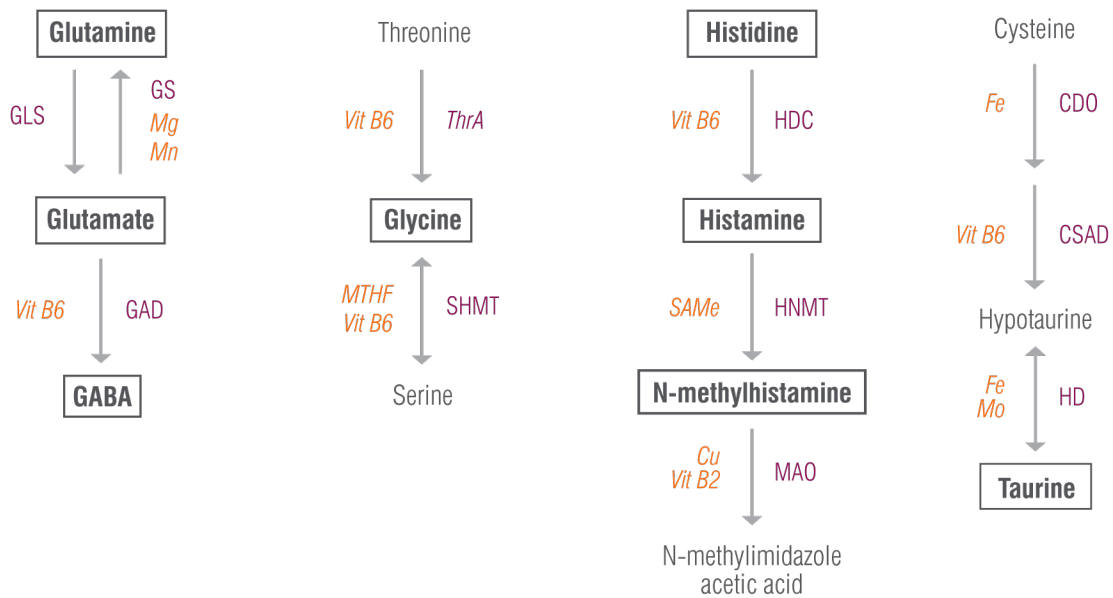
- The neurotransmitter test assumes proper kidney function. Neurotransmitter levels are reported in µg/g creatinine, where creatinine is measured from the same sample. This test should not be used in individuals with compromised renal function.
- The sample can become very dilute due to increased fluid consumption during the day. Therefore, on the day of testing, individuals are advised to restrict their liquid intake to normal consumption.
- On the day of testing, individuals are asked to refrain from consuming alcohol, nicotine, pineapple, and walnuts as they may interfere with testing.

Neurotransmitter Cascades

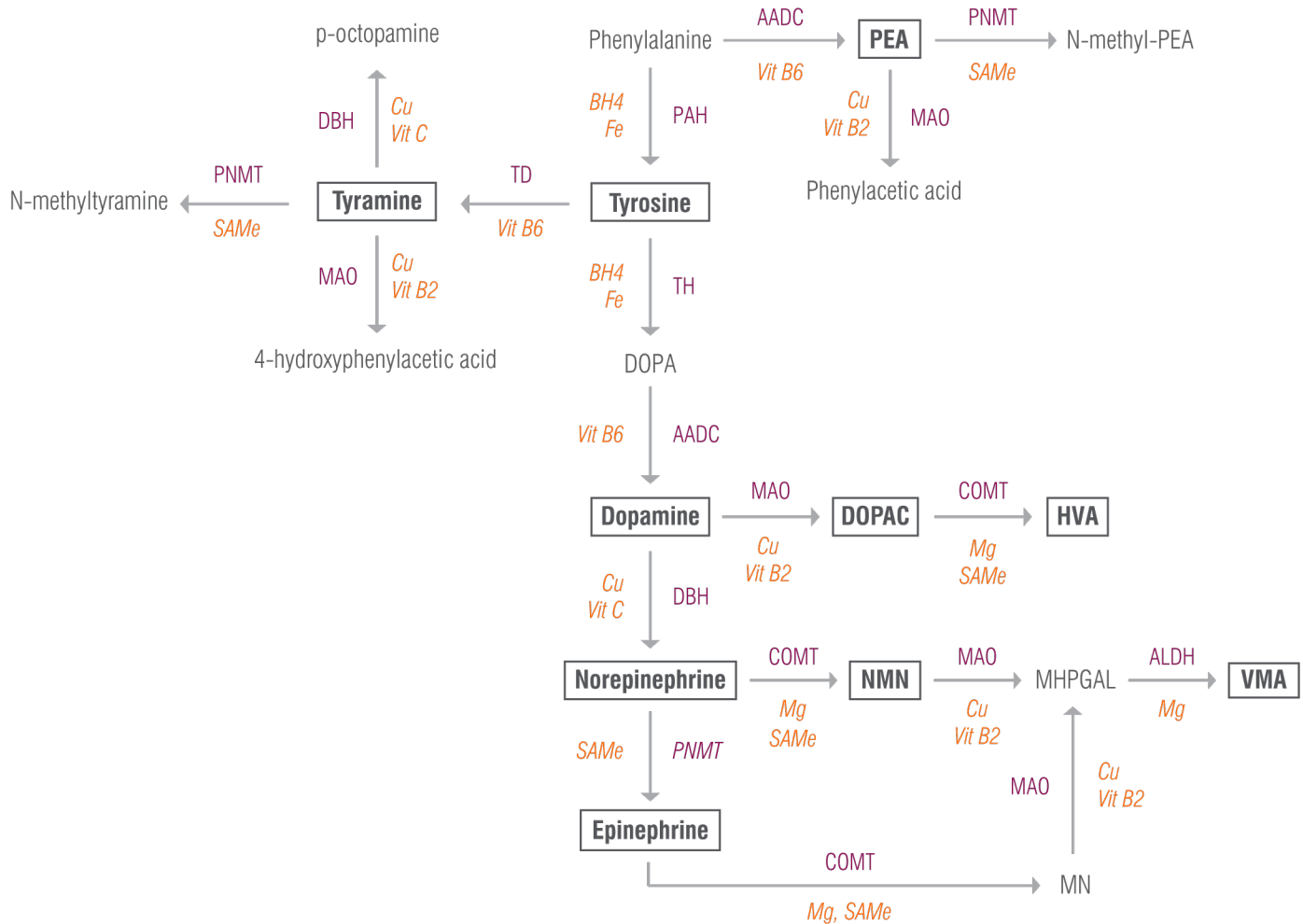
Tryptophan & Metabolites



Glutamate/GABA, Glycine, Histamine & Taurine



Catecholamines & Metabolites



Abbreviations & Key

Neurotransmitters & Metabolites:

| | |
|---------------|-------------------------------|
| HVA | homovanillic acid |
| NMN | normetanephrine |
| PEA | phenethylamine |
| VMA | vanillylmandelic acid |
| 5-HIAA | 5-hydroxyindole 3-acetic acid |

Cofactors:

| | |
|-------------|------------------------|
| BH4 | tetrahydrobiopterin |
| Cu | copper |
| Fe | iron |
| Mg | magnesium |
| Mn | manganese |
| Mo | molybdenum |
| MTHF | methyltetrahydrofolate |
| SAMe | S-adenosyl methionine |

Enzymes:

| | |
|--------------|-------------------------------------|
| AADC | aromatic L-amino acid decarboxylase |
| AANMT | arylalkylamine N-methyltransferase |
| ALDH | aldehyde dehydrogenase |
| AR | aldehyde reductase |
| CDO | cysteine dioxygenase |
| COMT | catechol-O-methyltransferase |

| | |
|--------------|--|
| CSAD | cysteinesulfinic acid decarboxylase |
| DBH | dopamine beta hydroxylase |
| FKF | N-Formyl kynurenine formamidase |
| GAD | glutamate decarboxylase |
| GLS | glutaminase |
| GS | glutamine synthetase |
| HD | hypotaurine dehydrogenase |
| HDC | histidine decarboxylase |
| HIOMT | hydroxyindole-O-methyltransferase |
| HNMT | histamine N-methyltransferase |
| IDO | indoleamine 2,3-dioxygenase |
| KAT | kynurenine aminotransferase |
| KMO | kynurenine hydroxylase/monooxygenase |
| MAO | monoamine oxidase |
| M6H | melatonin 6 hydroxylase |
| M6ST | melatonin 6 sulfotransferase |
| PAH | phenylalanine hydroxylase |
| PNMT | phenylethanolamine N-methyltransferase |
| SHMT | serine hydroxymethyltransferase |
| TD | tyrosine decarboxylase |
| TDO | tryptophan 2,3-dioxygenase |
| TH | tyrosine hydroxylase |
| ThrA | threonine aldolase |
| TPH | tryptophan hydroxylase |

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