Introduction
Diseases as seemingly diverse as restless leg syndrome, insomnia, depression, attention deficit hyperactivity disorder, and carbohydrate food cravings may reflect underlying imbalances or inadequacies in neurotransmitters. While every aspect of this hypothesis is not fully investigated, neurotransmitter deficiency states are not mere academic theory. They represent information for everyday use clinical practice! The biochemistry shown in Figure 1 shows how neurotransmitters are synthesized from amino acids. The two pathways interact with each other in ways that are currently under investigation. However, we’ll focus on patients in your clinic today.

Clinical Scenarios Introduced
Patient 1 asks you for advice on managing his food cravings. Your extensive work-up to this point suggests he may benefit from treatment with amino acid precursors of serotonin and dopamine. He currently participates in a medically supervised weight management program.

Patient 2 is concerned that she has been prescribed increasing doses of selective serotonin reuptake inhibitors (SSRIs) to help manage her symptoms of clinical depression. The medications are not as effective as they used to be in treating her clinical depression. You reason that SSRIs keep serotonin - and, to a lesser extent, catecholamines - in...
Urinary Neurotransmitters

> the synapses where they are more readily degraded. You speculate that one of the underlying causes of her clinical depression may be inadequate serotonin. The SSRIs may have too little serotonin to facilitate drug response. You further reason that providing the patient with a blood-brain-barrier-crossing precursor of serotonin, the amino acid 5-hydroxytryptophan, may improve the patient's symptoms when used along with tyrosine (Figure 1) and additional nutrients. However, you are also appropriately cautious about drug-nutrient interactions. You would like to use laboratory testing to guide your recommendations.

**Patient 3** has Parkinson's disease, managed medically by a neurologist. You have known this patient and his family for many years and are concerned about his recent onset of clinical depression. You consider the possibility that medical treatment aimed at increasing dopamine in affected areas of the brain may be lowering serotonin by competitive inhibition.

**Competitive Inhibition of Neurotransmitters**

The tyrosine-dopamine-adrenaline pathway and the 5-HTP-serotonin pathway communicate with each other. If you alter one pathway with a nutrient or medication, you may incur side effects along the other pathway.

Patients 3 and 4 have side effects that can be explained by competitive inhibition of these two axes. Depression can ensue from depleted serotonin following upregulation of the dopamine axis in the treatment of Parkinsonism. Self-treatment with tryptophan, a serotonin precursor, can reduce dopamine levels, perhaps triggering Patient 4's restless leg syndrome.

The competitive inhibition between these two axes adds a layer of complexity to clinical management. For this reason, supplementation of both tyrosine (dopamine axis) and 5-hydroxytryptophan (5-HTP) (serotonin axis) is recommended. Balancing these amino acid levels and the corresponding neurotransmitters is precisely where urinary neurotransmitter testing may prove especially useful.

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**Figure 2: Urine Neurotransmitter Excretion in Response to Administration of Precursors**

Two sequential urine tests can be used to determine the phase of serotonin and dopamine. Target treatment is phase 3 for each neurotransmitter. (Reproduced with permission from Hinz M. Depression. In: Kohlstadt I, ed. *Food and Nutrients in Disease Management*. Boca Raton, Florida: CRC Press; January 2009: 465-482.)

The three-phase determination of urinary serotonin and dopamine is the patent-pending intellectual property of DBS Labs.

**Figure 3: Associated Metabolic Pathways**

Increasing dopamine increases epinephrine, which requires the sulfur cycle, which in turn engages the folate cycle. Upregulating metabolic cycles alters nutrient requirements. (Reproduced with permission from Hinz M. Depression. In: Kohlstadt I, ed. *Food and Nutrients in Disease Management*. Boca Raton, Florida: CRC Press; January 2009: 465-482.)
Urine Testing of Neurotransmitters – Theory

Urine neurotransmitters are not a diagnostic test. The lab results do not tell you if the patient has restless leg syndrome, neurotransmitter imbalance-precipitated food cravings, Parkinsonism, or ADHD. In order to give a diagnosis of low neurotransmitter levels, serotonin, dopamine, norepinephrine, and epinephrine in the urine would need to be systemic neurotransmitters filtered by the kidneys and excreted in the urine. And, as you have already inferred, it’s not that simple.

Urine neurotransmitter testing is a guide during active treatment. It helps clinicians fine-tune treatment with supplemental amino acids and medications. Flux in the kidney with neurotransmitter synthesis and secretion and what is measured in the urine is representative of synthesis and secretion of neurotransmitters throughout the body.

Baseline testing prior to treatment of disease associated with low levels of neurotransmitters is of no value. The serotonin and dopamine found in the urine are synthesized in the proximal convoluted renal tubule cells. After synthesis, the serotonin and dopamine are either transported out of the proximal convoluted renal tubule cells by the basolateral transporter system into the interstitium, ultimately to the renal vein, or the apical transporter system, over 98% of which ends up in the final urine. Urinary serotonin and dopamine is serotonin, and dopamine transported by the apical transporter represent the serotonin and dopamine not transported by the basolateral transporter system. For purposes of illustration, conceptualize the basolateral transporter as having two gates that may impede access to the transporter, one for dopamine and one for serotonin. Each gate opens and closes in response to the total amount of serotonin and dopamine presenting at the transporter. It has never been observed where both the serotonin and dopamine gates were partially closed at the same time, i.e., urinary serotonin and dopamine are never in phase 1 (Figure 2) at the same time.

Urine analysis of serotonin and dopamine is an assay of the basolateral transporter status and function system-wide. From a clinical standpoint, proper manipulation of the basolateral transporter correlates with relief of symptoms throughout the body, not only in the kidney.

Urine Testing of Neurotransmitters – Practical

Urine samples can be collected following one week of treatment on a given dose of medication and/or amino acids. Patients should be careful not to miss a dose during the week before testing. Test results are generally available within a week.

Figure 2 depicts the three phases of urinary serotonin and dopamine response to administration of amino acid precursors. In phase 1, the gate to the transporter is partially closed, impeding access to the basolateral transporter system. In phases 2 and 3, the gates regulating access to the transporter are open. For optimal clinical results, the goal of treatment is to adjust the amino acid precursors until relief of symptoms is seen or until the urinary serotonin and dopamine are in the desired range within phase 3. Proper balance between these two systems is critical. Serotonin and dopamine are subject to competitive inhibition at the transporter. In phase 1, as the total amount of serotonin and dopamine presenting at the transporter is increased, impedance decreases causing urinary neurotransmitter levels to drop. In phase 2, there is full transporter access, and transport is not saturated. In phase 3, the transport is saturated. When serotonin or dopamine is in phase 3, competitive inhibition excludes the other from the transporter if it is phase 1 or phase 2. If both are in phase 3, competitive inhibition exists that needs to be balanced if the patient still has symptoms. The goal is to have both neurotransmitters in phase 3. However, symptoms can resolve as patients become closer to phase 3, making it unnecessary to reach phase 3.

Samples need to be collected five to six hours before bedtime. This is usually just before the 4 PM amino acid dosing. After the sample is collected, it needs to be placed in the proper stabilizer within one to two minutes after collection. The time of sample collection is critical. Samples obtained in the AM or at bedtime are not acceptable for phase determination. Previous intake history of foods and medications has little effect on the assay.
Clinical Scenarios – Revisited

Patient 1: You supplement the patient with 150 mg 5-HTP, 1,500 mg tyrosine, and cofactors twice daily. The patient’s food cravings subside. He no longer has trouble sticking with his medically supervised weight loss program. You decide not to order urine neurotransmitter testing. You continue the patient at his current amino acid dosing regimen and cofactors.

Patient 2: You supplement the patient with 150 mg 5-HTP, 1,500 tyrosine, and required cofactors twice daily and see the patient in one week. She reports that her current dose of SSRI appears to be sufficient now. You choose to order urine neurotransmitter testing. Her results are consistent with a Phase 2 response (Figure 2). She requests and you agree to monitor her at her starting dose of urinary neurotransmitters.

Patient 3: You supplement 150 mg 5-HTP, 1,500 mg tyrosine, 120 mg L-dopa, and cofactors twice daily. The patient has tolerated the treatment well, but without subjective or clinical improvement at the one-week follow-up. You increase the patient’s dosing to the next level, an additional 300 mg 5-HTP, 1,000 mg tyrosine, and 120 mg L-dopa per day. You then order urine neurotransmitter testing. Results confirm that a further change in amino acid dosing would be beneficial in order to balance the serotonin and dopamine. A second urine test is needed to distinguish between phase 1 and phase 3.

Biochemical Chain Reactions to Keep in Mind

The serotonin and dopamine axes are not the only metabolic pathways influenced by amino acid supplementation. Metabolic pathways are similar to the gears of fine watches. When one turns, so do the others. Figure 3 shows the other metabolic reactions that occur when amino acids are supplemented. Therefore, cysteine (a sulfur-containing amino acid), selenium, and folate also need to be supplemented. Additionally, vitamin C can help sustain glutathione levels, and vitamins B6 and B12 can facilitate the side reactions of the sulfur amino acid cycle.

Summary

Urinary neurotransmitters can guide treatment of various neurotransmitter imbalances including depression, Parkinson, obesity, ADHD, and sleep disorders. [Amino acid precursors of neurotransmitters are presented in Kohlstadt I, ed. Food and Nutrients in Disease Management. Boca Raton, Florida: CRC Press; January 28, 2009.]


Ingrid Kohlstadt MD, MPH, FACN, is an FDA Commissioner’s Fellow at the Food and Drug Administration, Office of Scientific and Medical Programs. There she works towards improving communication on food and drug interactions. She has been elected a Fellow of the American College of Nutrition and is an associate at the Johns Hopkins School of Public Health. She is the founder and chief medical officer of INGRIDients™, Inc., which provides medical nutrition information to colleagues, clients, and consumers.

Dr. Kohlstadt is a graduate of Johns Hopkins School of Medicine, Class of 1993. She earned her bachelor’s degree in biochemistry at the University of Maryland and as a Rotary Club scholar at Universität Tübingen, Germany in 1989.

Board-certified in General Preventive Medicine and with a graduate degree in epidemiology, she became convinced that nutrition is powerful and underutilized in preventing disease. She therefore focused her career on nutrition through fellowships at Johns Hopkins and The Centers for Disease Control and Prevention. She worked as a bariatric physician at the Johns Hopkins Weight Management Center and the Florida Orthopaedic Institute.

As a congressional intern and later with the FDA, USDA, health department, USAID, and United States Antarctic Program, Dr. Kohlstadt studied the rugged terrain of health policy, specifically how food and nutrients can be incorporated into primary care medicine. Prior to developing Food and Nutrients in Disease Management, she edited Scientific Evidence for Musculoskeletal, Bariatric, and Sports Nutrition (CRC Press, Boca Raton, FL, 2006).

Dr. Kohlstadt resides with her husband, Ellis Richman, and their daughter Raeha in historic Annapolis, Maryland.