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 nearly 7% of American adults live with major depression and approximately 18% live with anxiety disorders such as panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, generalized anxiety disorder, and phobias[1]. Mood disorders are the third most common cause of hospitalization in the U.S. for individuals aged 18 to 44[1]. The top-prescribed and top-selling prescription drugs in the U.S. in 2014 included antipsychotics, antidepressants, and attention-deficit disorder (ADHD) drugs[2].

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 and numerous patients can also develop mental health conditions that seem resistant to treatment. 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

NeuroAdvanced Profile

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)

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.

Add-On Options (dried urine, unless noted)

- Saliva Hormones: E2, Pg, T, DS, C
- Urine Hormones: E2, Pregnanediol, Allopregnanolone, Androstenedione, T, Epi-T, DHT, DHEA, 5α,3α-Androstanediol
- Diurnal Cortisol: Free Cortisol x 4, Free Cortisone x 4
- Diurnal Cortisol & Melatonin: Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4
- Diurnal Cortisol, Norepinephrine & Epinephrine: Free Cortisol x 4, Free Cortisone x 4, NE x 4, Epi x 4
- Diurnal Cortisol, Melatonin, Norepinephrine & Epinephrine: Free Cortisol x 4, Free Cortisone x 4, Melatonin (MT6s) x 4, NE x 4, Epi x 4
- Urine Elements: Iodine, Selenium, Bromine, Lithium, Arsenic, Cadmium, Mercury

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
Glutamine improves immune function, balances ammonia in the body, contributes to biosynthesis of proteins, amino acids, nucleic acids, glutathione, glutamate, and GABA.	Research on urinary high glutamine levels is scarce; however, high circulating levels of glutamine are associated with bipolar depression[43].	Low circulating glutamine levels are reported after intense exercise[44], in overtraining syndrome[45], in diabetes[46], depression[47], and in autism spectrum disorder[37,48]. Low glutamine levels are associated with high oxidative stress[49].
Glutamate functions as the major excitatory neurotransmitter and metabolic fuel throughout the body.	Glutamate is high in celiac disease[50] and hyperthyroidism[51]. Clinically, high glutamate is suspected in anxiety, autism spectrum disorder, depression, and sleep issues.	Glutamate is low in patients with migraines[52]. Clinically, low glutamate is implicated in depression, chronic fatigue, lack of concentration, low energy levels, and sleep disturbances.
Histidine ameliorates fatigue, promotes clear thinking and concentration, reduces appetite, decreases anxiety, improves sleep and glucose homeostasis, and gives rise to histamine.	Histidine excretion is high with histidine administration[53], in histidinemia[54], and in diabetic nephropathy[55].	Urinary histidine is low in folate deficiency[56]. Low histidine is also implicated in obesity[57], fatigue with multiple sclerosis[58], rheumatoid arthritis[59], obstructive pulmonary disease[60], and chronic kidney disease[61].
Histamine is a neurotransmitter and immunomodulator.	Histamine is high in cystitis[62], flushing disorder[63], food allergies[64], polycythemia[65], and pregnancy[66]. High histamine may implicate allergies, depression, headaches, migraines, OCD, and sleep difficulties.	Low histamine is associated with fatigue, low productivity, mild depression, tension headaches, and weight gain.
N-methylhistamine is a major metabolite of the neurotransmitter histamine.	N-methylhistamine excretion is elevated with a high protein diet[67], in gastrointestinal food allergies[64], in irritable bowel disease[68], in colitis[69], in histidinemia[70], in chronic urticaria[71], in angioedema[71], and with interstitial cystitis[62].	N-methylhistamine is low in depression[72], in lupus[73], in focal segmental glomerulosclerosis[73], and in idiopathic nephrotic syndrome[73]. Additionally, N-methylhistamine levels can be low in individuals with an alteration in the histamine N-methyltransferase gene.
PEA serves as a biomarker for ADHD.	PEA is elevated in individuals with bipolar major affective disorder[74], anxiety and insomnia[75], phenylketonuria[76] and with methylphenidate treatment[77].	PEA is low in patients with autism spectrum disorder[78], ADHD[77, 79, 80], depression[81], and inattentiveness[82, 83].
Tyrosine enhances cognitive performance, energy, and alertness, and improves memory after sleep deprivation.	Urinary tyrosine is high in hyperthyroidism[51] and in diabetes[84].	Tyrosine excretion is low in depression[85], in post-stroke depression[86], and in chronic kidney disease[84].
Tyramine is a trace amine derived from tyrosine, found naturally in food. Tyramine has vasoconstrictive properties and can increase blood pressure and trigger migraines.	High tyramine ingestion from food that has been aged, cured, smoked or fermented, can trigger migraines[87].	Clinical utility has not been established at this time.
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.	High dopamine is reported in patients with high anxiety[88], stress[89], paroxysmal hypertension[90], primary aldosteronism[91], PTSD[92], and mercury toxicity[93].	Dopamine is low in Alzheimer's disease[94], anorexia nervosa[95], fibromyalgia[96], hypertension[97], periodic limb movement disorder[98], sleep disturbances[99], hypoadrenergic orthostatic hypotension[100].
Epinephrine and **norepinephrine** regulate the "fight or flight" response. **Normetanephrine** is a norepinephrine metabolite. VMA is a norepinephrine and epinephrine metabolite.	Epinephrine and norepinephrine levels are high in patients with anxiety[101, 102], ADHD[82, 83], bipolar disorder[103], depression[104], hyperglycemia[105], sleep apnea[26], PTSD[92], and stress[106, 107].	Epinephrine and norepinephrine levels are low in Alzheimer's disease[94], metabolic syndrome[108], and obesity[109].

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 urine[36]. 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

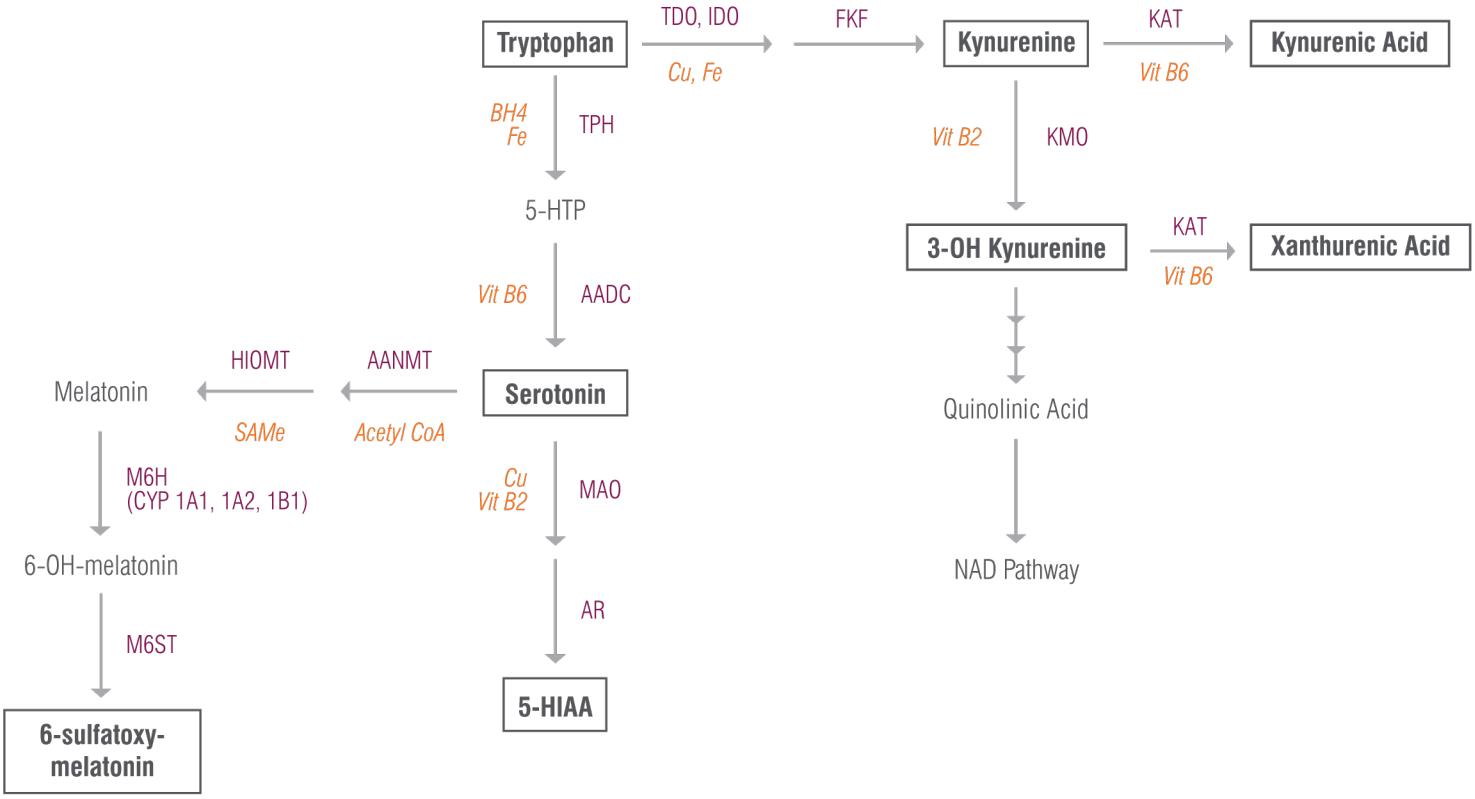
The nature of urine collection is noninvasive and preferable over the traditional invasive collection approaches such as measurement of cerebrospinal fluid. Even with liquid urine collection the patient experiences the enormous hassle of collecting all urine voids over a 24-hour period into a large jug. 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

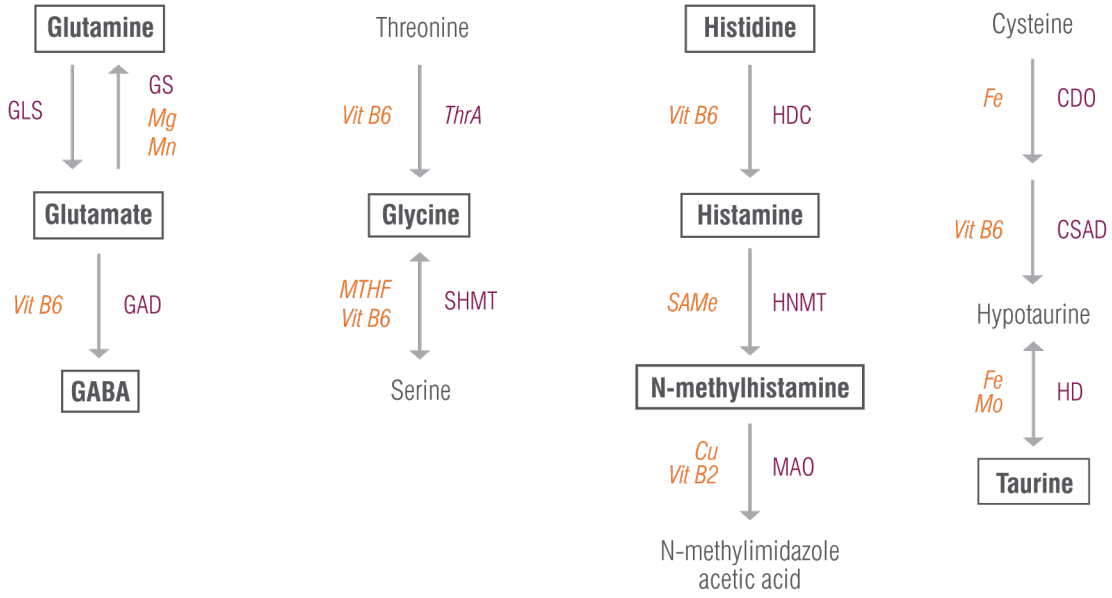
- The neurotransmitter test assumes proper kidney function. Neurotransmitter levels are reported in µg/g creatinine, where creatinine is measured from the same sample. This test should not be used in individuals with compromised renal function.
- The sample can become very dilute due to increased fluid 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

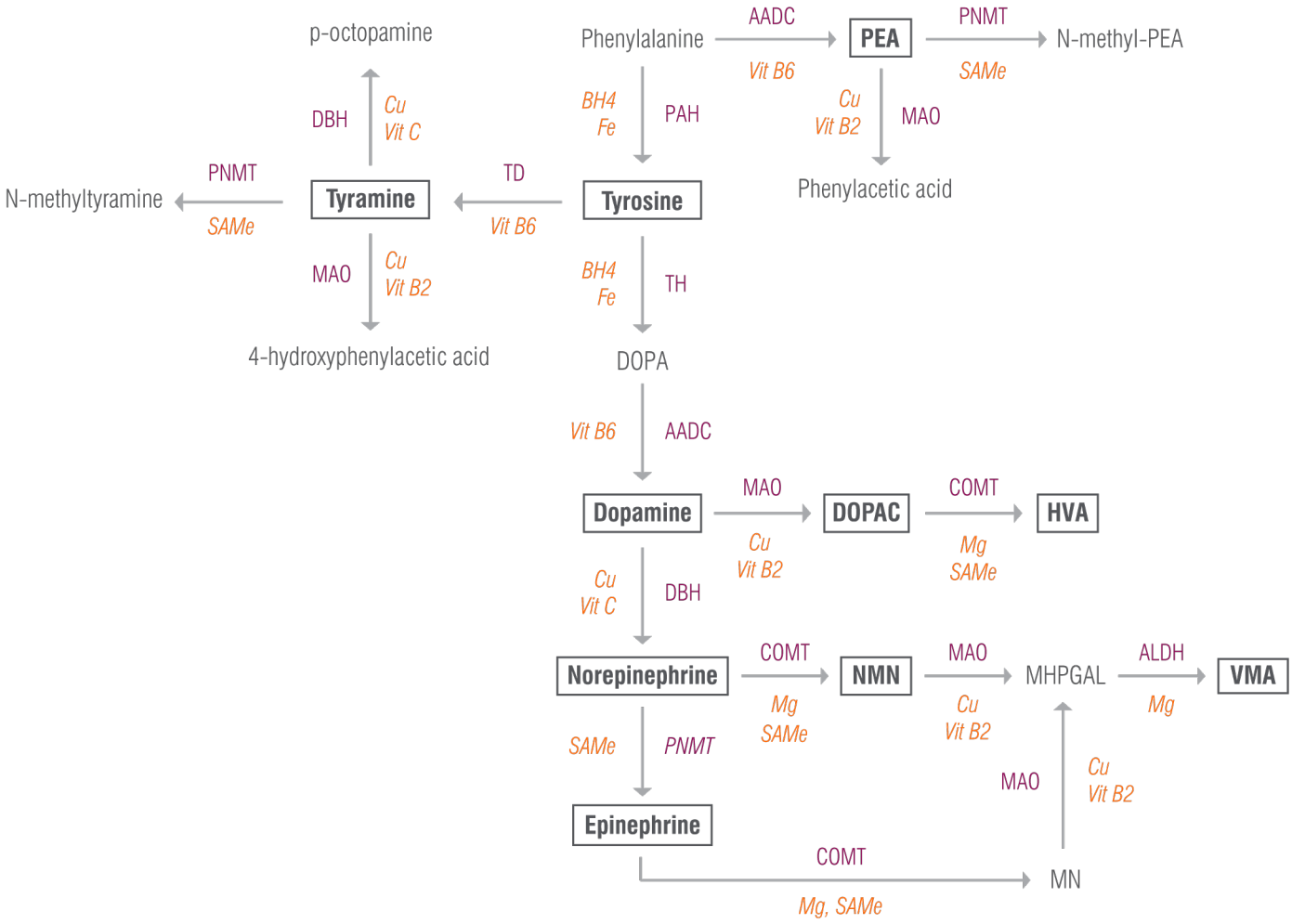
Tryptophan & Metabolites



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

References

1. National Alliance on Mental Illness. Facts and Numbers. 2013.
2. Brooks M. Top 100 most prescribed, top-selling drugs. Medscape. 2014.
3. Eby GA III, Eby KL. Magnesium for treatment-resistant depression: a review and hypothesis. Med Hypotheses. 2010;74(4):649-660.
4. Michael AF, Drummond KN, Doeden D, et al. Tryptophan metabolism in man. J Clin Invest. 1964;43(9):1730-1746.
5. Poesen R, Mutsaers HA, Windey K, et al. The influence of dietary protein intake on mammalian tryptophan and phenolic metabolites. PLoS One. 2015;10(10):e0140820.
6. Curto M, Lionetto L, Negro A, et al. Altered serum levels of kynurenine metabolites in patients affected by cluster headache. J Headache Pain. 2015;17(1):27.
7. Mackay GM, Forrest CM, Christofides J, et al. Kynurenine metabolites and inflammation markers in depressed patients treated with fluoxetine or counselling. Clin Exp Pharmacol Physiol. 2009;36(4):425-435.
8. Kaluzna-Czaplinska J, Michalska M, Rynkowski J. Determination of tryptophan in urine of autistic and healthy children by gas chromatography/mass spectrometry. Med Sci Monit. 2010;16(10):CR488-92.
9. Comai S, Bertazzo A, Vachon J, et al. Tryptophan via serotonin/kynurenine pathways abnormalities in a large cohort of aggressive inmates: markers for aggression. Prog Neuropsychopharmacol Biol Psychiatry. 2016;70:8-16.
10. Maes M, Wauters A, Verkerk R, et al. Lower serum L-tryptophan availability in depression as a marker of a more generalized disorder in protein metabolism. Neuropsychopharmacology. 1996;15(3):243-251.
11. Messaoud A, Mensi R, Douki W, et al. Reduced peripheral availability of tryptophan and increased activation of the kynurenine pathway and cortisol correlate with major depression and suicide. World J Biol Psychiatry. 2019;20(9):703-711.
12. Walderhaug E, Lunde H, Nordvik JE, et al. Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. Psychopharmacology. 2002;164(4):385-391.
13. Ledochowski M, Widner B, Murr C, et al. Fructose malabsorption is associated with decreased plasma tryptophan. Scand J Gastroenterol. 2001;36(4):367-371.
14. Gulaj E, Pawlak K, Bien B, et al. Kynurenine and its metabolites in Alzheimer's disease patients. Adv Med Sci. 2010;55(2):204-211.
15. Gupta NK, Thaker AI, Kanuri N, et al. Serum analysis of tryptophan catabolism pathway: correlation with Crohn's disease activity. Inflamm Bowel Dis. 2012;18(7):1214-1220.
16. Monaco F, Fumero S, Mondino A, et al. Plasma and cerebrospinal fluid tryptophan in multiple sclerosis and degenerative diseases. J Neurol Neurosurg Psychiatry. 1979;42(7):640-641.
17. Yunus MB, Dailey JW, Aldag JC, et al. Plasma tryptophan and other amino acids in primary fibromyalgia: a controlled study. J Rheumatol. 2992;19(1):90-94.
18. Herrera R, Manjarrez G, Nishimura E, et al. Serotonin-related tryptophan in children with insulin-dependent diabetes. Pediatr Neurol. 2003;28(1):20-23.
19. Mitani H, Shirayama Y, Yamada T, et al. Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(3):531-534.
20. Audhya T, Adams JB, Johansen L. Correlation of serotonin levels in CSF, platelets, plasma, and urine. Biochim Biophys Acta. 2012;1820(10):1496-1501.
21. Joy T, Walsh G, Tokmakejian S, et al. Increase of urinary 5-hydroxyindoleacetic acid excretion but not serum chromogranin A following over-the-counter 5-hydroxytryptophan intake. Can. J Gastroenterol. 2008;22(1):49-53.
22. Gevi F, Zolla L, Gabriele S, et al. Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism. Mol Autism. 2016;7:47.
23. Nichkova MI, Huisman H, Wynveen PM, et al. Evaluation of a novel ELISA for serotonin: urinary serotonin as a potential biomarker for depression. Anal Bioanal Chem. 2012;402(4):1593-1600.
24. Shaarawy M, Fayad M, Nagui AR, et al. Serotonin metabolism and depression in oral contraceptive users. Contraception. 1982;26(2):193-204.
25. Var C, Keller S, Tung R, et al. Supplementation with vitamin B6 reduces side effects in Cambodian women using oral contraception. Nutrients. 2014;6(9):3353-3362.
26. Kheirandish-Gozal L, McManus CJ, Kellermann GH, et al. Urinary neurotransmitters are selectively altered in children with obstructive sleep apnea and predict cognitive morbidity. Chest. 2013;143(6):1576-1583.
27. Nicholson-Guthrie CS, Guthrie GD, Sutton GP, et al. Urine GABA levels in ovarian cancer patients: elevated GABA in malignancy. Cancer Lett. 2001;162(1):27-30.
28. Perlmutter D. Brain Maker: The Power of Gut Microbes to Heal and Protect Your Brain for Life. Unabridged Edition. New York, NY. Little, Brown Spark. 2015.
29. Sasaki M, Sato K, Maruhama Y. Rapid changes in urinary serine and branched-chain amino acid excretion among diabetic patients during insulin treatment. Diabetes Res Clin Pract. 1988;5(3):219-224.
30. Friedrich N, Pietzner M, Cannet C, et al. Urinary metabolomics reveals glycemic and coffee associated signatures of thyroid function in two population-based cohorts. PLoS One. 2017;12(3):e0173078.
31. Ahmad MS, Alsaleh M, Kimhofer T, et al. Metabolic phenotype of obesity in a Saudi population. J Proteome Res. 2017;16(2): 635-644.
32. Corsetti R, Barassi A, Perego S, et al. Changes in urinary amino acids excretion in relationship with muscle activity markers over a professional cycling stage race: in search of fatigue markers. Amino Acids. 2016;48(1):183-192.
33. Gao R, Bae MA, Han SH, et al. Effects of dietary taurine supplementation on blood and urine taurine concentrations in the elderly women with dementia. Adv Exp Med Biol. 2019;1155:231-238.

References (cont'd.)

34. Turner FP, Brum VC, Paquette WW Jr, et al. The urinary excretion of free taurine in acute and chronic disease, following surgical trauma, and in patients with acute alcoholism. J Surg Res. 1964;4(9):423-431.
35. Cuisinier C, Ward RJ, Francaux M, et al. Changes in plasma and urinary taurine and amino acids in runners immediately and 24h after a marathon. Amino Acids. 2001;20(1):13-23.
36. Srivastava S, Roy S, Singh S, et al. Taurine - a possible fingerprint biomarker in non-muscle invasive bladder cancer: A pilot study by 1H NMR spectroscopy. Cancer Biomark. 2010;6(1):11-20.
37. Moreno-Fuenmayor H, Borjas L, Arrieta A, et al. Plasma excitatory amino acids in autism. Invest Clin. 1996;37(2):113-128.
38. Altamura C, Maes M, Dai L, et al. Plasma concentrations of excitatory amino acids, serine, glycine, taurine and histidine in major depression. Eur Neuropsychopharmacol. 1995;5 Suppl:71-75.
39. Hortin GL, Landt M, Powderly WG. Changes in plasma amino acid concentrations in response to HIV-1 infection. Clin Chem. 1994;40(5):785-789.
40. Rana SK, Sanders TA. Taurine concentrations in the diet, plasma, urine and breast milk of vegans compared with omnivores. 1986;56(1):17-27.
41. Sak D, Erdenen F, Müderrisoglu C, et al. The relationship between plasma taurine levels and diabetic complications in patients with type 2 diabetes mellitus. Biomolecules. 2019;9(3):96.
42. El Agouza IM, Eissa SS, El Houseini MM, et al. Taurine: a novel tumor marker for enhanced detection of breast cancer among female patients. Angiogenesis. 2011;14(3):321-330.
43. Pålsson E, Jakobsson J, Södersten K, et al. Markers of glutamate signaling in cerebrospinal fluid and serum from patients with bipolar disorder and healthy controls. Eur Neuropsychopharmacol. 2015;25(1):133-140.
44. Keast D, Arstein D, Harper W, et al. Depression of plasma glutamine concentration after exercise stress and its possible influence on the immune system. Med J Aust. 1995;162(1):15-18.
45. Rowbottom DG, Keast D, Morton AR. The emerging role of glutamine as an indicator of exercise stress and overtraining. Sports Med. 1996;21(2):80-97.
46. Liu X, Zheng Y, Guasch-Ferré M, et al. High plasma glutamate and low glutamine-to-glutamate ratio are associated with type 2 diabetes: Case-cohort study within the PREDIMED trial. Nutr Metab Cardiovasc Dis. 2019;29(10):1040-1049.
47. Umehara H, Numata S, Watanabe SY, et al. Altered KYN/TRP, Gln/Glu, and Met/methionine sulfoxide ratios in the blood plasma of medication-free patients with major depressive disorder. Sci Rep. 2017;7(1):4855.
48. Rolf LH, Haarmann FY, Grotemeyer KH, et al. Serotonin and amino acid content in platelets of autistic children. Acta Psychiatr Scand. 1993;87(5):312-316.
49. Pietzner M, Kaul A, Henning AK, et al. Comprehensive metabolic profiling of chronic low-grade inflammation among generally healthy individuals. BMC Med. 2017;15(1):210.
50. Marko AM, Gerrard JW, Buchan DJ. Glutamic acid derivatives in adult celiac disease. II. Urinary total glutamic acid excretion. Can Med Assoc J. 1960;83(25):1324-1325.
51. Bélanger R, Chandramohan N, Misbin R, et al. Tyrosine and glutamic acid in plasma and urine of patients with altered thyroid function. Metabolism. 1972;21(9):855-865.
52. Ragginer C, Lechner A, Bernecker C, et al. Reduced urinary glutamate levels are associated with the frequency of migraine attacks in females. Eur J Neurol. 2012;19(8):1146-1150.
53. Du S, Sun S, Liu L, et al. Effects of histidine supplementation on global aerum and urine^{1} H NMR-based metabolomics and serum amino acid profiles in obese women from a randomized controlled study. J Proteome Res. 2017;16(6):2221-2230.
54. Auerbach VH, DiGeorge AM, Baldridge RC, et al. Histidinemia: A deficiency in histidase resulting in the urinary excretion of histidine and of imidazolepyruvic acid. J Pediatr. 1962;60(4):487-497.
55. Shao M, Lu H, Yang M, et al. Serum and urine metabolomics reveal potential biomarkers of T2DM patients with nephropathy. Ann Transl Med. 2020;8(5):199.
56. Cooperman JM, Lopez R. The role of histidine in the anemia of folate deficiency. Exp Biol Med. (Maywood). 2002;227(11):998-1000.
57. Niu YC, Feng RN, Hou Y, et al. Histidine and arginine are associated with inflammation and oxidative stress in obese women. Br J Nutr. 2012;108(1):57-61.
58. Loy BD, Fling BW, Sage KM, et al. Serum histidine is lower in fatigued women with multiple aclerosis. Fatigue. 2019;7(2):69-80.
59. Gerber DA. Low free serum histidine concentration in rheumatoid arthritis. A measure of disease activity. J Clin Invest. 1975;55(6):1164-1173.
60. Diao W, Labaki WW, Han MK, et al. Disruption of histidine and energy homeostasis in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2019;14:2015-2025.
61. Watanabe M, Suliman ME, Qureshi AR, et al. Consequences of low plasma histidine in chronic kidney disease patients: associations with inflammation, oxidative stress, and mortality. Am J Clin Nutr. 2008;87(6):1860-1866.
62. el-Mansoury M, Boucher W, Sant GR, et al. Increased urine histamine and methylhistamine in interstitial cystitis. J Urol. 1994;152(2 Pt 1):350-353.
63. Myers G, Donlon M, Kaliner M. Measurement of urinary histamine: development of methodology and normal values. J Allergy Clin Immunol. 1981;67(4):305-311.
64. Raithel M, Hagel A, Albrecht H, et al. Excretion of urinary histamine and N-tele methylhistamine in patients with gastrointestinal food allergy compared to non-allergic controls during an unrestricted diet and a hypoallergenic diet. BMC Gastroenterol. 2015;15:41.
65. Horakova Z, Keiser HR, Beaven MA. Blood and urine histamine levels in normal and pathological states as measured by a radiochemical assay. Clin Chim Acta. 1977;79(2):447-456.
66. Harrison VC, Peat G, de Heese HV. Fetal growth in relation to histamine concentration in urine. J Obstet Gynaecol Br Commonw. 1974;81(9):686-690.

References (cont'd.)

67. Keyzer JJ, Breukelman H, Wolthers BG, et al. Urinary excretion of histamine and some of its metabolites in man: influence of the diet. Agents Actions. 1984;15(3-4):189-194.
68. Winterkamp S, Weidenhiller M, Otte P, et al. Urinary excretion of N-methylhistamine as a marker of disease activity in inflammatory bowel disease. Am J Gastroenterol. 2002;97(12):3071-3077.
69. Schwab D, Hahn EG, Raithel M. Enhanced histamine metabolism: a comparative analysis of collagenous colitis and food allergy with respect to the role of diet and NSAID use. Inflamm Res. 2003;52(4):142-147.
70. Imamura I, Watanabe T, Hase Y, et al. Histamine metabolism in patients with histidinemia: determination of urinary levels of histamine, N tau-methylhistamine, imidazole acetic acid, and its conjugate(s). J Biochem. 1984;96(6):1925-1929.
71. Patel B, Divekar R. Urinary N-methyl histamine levels relate to the presence of angioedema and decrease with the duration of chronic urticaria. J Allergy Clin Immunol Pract. 2017;5(1):201-203.
72. Gagne MA, Wollin A, Navert H, et al. Anomaly of histamine methylation in endogenous depression. Prog Neuropsychopharmacol Biol Psychiatry. 1982;6(4-6):483-486.
73. Trachtman H, Tejani A, Keyzer JJ, et al. Urinary histamine excretion in proteinuric states. Nephron. 1987;47(1):12-16.
74. Karoum F, Linnoila M, Potter WZ, et al. Fluctuating high urinary phenylethylamine excretion rates in some bipolar affective disorder patients. Psychiatry Res. 1982;6(2):215-222.
75. Delisi LE, Murphy DL, Karoum F, et al. Phenylethylamine excretion in depression. Psychiatry Res. 1984;13(3):193-201.
76. Reynolds GP, Seakins JW, Gray DO. The urinary excretion of 2-phenylethylamine in phenylketonuria, Clin Chim Acta. 1978;83(1-2):33-39.
77. Kusaga A, Yamashita Y, Koeda T, et al. Increased urine phenylethylamine after methylphenidate treatment in children with ADHD. Ann Neurol. 2002;52(3)372-374.
78. Akira K. Decreased beta-phenylethylamine in urine of children with attention deficit hyperactivity disorder and autistic disorder. No To Hattasu. 2002;34(3):243-248.
79. Baker GB, Bornstein RA, Rouget AC, et al. Phenylethylaminergic mechanisms in attention-deficit disorder. Biol Psychiatry. 1991;29(1):15-22.
80. Irsfeld M, Spadafore M, Prüß BM. Beta-phenylethylamine, a small molecule with a large impact. Webmedcentral. 2013;4(9):4409.
81. Sabelli HC, Fawcett J, Gusovsky F, et al. Urinary phenyl acetate: a diagnostic test for depression? Science. 1983;220(4602):1187-1188.
82. Faraone SV, Bonvicini C, Scassellati. Biomarkers in the diagnosis of ADHD--promising directions. Curr Psychiatry Rep. 2014;16(11):497.
83. Scassellati C, Bonvicini C, Faraone SV, et al. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry. 2012;51(10):1003-1019.
84. Molnár GA, Wagner Z, Markó L, et al. Urinary ortho-tyrosine excretion in diabetes mellitus and renal failure: evidence for hydroxyl radical production. Kidney Int. 2005;68(5):2281-2287.
85. Zheng P, Chen JJ, Zhou CJ, et al. Identification of sex-specific urinary biomarkers for major depressive disorder by combined application of NMR- and GC-MS-based metabonomics. Transl Psychiatry. 2016;6(11):e955.
86. Xie J, Han Y, Hong Y, et al. Identification of potential metabolite markers for middle-aged patients with post-stroke depression using urine metabolomics. Neuropsychiatr Dis Treat. 2020;16:2017-2024.
87. Burns C, Kidron A. Biochemistry, tyramine. In: StatPearls [Internet]. Treasure Island, Fla. StatPearls Publishing. 2021.
88. Field T, Diego M, Hernandez-Reif M, et al. Prenatal dopamine and neonatal behavior and biochemistry. Infant Behav Dev. 2008;31(4):590-593.
89. Ghaddar A, Omar KH, Dokmak M, et al. Work-related stress and urinary catecholamines among laboratory technicians. J Occup Health. 2014;55(5):398-404.
90. Kuchel O, Buu NT, Larochelle P, et al. Episodic dopamine discharge in paroxysmal hypertension. Page's syndrome revisited. Arch Intern Med. 1986;146(7):1315-20.
91. Ishiguro T, Shimamoto K, Sakamoto T, et al. Renal dopaminergic activity in patients with primary aldosteronism. Hypertens Res. 1995;18 Suppl 1:S193-S195.
92. Yehuda R, Southwick S, Giller EL, et al. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. J Nerv Ment Dis. 1992;180(5):321-325.
93. Houston MC. Role of mercury toxicity in hypertension, cardiovascular disease, and stroke. J Clin Hypertens. (Greenwich). 2011;13(8):621-627.
94. Liu L, Li Q, Li N, et al. Simultaneous determination of catecholamines and their metabolites related to Alzheimer's disease in human urine. J Sep Sci. 2011;34(10):1198-1204.
95. Van Binsbergen CJ, Odink J, Van der Beek EJ, et al. Biogenic amines in anorexia nervosa: circadian rhythm in urinary excretion and influence of posture and physical task load on plasma catecholamines. Psychosom Med. 1991;53(4):440-452.
96. Riva R, Mork PJ, Westgaard RH, et al. Catecholamines and heart rate in female fibromyalgia patients. J Psychoso Res. 2012;72(1):51-57.
97. Gill JR Jr, Grossman E, Goldstein DS. High urinary dopa and low urinary dopamine-to-dopa ratio in salt-sensitive hypertension. Hypertension. 1991;18(5):614-621.
98. Cohrs S, Guan Z, Pohlmann K, et al. Nocturnal urinary dopamine excretion is reduced in otherwise healthy subjects with periodic leg movements in sleep. Neurosci Lett. 2004;360(3):161-164.
99. Seay JS, McIntosh R, Fekete EM, et al. Self-reported sleep disturbance is associated with lower CD4 count and 24-h urinary dopamine levels in ethnic minority women living with HIV. Psychoneuroendocrinology. 2013;38(11):2647-2653.

References (cont'd.)

100. Kuchel O, Buu NT, Hamet P, et al. Orthostatic hypotension: a posture-induced hyperdopaminergic state. Am J Med Sci. 1985;289(1):3-11.
101. Paine NJ, Watkins LL, Blumenthal JA, et al. Association of depressive and anxiety symptoms with 24-hour urinary catecholamines in individuals with untreated high blood pressure. Psychosom Med. 2015;77(2):136-144.
102. Hughes JW, Watkins L, Blumenthal JA, et al. Depression and anxiety symptoms are related to increased 24-hour urinary norepinephrine excretion among healthy middle-aged women. J Psychosom Res. 2004;57(4):353-358.
103. Koslow SH, Maas JW, Bowden CL, et al. CSF and urinary biogenic amines and metabolites in depression and mania. A controlled, univariate analysis. Arch Gen Psychiatry. 1983;40(9):999-1010.
104. Grossman F, Potter WZ. Catecholamines in depression: a cumulative study of urinary norepinephrine and its major metabolites in unipolar and bipolar depressed patients versus healthy volunteers at the NIMH. Psychiatry Res. 1999;87(1):21-27.
105. Troisi RJ, Weiss ST, Parker DR, et al. Relation of obesity and diet to sympathetic nervous system activity. Hypertension. 1991;17(5):669-677.
106. Holzman C, Senagore P, Tian Y, et al. Maternal catecholamine levels in midpregnancy and risk of preterm delivery. Am J Epidemiol. 2009;170(8):1014-1024.
107. Fujiwara K, Tsukishima E, Kasai S, et al. Urinary catecholamines and salivary cortisol on workdays and days off in relation to job strain among female health care providers. Scand J Work Environ Health. 2004;30(2):129-138.
108. Lee ZS, Critchley JA, Tomlinson B, et al. Urinary epinephrine and norepinephrine interrelations with obesity, insulin, and the metabolic syndrome in Hong Kong Chinese. Metabolism. 2001;50(2):135-143.
109. Landsberg L, Troisi R, Parker D, et al. Obesity, blood pressure, and the sympathetic nervous system. Ann Epidemiol. 1991;1(4):295-303.
110. Rose DP, Braidman IP. Excretion of tryptophan metabolites as affected by pregnancy, contraceptive steroids, and steroid hormones. Am J Clin Nutr. 1971;24(6):673-683.
111. Oh JS, Seo HS, Kim KH, et al. Urinary profiling of tryptophan and its related metabolites in patients with metabolic syndrome by liquid chromatography-electrospray ionization/mass spectrometry. Annal Bioanal Chem. 2017;409(23):5501-5512.
112. Pedersen ER, Svingen GF, Schartum-Hansen H, et al. Urinary excretion of kynurenine and tryptophan, cardiovascular events, and mortality after elective coronary angiography. Eur Heart J. 2013;34(34):2689-2696.
113. Fitzgerald P, Eugene MC, Clarke G, et al. Tryptophan catabolism in females with irritable bowel syndrome: relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity. Neurogastroenterol Motil. 2008;20(12):1291-1297.
114. Akesson K, Pettersson S, Ståhl S, et al. Kynurenine pathway is altered in patients with SLE and associated with severe fatigue. Lupus Sci Med. 2018;5(1):e000254.
115. Chatterjee P, Goozee K, Lim CK, et al. Alterations in serum kynurenine pathway metabolites in individuals with high neocortical amyloid-β load: A pilot study. Sci Rep. 2018;8(1):8008.
116. Orlikov A, Ryzov I. Caffeine-induced anxiety and increase of kynurenine concentration in plasma of healthy subjects: a pilot study. Biol Psychiatry. 1991;29(4):391-396.
117. Gostner JM, Becker K, Croft KD, et al. Regular consumption of black tea increases circulating kynurenine concentrations: A randomized controlled trial. BBA Clin. 2015;3:31-35.
118. Fazio F, Lionetto L, Curto M, et al. Xanthurenic acid activates mGlu2/3 metabotropic glutamate receptors and is a potential trait marker for schizophrenia. Sci Rep. 2015;5:17799.
119. Baranyi A, Amouzadeh-Ghadikolai O, von Lewinski D, et al. Revisiting the tryptophan-serotonin deficiency and the inflammatory hypotheses of major depression in a biopsychosocial approach. PeerJ. 2017;5:e3968.
120. Birner A, Platzer M, Bengesser SA, et al. Increased breakdown of kynurenine towards its neurotoxic branch in bipolar disorder. PLoS One. 2017;12(2):e0172699.
121. Theofylaktopoulou D, Ulvik A, Midttun Ø, et al. Vitamins B2 and B6 as determinants of kynurenines and related markers of interferon-gamma-mediated immune activation in the community-based Hordaland Health Study. Br J Nutr. 2014;112(7):1065-1072.
122. Schwarz MJ, Guillemin GJ, Teipel SJ, et al. Increased 3-hydroxykynurenine serum concentrations differentiate Alzheimer's disease patients from controls. Eur Arch Psychiatry Clin Neurosci. 2013;263(4):345-352.
123. Chiang EP, Selhub J, Bagley PJ, et al. Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1404-1411.
124. Ravindran AV, Bialik RJ, Brown GM, et al. Primary early onset dysthymia, biochemical correlates of the therapeutic response to fluoxetine: II. Urinary metabolites of serotonin, norepinephrine, epinephrine and melatonin. J Affect Disord. 1994;31(2):119-23.
125. Maas JW, Koslow SH, Katz MM, et al. Pretreatment neurotransmitter metabolite levels and response to tricyclic antidepressant drugs. Am J Psychiatry. 1984;141(10):1159-1171.