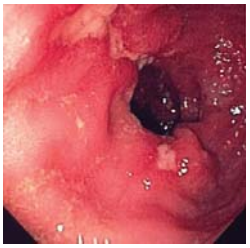
CHK MEDICAL FOODS
Clinical Optimization of Transporter Function



CROHN'S DISEASE

Treatment with serotonin and dopamine amino acid precursors administered under the guidance of organic cation transporter (OCT) assay interpretation

PERSPECTIVE

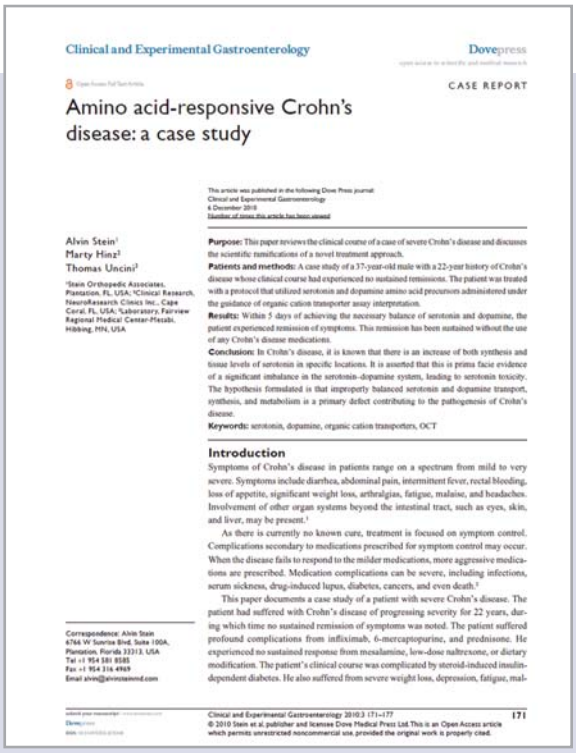
In recent years, a genetic defect of the OCTN1 and OCTN2 of the colon has been identified in patients with Crohn's disease. The OCTN1 and OCTN2 are responsible for transport of cations, including the monoamines of the serotonin–dopamine system and their precursors. It is known with Crohn's disease patients that there is a marked increased in serotonin levels of the proximal and distal colon associated with a defect in serotonin synthesis. (Stein et al 2010)

Based on OCT assay interpretation, it appears that a severe imbalance between serotonin and dopamine transport, synthesis, and metabolism is at the heart of Crohn's disease. (Stein et al 2010)

An imbalance of the serotonin–dopamine transport system has been linked to numerous diseases. It is proposed that much of the clinical constellation found with Crohn's disease may be induced by a serotonin toxicity of the colon exacerbated by relatively low levels of dopamine resulting from defective OCTN transport. (Stein et al 2010)

In the GI tract, serotonin is contained primarily in the enteroendocrine cells (ECs). The serotonin-dopamine transporter balance of the ECs controls paracrine–autocrine and/or endocrine mediators that modulate GI function. It is asserted that proper treatment needs to include correct management of the serotonin and dopamine imbalance in transport, synthesis, and metabolism. The only definitive way to address these problems optimally is with OCT analysis interpretation in the competitive inhibition state that is established with proper amino acid precursor administration. (Stein et al 2010)

This Approach is Based On This Peer-reviewed Scientific Literature



Clinical and Experimental Gastroenterology — Dovepress

CASE REPORT

Amino acid-responsive Crohn's disease: a case study

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Purpose: This paper reviews the clinical course of a case of severe Crohn's disease and discusses the scientific ramifications of a novel treatment approach.

Patients and methods: A case study of a 37-year-old male with a 22-year history of Crohn's disease whose clinical course had experienced no sustained remissions. The patient was treated with a protocol that utilized serotonin and dopamine amino acid precursors administered under the guidance of organic cation transporter assay interpretation.

Results: Within 5 days of achieving the necessary balance of serotonin and dopamine, the patient experienced remission of symptoms. This remission has been sustained without the use of any Crohn's disease medications.

Conclusion: In Crohn's disease, it is known that there is an increase of both synthesis and tissue levels of serotonin in specific locations. It is asserted that this is prima facie evidence of a significant imbalance in the serotonin–dopamine system, leading to serotonin toxicity. The hypothesis formulated is that improperly balanced serotonin and dopamine transport, synthesis, and metabolism is a primary defect contributing to the pathogenesis of Crohn's disease.

Keywords: serotonin, dopamine, organic cation transporters, OCT

Introduction

Symptoms of Crohn's disease in patients range on a spectrum from mild to very severe. Symptoms include diarrhea, abdominal pain, intermittent fever, rectal bleeding, loss of appetite, significant weight loss, arthralgias, fatigue, malaise, and headaches. Involvement of other organ systems beyond the intestinal tract, such as eyes, skin, and liver, may be present.[1]

As there is currently no known cure, treatment is focused on symptom control. Complications secondary to medications prescribed for symptom control may occur. When the disease fails to respond to the milder medications, more aggressive medications are prescribed. Medication complications can be severe, including infections, serum sickness, drug-induced lupus, diabetes, cancers, and even death.[2]

This paper documents a case study of a patient with severe Crohn's disease. The patient had suffered with Crohn's disease of progressing severity for 22 years, during which time no sustained remission of symptoms was noted. The patient suffered profound complications from infliximab, 6-mercaptopurine, and prednisone. He experienced no sustained response from mesalamine, low-dose naltrexone, or dietary modification. The patient's clinical course was complicated by steroid-induced insulin-dependent diabetes. He also suffered from severe weight loss, depression, fatigue, mal-

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Medical Foods

CHK Nutrition
5051 Miller Trunk Highway
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877-538-8388
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PROPERLY BALANCED AMINO ACIDS

The amino acid precursors of serotonin and dopamine need to be properly balanced. Improper balance depletes neurotransmitters. Giving only 5-HTP depletes dopamine. Giving only L-tyrosine or L-dopa depletes serotonin.

Adult Crohn's Disease Protocol

Progress through the levels week to week if symptoms persist

	AM	NOON	4 PM	7 PM
LEVEL 1	**4 NeuroReplete**	**—**	**4 NeuroReplete**	**—**
LEVEL 2	**4 NeuroReplete**	**4 NeuroReplete**	**4 RepleteExtra**	**—**
LEVEL 3	**4 NeuroReplete**	**4 NeuroReplete**	**4 RepleteExtra**	**4 RepleteExtra**

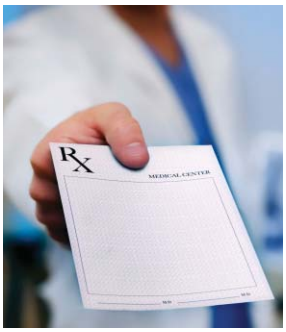
If symptoms of Crohn's are still present one week after starting level 3, obtain a urine sample and submit it for transporter interpretation (see pages 8 and 9).

CysReplete

All patients need to take CysReplete to prevent depletion of sulfur amino acids by L-tyrosine and L-dopa.

- **ADULT DOSING:** 2 pills of CysReplete 3 times a day (with the first dose at noon).

SUGGESTED TREATMENT:



- See patients weekly until stable.
- There is no benefit in waiting longer than one week to see if there is a further improvement prior to a dosing change or obtaining a urine sample.
- While many patients stabilize in one to six weeks insure all patients are able to participate in weekly visits for 2 to 4 months if needed at the start of treatment.
- Continue all drugs the patient is taking at the start of treatment.
- If a drug side effect develops treat it as a drug side effect and do not decrease or stop the amino acids.
- Read pages 6 and 7 of the brochure for management of treatment problems
- If the child has problems swallowing a capsule, twist it open and put the powder in juice or other water soluble liquid.

TyrosineReplete and D5 Mucuna 40% are only used under the guidance of transporter status determination

MEDICAL FOODS STATEMENT: 1) These medical foods are specially formulated and processed products for partial feeding of the patient by means of oral intake. 2) These medical foods are intended for the dietary management of a patient who has other special medically determined nutrient requirements needing increased levels of monoamine neurotransmitters, the dietary management of which cannot be achieved by the modification of normal diet alone. 3) These medical foods are intended to be used under active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food. 4) These medical foods provide nutritional support specifically modified for the management of the unique (distinctive) nutrient needs that result from the specific disease or condition as determined by medical evaluation.

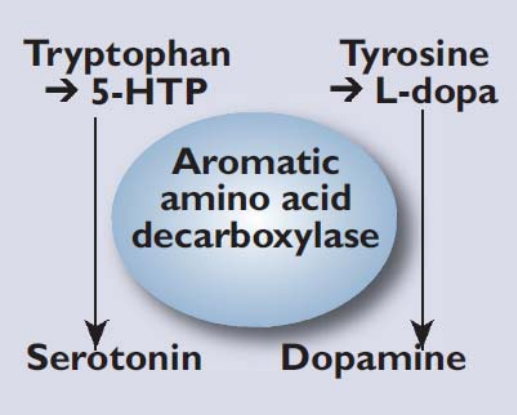
THE COMPETITIVE INHIBITION STATE

Observed only when serotonin and dopamine precursors are given in significant amounts.

In the competitive inhibition state, the serotonin and dopamine systems function as one system in transport, synthesis, and metabolism. Effecting change to one system will affect both systems in their functions.

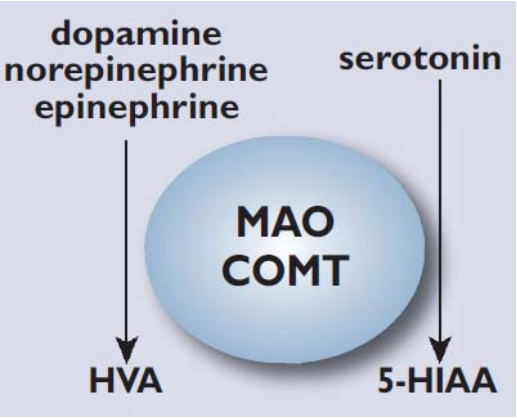
SYNTHESIS

The same enzyme, the L-aromatic amino acid decarboxylase enzyme (AAAD), is responsible for synthesis of serotonin and dopamine. Creating an environment where precursors of one system are significantly increased without significantly increasing the precursors of the other system leads to decreased access to the AAAD by precursors of the other system, with associated decreased synthesis or depletion due to competitive inhibition.



METABOLISM

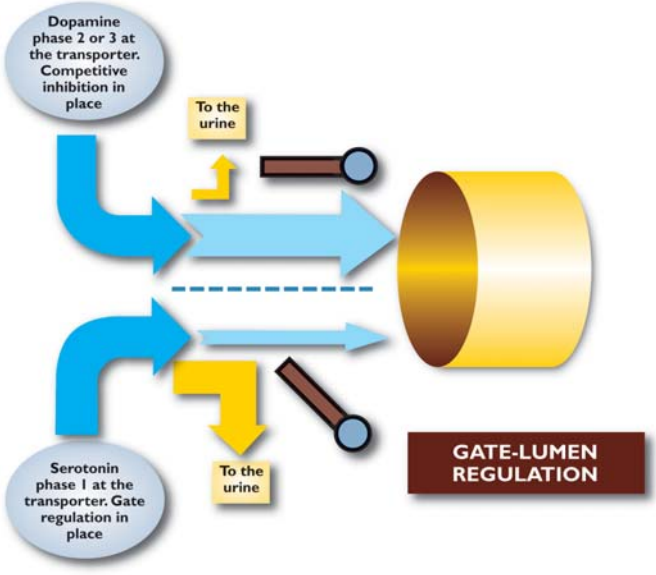
Both serotonin and dopamine are metabolized by the monoamine oxidase (MAO) enzyme system. A significant increase in levels of one system will increase MAO activity, leading to increased metabolism and depletion of the other system.



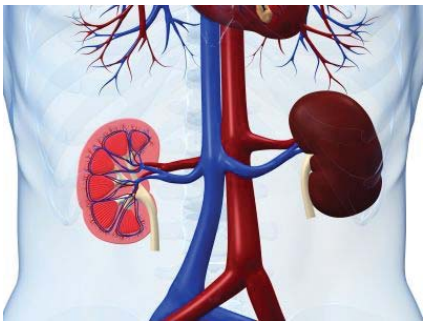
TRANSPORT

Serotonin, dopamine, and their amino acid precursors compete for transport at the OCTs. Significant increases in one monoamine will decrease monoamine and precursor transport of the other system through competitive inhibition. Transport of precursors into the cells is required in order to place them in an environment where synthesis takes place.

When serotonin and/or dopamine become depleted enough the amino acid precursors in treatment and the drugs that work with neurotransmitters will not work.



SELECT PEER-REVIEWED SCIENCE RELATING TO TRANSPORTER STATUS DETERMINATION™



Scientific knowledge of the monoamines (serotonin, dopamine, norepinephrine, and epinephrine) has grown significantly since 1990. Along with this growth in knowledge, some of the science originally thought to be correct has been discredited. In contrast to earlier writings it is now known that monoamines do not cross the blood-brain barrier. Monoamines are not simply filtered at the glomerulous then excreted into the urine. Urinary monoamine levels are not a direct assay of the peripheral or central nervous system monoamine levels. Interpretation of urinary monoamine assays is more complex than simply determining if urinary serotonin and dopamine levels found on assay are high or low. Under normal conditions, significant amounts of serotonin and dopamine filtered at the glomerulous do not make it to the final urine. Serotonin and dopamine (herein referred to as "monoamines") found in the final urine are newly synthesized in the kidneys. (Hinz et al 2010a)

The monoamines and their amino acid precursors are filtered at the glomerulous then enter the proximal tubules of the kidneys. They are transported by organic cation transporters out of the proximal tubules into the proximal convoluted renal tubule cells. The monoamines filtered at the glomerulous are metabolized in the proximal convoluted renal tubule cells. Very little of these monoamines filtered at the glomerulous are found in the final urine of normal subjects. Monoamine amino acid precursors filtered at the glomerulous are synthesized in the proximal convoluted renal tubule cells into new monoamines, which are then detected in the final urine. Serotonin and dopamine exist in two states: the "endogenous state" found when no additional amino acid precursors are being administered, and the "competitive inhibition state" found when the amino acid precursors of both serotonin and dopamine are being administered. Prior to discussing the dual-gate lumen model, the following discussion of the three-phase urinary response is put forth based on previous peer reviewed literature. Literature notes: "Urinary monoamine neurotransmitter testing prior to initiation of serotonin and dopamine amino acid precursors is of no value. There is no correlation between baseline testing and urinary neurotransmitter phases once the patient is taking amino acid precursors. It is not necessary or even useful to measure baseline urinary neurotransmitters in treatment". (Hinz et al 2010a)

Monoamine secreting tumors can't be diagnosed with spot baseline urinary testing

Monoamine-secreting tumors such as carcinoid syndrome and pheochromocytoma are associated with the highest reported individual and/or group urinary monoamine laboratory values in comparison with all the alleged clinical applications discussed in the Marc et al. 2010 paper. Even in these extreme monoamine disease states, spot baseline urinary neurotransmitter testing is nothing more than a screening tool to determine if definitive testing with a 24-hour urine sample may be indicated to formally make the diagnosis. Spot urinary neurotransmitter testing under these conditions does not allow for diagnosis, predictability of treatment outcomes, or any of the other alleged benefits promoted by the Marc et al. 2010 paper. The randomness of spot baseline test results differ significantly from one day to the next causing the lack of diagnostic ability and clinical specificity in treating these disease states (Hinz et al. 2010b, 2011b).

REPONSE TO AMINO ACIDS IS NOT SIMPLE

The data presented in this study indicate that consumption of specific dietary precursors of serotonin or dopamine only increases the urinary excretion of these neurotransmitters approximately 50% of the time. Probably the most surprising finding of this study is that 20% to 40% of these same individuals respond to the precursors with an unexpected reduction in excretion of the neurotransmitters, particularly dopamine. These observations indicate that the simplistic expectation that increased ingestion of neurotransmitter precursors will increase excretion of the mature neurotransmitters in the urine. (Trachte et al 2009)

BASELINE TESTING PRIOR TO STARTING AMINO ACIDS IS OF NO VALUE; IT IS NOT REPRODUCIBLE FROM DAY TO DAY.

These findings indicate that **baseline urinary serotonin** levels do differ in a statistically significant manner when baseline assays are performed on different days for the same subject and are not uniform or reproducible from day to day. (Hinz et al 2010b)

These findings indicate that **baseline urinary dopamine** levels do differ in a statistically significant manner when baseline assays are performed on different days in the same subject, and are not uniform or reproducible from day to day. (Hinz et al 2010b)

These findings indicate that spot **baseline urinary epinephrine** levels do differ in a statistically significant manner when spot baseline assays are performed on different days from the same subject. This supports the assertion that spot urinary epinephrine values are not uniform or reproducible from day to day. (Hinz et al 2011b)

These findings indicate that spot **baseline urinary norepinephrine** levels do differ in a statistically significant manner when spot baseline assays are performed on different days from the same subject. This supports the assertion that spot urinary norepinephrine values are not uniform or reproducible from day to day. (Hinz et al 2011b)

A FEW THINGS BASELINE TESTING CAN'T DO

Spot baseline urinary neurotransmitter testing of norepinephrine, epinephrine, serotonin, and dopamine **is not reproducible from day to day in the same subject**; therefore, this type of testing is not valid. An infinite number of assays performed on an infinite number of days would generate an infinite number of differing test results. The following are true, based on the statistics put forth in this paper and the lack of reproducibility as demonstrated in this writing:

- Spot urinary neurotransmitter testing is not a reliable assay for peripheral or central nervous system function; the majority of serotonin and catecholamine molecules found in the urine of patients not suffering from a monoamine- secreting tumor have never been in the peripheral or central nervous system, having been synthesized by renal structures
- Spot urinary neurotransmitter testing does not correlate with monoamine neurotransmitter-related disease states in patients not suffering from a monoamine-secreting tumor
- Spot urinary neurotransmitter testing, due to lack of reproducibility, cannot assist the health care practitioner in making informed decisions regarding the choice of amino acids, or the dosing value for intervention with a disease state associated with monoamine Neurotransmitters
- Spot urinary neurotransmitter testing, due to lack of reproducibility, does not have a place in clinical practice for identifying biomarkers of peripheral or central nervous system function and disease states
- Spot urinary neurotransmitter testing cannot determine monoamine imbalances that exist in subjects because the results are not reproducible
- Spot baseline monoamine assays cannot serve as a predictor of expected efficacy once amino acid precursors are started due to lack of reproducibility. There is evidence that urinary monoamines, such as norepinephrine reported on 24-hour urine samples, may be elevated in a specific group of patients with depression. However, these are group findings, and do not necessarily translate to individual testing validity on spot testing due to the lack of reproducibility of the test from day to day in the same subject.

PROPER MANAGEMENT OF AMINO ACIDS

PATIENT ORIENTATION:

At the first visit all patients need to be instructed as follows: **"If there are any problems in the first week of treatment, stop the amino acids until you get back to clinic and I will tell you what to do."** Failure to properly orient patients at the first visit will result in patients dropping out of care if problems are experienced in the first week of treatment.

GI UPSET → ON START UP

THE PROBLEM: Approximately 1% to 2% of patients (higher in some medical practices where patients have been exposed at a higher rate to drugs that deplete neurotransmitters) experience GI upset or nausea on starting the amino acids. Typically, this starts with the first dose and builds with every dose until the third day, at which point the patient can no longer tolerate the symptoms.

THE CAUSE: The patients who are most depleted of neurotransmitters experience GI upset or nausea on starting the amino acids. *These are the very patients who need the amino acids the most*.

MANAGEMENT: Restart the NeuroReplete taking only one pill at bedtime. Bedtime is when the patient is ready to get in bed and go to sleep, not when the patient gets in bed and reads a book for an hour. If the patient can fall asleep within 20 minutes after taking the one pill of NeuroReplete there should be no problems with GI upset. After 3 or 4 nights with no GI problems increase the NeuroReplete to 2 pills at bedtime. When the patient is able to take 2 pills at bedtime with no problems, start 1 pill in the AM then increase to two pills after 3 or 4 days of no problems. In adults, when the patient is taking 2 pills of NeuroReplete twice a day, submit a urine sample for transporter evaluation.

GI UPSET → CARBOHYDRATE INTOLERANCE

THE PROBLEM: Once the proper dosing values of the amino acids have been established, patients may experience transient nausea lasting 45 to 60 minutes periodically during the day. The etiology of this problem is distinctly different than "GI upset on start up" discussed above.

THE CAUSE: With optimization of neurotransmitter transporters, the way the body reacts to specific carbohydrates may change causing nausea.

MANAGEMENT: Usually only one food needs to be changed. Most of the time, it is a bread, cereal, or noodle that needs to be changed. Examples of effective management include 1) Changing from white to whole wheat bread. 2) Changing from one type of noodle to another. 3) Changing from one cereal to another, for example changing from Wheaties to Shredded Wheat. At times identification of the food can be difficult. One case of carbohydrate intolerance was tracked down to the breading on chicken eaten with most lunches.

HEARTBURN (PYROSIS)

THE PROBLEM: Intense substernal or epigastric burning or nausea after taking the pills.

THE CAUSE: When the veggie caps are simply gulped down with some water the surface does not liquefy properly causing the pills to stick in the esophagus and dissolve, at which time an intense substernal and/or epigastric burning is experienced.

MANAGEMENT: Hold the pills in the mouth with water for 10 to 15 seconds before swallowing so that the capsule surface starts to liquefy and slides down easily.

PRESCRIPTION DRUG SIDE EFFECTS

THE PROBLEM: The recommendation is to leave all drugs in place when starting the amino acids. Side effects not associated with the amino acids may occur in 3% to 5% of patients while starting or changing the amino acid dosing.

THE CAUSE: Drugs that work with neurotransmitters not only become more effective as neurotransmitter levels increase with amino acid administration; the side effects of these drugs may display as well.

MANAGEMENT: Proper management is to treat the event like a drug side effect. DO NOT stop the amino acids. Tapering or stopping the drug causing the side effect is proper management.

Amino acid only side effect profile

Dry mouth	2.1%
Insomnia	0.9%
Headache	0.7%
Nausea	0.6%
Dizziness	0.4%
Constipation	0.4%

All other side effects occur at a rate less than 1 in 500 visits

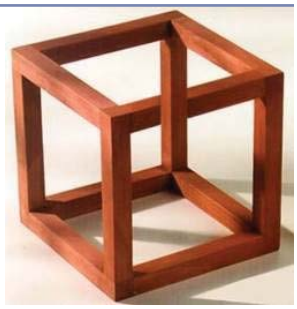
WHEN AMINO ACIDS STOP WORKING

THE PROBLEM: The patient's symptoms are under control, then it appears that the pills stopped working and symptoms of disease return.

THE CAUSE: Missing one or more doses of amino acids can cause symptoms of disease to return. It then may take three to five days for symptoms to get back under control once the pills are taken correctly. If the patient misses one pill dosing every three to four days multiple times, it may appear that the amino acids have quit working.

MANAGEMENT: In 99% of patients for whom the pills stop working it is a compliance issue relating to taking the pills properly. Have the patient journal (write down) all pills taken for 7 to 10 days. After journaling if the patient's symptoms are not under control, submit a urine sample for transporter assay. Only 1% of patients experience a change in dosing needs during treatment and retesting can manage this problem.

PARADOXICAL REACTIONS



THE PROBLEM: A specific amino acid dosing value is started or changed and the patient complains of an exacerbation of symptoms related to one or more monoamine neurotransmitter related diseases (see page 8). For example, depression may get worse, sleep may get worse, the patient may get more agitated, anxiety may get worse, migraines may get worse, etc.

THE CAUSE: The exact cause of paradoxical reactions is unknown, but it is known that there is a dosing range within which they do occur.

MANAGEMENT: When a paradoxical reaction is identified, it is an indication that the amino acid dosing value needs to be increased, at which point the paradoxical symptoms will resolve in one to two days. If the dose is lowered in hopes of increasing the dosing values slowly, the patient's suffering will be unnecessarily prolonged as the patient is subjected to the dosing value range where symptoms occur for a prolonged period of time.

DIZZINESS

THE PROBLEM: Dizziness (vertigo) may be caused by many different things when taking amino acids. As with paradoxical reactions, in many cases it is an indication to increase the amino acid dosing.

THE CAUSE: While complaints of dizziness may have many etiologies, dizziness associated with inadequate amino acid dosing is responsive to food intake. If the patient complains of dizziness that resolves after eating a small amount of carbohydrate, such as a candy, cookie, pastry, etc., it is a carbohydrate-dependent vertigo which can develop during amino acid treatment.

MANAGEMENT: Management of "carbohydrate-dependent vertigo" involves increasing the amino acid dosing to the level where symptoms will resolve in one to two days. Any patient taking amino acids with complaints of dizziness needs to be properly evaluated for "carbohydrate-dependent vertigo".

HYPERSOMNOLENCE

THE PROBLEM: The patient recently started on amino acids may present at the clinic complaining of excess sleepiness to the point of having problems staying awake at work or during other daily activities.

THE CAUSE: In general, these patients were suffering from poor sleep prior to treatment and have a "sleep debt" that needs to be repaid prior to feeling optimal again.

MANAGEMENT: The first thing to do when complaints of excessive tiredness are encountered is to take a medical history to determine whether the cause is an imbalance in the amino acids or if the patient is suffering from a sleep debt that needs to be repaid. In patients with very poor sleep prior to treatment (3 to 4 hours per night), stop the amino acids and restart them on a Friday if the patient has the weekend off, telling the patient to sleep all weekend. If sleep was not a problem prior to treatment, cut the amino acid dosing in half, then obtain a urinary transporter analysis in order to determine the proper level of amino acids needed.

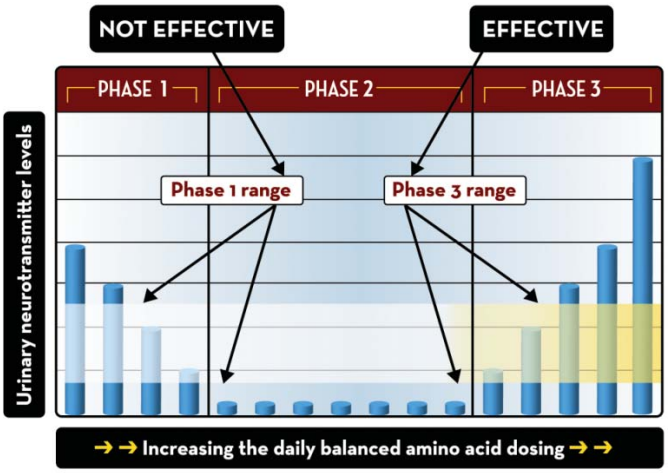
Two heads are better than one, and experience trumps all. There are no problems that should require long-term stoppage of the amino acids other than the patient quitting treatment.

ORGANIC CATION TRANSPORTER ASSAY INTERPRETATION

DBS Labs
8723 Falcon Street
Duluth, MN 55808
877-476-7229
www.DBSlabs.com

The source of urinary monoamine neurotransmitters

"The serotonin and dopamine filtered at the glomerulous are metabolized by the kidneys, and significant amounts do not make it to the final urine. Serotonin and dopamine found in the urine are monoamines synthesized in the proximal convoluted renal tubule cells and have never been found in the central nervous system or peripheral system. Serotonin and dopamine that are newly synthesized by the kidneys meet one of two fates. Urinary serotonin and dopamine levels are primarily dependent on the interaction of the basolateral monoamine transporters (OCT2s) and the apical monoamine transporters (OCTN2s) of the proximal convoluted renal tubule cells of the kidneys. The OCTN2s of the proximal convoluted renal tubule cells transport serotonin and dopamine that is not transported by the OCT2. While in the competitive inhibition state, serotonin and dopamine not transported by the OCT2s are found in the final urine as waste. Although there are numerous other forces that interact with the newly synthesized renal monoamines, they are small compared with the effects of these transporters. Proper interpretation of urinary serotonin and dopamine levels in the competitive inhibition state determines the functional status of the OCT2s of the proximal convoluted renal tubule cells of the kidneys, known as OCT assay interpretation. The OCT2s exist in three different phases dependent on the status of the entrance gate and lumen saturation." (Hinz et al 2011)



ORGANIC CATION TRANSPORTER RESPONSE

The goal of this approach is to achieve the:

- urinary serotonin in the phase 3 therapeutic range of 80 to 240 µg serotonin/g of creatinine
- urinary dopamine in the phase 3 therapeutic range of 475 to 1,100 µg dopamine/g of creatinine (Hinz et al 2011)

The 3 phase response of the organic cation transporters

Serotonin and dopamine exist in two states. "The endogenous state" is found when no amino acid precursors are being administered. "The competitive inhibition state" is found when significant amounts of amino acid precursors of both serotonin and dopamine are administered simultaneously.

"The basis for OCT assay interpretation requires that the entire system be placed into the competitive inhibition state and then two or more urinary serotonin and dopamine assays performed while taking serotonin and dopamine amino acid precursors at significantly varied dosing values. The results are then compared in order to determine the change in urinary serotonin and dopamine levels in response to the change in amino acid precursor dosing values. Urinary serotonin and dopamine values found on assay were reported in micrograms of monoamine per gram of creatinine in order to compensate for fluctuations in urinary specific gravity. A urinary serotonin or dopamine value less than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is defined as a Phase 2 response. A urinary serotonin or dopamine value greater than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is interpreted as being in Phase 1 or Phase 3. Differentiation of Phase 1 from Phase 3 is a follows. If a direct relationship is found between amino acid dosing and urinary assay response, it is referred to as a Phase 3 response. An inverse relationship is referred to as a Phase 1 response. The Phase 3 therapeutic range for urinary serotonin is defined as 80–240 µg of serotonin per g of creatinine. The Phase 3 therapeutic range for urinary dopamine is defined as 475–1100 µg of dopamine per g of creatinine." (Hinz et al 2011)

RESPONSE is like a light switch

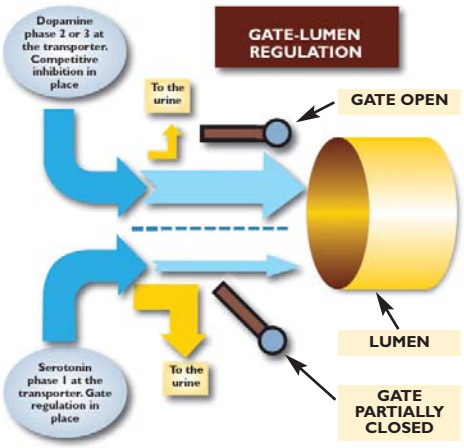
Some patients get relief of symptoms in one week while others may not get relief of symptoms until 2 or 3 months into treatment. Along the way most patients do not get better gradually with each amino acid dosing value adjustment. For most the response to amino acids is like a light switch, "on or off", with no relief of symptoms occurring until the proper amino acid dosing value is found secondary to several urinary transporter assays being performed.

TRANSPORTER FUNCTIONAL STATUS DETERMINATION

Neurotransmitter levels for all systems are primarily dependent on the functional status of the organic cation transporters.

GATE-LUMEN TRANSPORTER STATUS FOR EACH PHASE

	Gate	Lumen
Phase 1	Partially closed	Unsaturated
Phase 2	Open	Unsaturated
Phase 3	Open	Saturated



**Dual-gate lumen organic cation transporter model developed by Hinz et al 2010.*

As noted in numerous peer-reviewed scientific writings, determination of transporter functional status can only be done in the "competitive inhibition state" found when significant amounts of serotonin and dopamine amino acid precursors are being taken simultaneously. Assays in the endogenous state performed while taking no amino acids are meaningless.

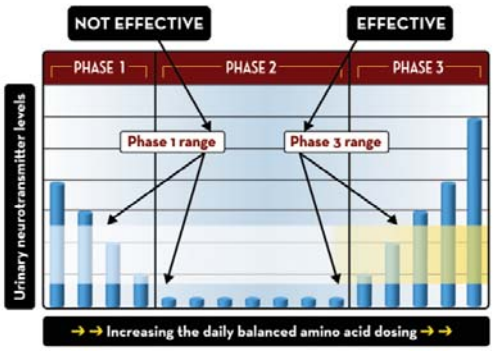
The goal of treatment is to get both the serotonin and dopamine into the phase 3 responses with urinary levels just over the phase 2 threshold (80 to 240 µ of serotonin per g of creatinine and 475 to 1,100 µ of dopamine per g of creatinine).

Interpretation of urinary data for phase determination rests on some simple concepts, but actual interpretation can become quite complex.

With each urine sample submitted to DBS Labs, a formal lab report is generated, followed the next day by a phase interpretation with suggested recommendations for moving serotonin and dopamine closer to the desired phase 3 ranges.

The phases of serotonin and dopamine occur independent of each other. Serotonin and dopamine can be in any of the three phases independent of each other.

Relief of symptoms is like shooting at a target, where urinary serotonin and dopamine in the phase 3 therapeutic ranges is the bull's eye. Some patients are symptom free by merely hitting the edge of the target; others need to be fully into the phase 3 therapeutic ranges before relief of symptoms is seen.



The organic cation transporters of the kidneys, brain, liver, and bowels are "identical and homologous". Once the amino acids and neurotransmitters are at equilibrium, determining the functional status of one set of transporters will give insight into other sets of transporters.

Monoamine Neurotransmitter Diseases

(Partial listing)

- Parkinsonism
- Obesity
- Bulimia
- Anorexia
- Depression
- Anxiety
- Panic Attacks
- Migraine Headaches
- Tension Headaches
- Premenstrual Syndrome (PMS)
- Menopause Symptoms
- Obsessive Compulsive Disorder (OCD)
- Compulsivity
- Insomnia
- Impulsivity
- Obsessionality
- Inappropriate Aggression
- Inappropriate Anger
- Psychotic Illness
- Fibromyalgia
- Chronic Fatigue Syndrome
- Adrenal Fatigue/Burnout
- Hyperactivity
- ADHD/ADD
- Hormone Dysfunction
- Adrenal Dysfunction
- Dementia
- Alzheimer's Disease
- Traumatic Brain Injury
- Phobias
- Chronic Pain
- Nocturnal Myoclonus
- Irritable Bowel Syndrome
- Crohn's Disease
- Ulcerative Colitis
- Cognitive Deterioration
- Functional Deterioration
- Increased Mortality Rate
- Organ System Dysfunction
- Chronic Stress
- Cortisol Dysfunction
- Hormone Dysfunction
- Restless Leg Syndrome

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MEDICAL FOODS based on scientific writings found in the following peer-reviewed scientific research:

Hinz, M. 2009 Depression, In: Kohlstadt I. editor. Food and Nutrients in Disease Management CRC Press; 465-481.

Hinz, M. Stein, A, Uncini T. 2010a The dual-gate lumen model of renal monoamine transport Neuropsychiatric Disease and Treatment 6 387–392

Hinz, M. Stein, A, Trachte, G, Uncini T. 2010b Neurotransmitter testing of the urine; a comprehensive analysis. Open Access Journal of Urology 2010:2 177–183

Hinz, M. Stein, A. Uncini T. 2010c A pilot study differentiating recurrent major depression from bipolar disorder cycling on the depressive pole, NeuroPsychiatric Disease and Treatment Neuropsychiatric Disease and Treatment:6 741–747

Hinz, M. Stein A. Uncini T. 2011a Treatment of attention deficit hyperactivity disorder with monoamine amino acid precursors and organic cation transporter assay interpretation Neuropsychiatric Disease and Treatment 2011:7 31–38

Hinz, M. Stein, A. Uncini T. 2011b Urinary neurotransmitter testing: considerations of spot baseline norepinephrine and epinephrine Open Access Journal of Urology 2011:3 19–24

Hinz, M. Stein, A. Uncini T. 2011c Amino acid management of Parkinson's disease: A case study International Journal of General Medicine 2011:4 1–10

Stein, A. Hinz, M. Uncini T. Amino acid responsive Crohn's disease, a case study. Clinical and Experimental Gastroenterology 2010:3 171–177

Trachte, G. Uncini, T. Hinz, M, 2009 Both stimulatory and inhibitory effects of dietary 5-hydroxytryptophan and tyrosine are found on urinary excretion of serotonin and dopamine in a large human population Neuropsychiatric Disease and Treatment:5 227–235

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CASE REPORT

Amino acid-responsive Crohn's disease: a case study

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Purpose: This paper reviews the clinical course of a case of severe Crohn's disease and discusses the scientific ramifications of a novel treatment approach.

Patients and methods: A case study of a 37-year-old male with a 22-year history of Crohn's disease whose clinical course had experienced no sustained remissions. The patient was treated with a protocol that utilized serotonin and dopamine amino acid precursors administered under the guidance of organic cation transporter assay interpretation.

Results: Within 5 days of achieving the necessary balance of serotonin and dopamine, the patient experienced remission of symptoms. This remission has been sustained without the use of any Crohn's disease medications.

Conclusion: In Crohn's disease, it is known that there is an increase of both synthesis and tissue levels of serotonin in specific locations. It is asserted that this is prima facie evidence of a significant imbalance in the serotonin–dopamine system, leading to serotonin toxicity. The hypothesis formulated is that improperly balanced serotonin and dopamine transport, synthesis, and metabolism is a primary defect contributing to the pathogenesis of Crohn's disease.

Keywords: serotonin, dopamine, organic cation transporters, OCT

Introduction

Symptoms of Crohn's disease in patients range on a spectrum from mild to very severe. Symptoms include diarrhea, abdominal pain, intermittent fever, rectal bleeding, loss of appetite, significant weight loss, arthralgias, fatigue, malaise, and headaches. Involvement of other organ systems beyond the intestinal tract, such as eyes, skin, and liver, may be present.[1]

As there is currently no known cure, treatment is focused on symptom control. Complications secondary to medications prescribed for symptom control may occur. When the disease fails to respond to the milder medications, more aggressive medications are prescribed. Medication complications can be severe, including infections, serum sickness, drug-induced lupus, diabetes, cancers, and even death.[2]

This paper documents a case study of a patient with severe Crohn's disease. The patient had suffered with Crohn's disease of progressing severity for 22 years, during which time no sustained remission of symptoms was noted. The patient suffered profound complications from infliximab, 6-mercaptopurine, and prednisone. He experienced no sustained response from mesalamine, low-dose naltrexone, or dietary modification. The patient's clinical course was complicated by steroid-induced insulin-dependent diabetes. He also suffered from severe weight loss, depression, fatigue, mal-

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aise, headaches, purulent-mucinous diarrhea, rectal bleeding, bilious vomiting, and diffuse arthralgias. Complaints of back pain resulted in back surgery with negative operative findings and no relief of symptoms. Exploratory gallbladder surgery was done in response to abdominal pain. The pathologist's report of tissue submitted from the gallbladder surgery was negative for any pathology. In February 2004, the patient had progressed to the most severe state of his disease, losing 25% of his body weight. The patient was fully disabled and unable to work. He experienced constant symptoms of Crohn's disease despite attempts at medication alteration. At all times from his first confirmed attack of Crohn's disease in 1990 at age 19 years, he was on one or more prescription drugs to try to control the disease symptoms.

The patient achieved full remission of symptoms in a matter of days once the proper orally administered serotonin and dopamine amino acid precursor dosing values were established with the guidance of urinary organic cation transporter (OCT) functional status determination (herein referred to as OCT assay interpretation).

Material and methods

The patient was treated with a novel treatment protocol developed by NeuroResearch Clinics (Duluth, Minnesota, MN, USA). Peer-reviewed publications from 2009[3,4] and 2010[5–7] outlined a novel "three-phase model" of OCT response to simultaneous administration of serotonin and dopamine amino acid precursors in significant amounts, which is the basis for OCT assay interpretation. Outlined in this paper is a proposed novel OCT model that potentially describes the etiology of the "three-phase response" of serotonin and dopamine during simultaneous administration of their amino acid precursors in varied daily dosing values.[5]

The protocol

Serotonin and dopamine exist in two states. The endogenous state is found when no amino acid precursors are being administered. The competitive inhibition state is found when significant amounts of amino acid precursors of both serotonin and dopamine are administered simultaneously. This novel approach places serotonin and dopamine in the competitive inhibition state and then optimizes their transport in proper balance through the OCTs with OCT analysis interpretation. The approach was developed by medical research that started in 1997. Peer-reviewed research covering methodology, applications, and the scientific foundation of this novel approach was published in 2009[3,4] and 2010.[5–7] Optimization of the serotonin–dopamine system has applications in any condition where an imbalance between serotonin and dopamine in transport, synthesis, or metabolism is present. The potential scope of applications is far-reaching.

The protocol utilized for treatment of Crohn's disease consisted of the amino acid dosing values listed in Table 1. This protocol has been covered in previous peer-reviewed research.[3,7]

The initial step of the protocol is the simultaneous administration of serotonin and dopamine amino acid precursors with no OCT functional status determination in order to place the system into a competitive inhibition state. Three dosing levels were available, as noted in Table 1. At the first visit, the patient was started on level 1 amino acid dosing. The patient was then followed weekly for evaluation of response to the start or change in amino acid dosing levels. As described in the results section of this paper, dosing was implemented as per Table 1. The patients took the amino acid dosing values of each level at the times indicated in Table 1.

If the patient failed to achieve full relief of symptoms on level 3 dosing, a urine sample was collected and submitted for urinary serotonin and dopamine laboratory assay. This was followed by OCT assay interpretation. Based on OCT assay interpretation, the amino acid precursors of serotonin and dopamine were adjusted in an effort to achieve full relief of symptoms or a balance of urinary serotonin and dopamine in the Phase 3 therapeutic range, whichever came first.[3,7]

OCT assay interpretation

The serotonin and dopamine filtered at the glomerulous are metabolized by the kidneys, and significant amounts do not make it to the final urine. Serotonin and dopamine found in the urine are monoamines synthesized in the proximal convoluted renal tubule cells and have never been found in the central nervous system or peripheral system. Serotonin and dopamine that are newly synthesized by the kidneys meet one of two fates. Urinary serotonin and dopamine levels are primarily dependent on the interaction of the basolateral monoamine transporters (OCT2s) and the apical monoamine transporters (OCTN2s) of the proximal convoluted

Table 1 Individual dosing value: milligrams of L-tyrosine/milligrams of 5-hydroxytryptophan*

Level	AM	Noon	4 PM	7 PM
Level 1	1500/150		1500/150	
Level 2	1500/150	1500/150	1000/300	
Level 3	1500/150	1500/150	1000/300	1000/300

Note: *The patient also received the following daily dosing values: 1000 mg of vitamin C, 220 mg of calcium citrate, 75 mg of vitamin B6, 400 μg of folate, 4500 mg L-cysteine, and 400 μg of selenium.

renal tubule cells of the kidneys.[5,8] The OCTN2s[8] of the proximal convoluted renal tubule cells transport serotonin and dopamine that is not transported by the OCT2.[5] While in the competitive inhibition state, serotonin and dopamine not transported by the OCT2s are found in the final urine as waste.[6] Although there are numerous other forces that interact with the newly synthesized renal monoamines, they are small compared with the effects of these transporters.[5] Proper interpretation of urinary serotonin and dopamine levels in the competitive inhibition state determines the functional status of the OCT2s of the proximal convoluted renal tubule cells of the kidneys, known as OCT assay interpretation. The OCT2s exist in three different phases dependent on the status of the entrance gate and lumen saturation.[3–7] Table 2 outlines the correlation between entrance gate status and lumen saturation.

The basis for OCT assay interpretation requires that the system be placed into the competitive inhibition state and then two or more urinary serotonin and dopamine assays performed while taking serotonin and dopamine amino acid precursors at significantly varied dosing values. The results are then compared in order to determine the change in urinary serotonin and dopamine levels in response to the change in amino acid precursor dosing values.[3–7]

Urinary serotonin and dopamine values found on assay were reported in micrograms of monoamine per gram of creatinine in order to compensate for fluctuations in urinary-specific gravity. A urinary serotonin or dopamine value less than 80 or 475 μg of monoamine per 1 g of creatinine, respectively, is defined as a Phase 2 response. A urinary serotonin or dopamine value greater than 80 or 475 μg of monoamine per 1 g of creatinine, respectively, is interpreted as being in Phase 1 or Phase 3. Differentiation of Phase 1 from Phase 3 is a follows. If a direct relationship is found between amino acid dosing and urinary assay response, it is referred to as a Phase 3 response. An inverse relationship is referred to as a Phase 1 response. The Phase 3 therapeutic range for urinary serotonin is defined as 80–240 μg of serotonin per 1 g of creatinine. The Phase 3 therapeutic range for urinary dopamine is defined as 475–1100 μg of dopamine per 1 g of creatinine.[3,5–7]

Table 2 The following considerations exist with regard to the basolateral monoamine organic cation transporters of the proximal convoluted renal tubule cells*

	Phase 1	Phase 2	Phase 3
Serotonin or dopamine transporter entrance gates	Partially closed	Open	Open
Transporter lumen saturation	Unsaturated	Unsaturated	Saturated

Note: *In Phase 1, the serotonin and dopamine gates are partially closed, restricting access to the transporter. In Phases 2 and 3, the gates are open, allowing full access to the transporter by serotonin and dopamine. In Phases 1 and 2, the lumen of the transporter is not saturated with serotonin and dopamine. In Phase 3, the lumen of the transporter is saturated with serotonin or dopamine.[5]

Processing, management, and assay of the urine samples collected for this study were as follows. Urine samples were collected 6 hours prior to bedtime with 4:00 PM being the most frequent collection time point. The samples were stabilized in 6 N hydrochloric acid to preserve the dopamine and serotonin. The urine samples were collected after a minimum of 1 week, during which the patient was taking a specific daily dosing of amino acid precursors of serotonin and dopamine. No doses were missed. Samples were shipped to DBS Laboratories (Duluth, MN). Urinary dopamine and serotonin were assayed utilizing commercially available radioimmunoassay kits (3 CAT RIA IB88501 and IB89527, both from Immuno Biological Laboratories, Inc., Minneapolis, MN). The DBS laboratory is accredited by Clinical Laboratory Improvement Amendments as a high-complexity laboratory. OCT assay interpretation was performed. Results were reported in micrograms of monoamine per gram of creatinine to compensate for specific gravity variances in the urine.

Results

An endoscopy examination, prior to treatment with amino acids while the disease was active, was performed in September 2005. Results revealed several apthous ulcers in the terminal ileum. Tissue biopsy confirmed this diagnosis.

At the initiation of the amino acid protocol, the patient was still taking mesalamine, low-dose naltrexone, and escitalopram. The patient reported no relief of symptoms after any of these drugs were started. The escitalopram was discontinued at the start of amino acid treatment, and the mesalamine and low-dose naltrexone were continued.

At the first visit, the patient was started on level 1 amino acid dosing as per Table 1. One week later there was no change in symptoms, and the patient's amino acid dosing values were increased to level 2 (see Table 1). The patient achieved lessening of the symptoms when he was on level 2 amino acid dosing. At that point, the patient revealed that he felt that this approach was the best treatment he had experienced during the course of his 22-year illness. The amino acids were increased to level 3 dosing (see Table 1), with no further change in symptoms. After 1 week of level 3 dosing, a urine sample was obtained and analyzed. The reported values were then submitted for OCT assay interpretation.

When the first urine sample was collected for OCT assay interpretation, the patient was taking level 3 dosing: 900 mg 5-hydroxytryptophan (5-HTP), 5000 mg L-tyrosine, and 4500 mg L-cysteine with cofactors.

The first urinary assay revealed serotonin to be in Phase 3 (Table 2) with a reported value of 5150.7 µg of serotonin per 1 g of creatinine, and a dopamine in Phase 2 (Table 2) with a reported value of 206.4 µg of dopamine per 1 g of creatinine.

After the first OCT assay interpretation, the patient's daily amino acid dosing was increased by 1000 mg of L-tyrosine and 240 mg of L-dopa. At that point, the patient was taking the following in divided daily doses: 900 mg 5-HTP, 6000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors. After 1 week taking these new amino acid dosing values, there was no change in the patient's symptoms.

A second urine sample was submitted for analysis, followed by OCT assay interpretation. This revealed that the patient's urinary serotonin was in Phase 3 (Table 2) at 12,611.1 µg of serotonin per 1 g of creatinine, and his dopamine was in Phase 3 (Table 2) at 741.3 µg of dopamine per 1 g of creatinine.

The recommendation was to decrease the daily 5-HTP dosing by 300 mg per day, increase L-tyrosine by 1000 mg per day, and continue other amino acids as before. The patient was then taking the following in divided daily doses: 600 mg 5-HTP, 7000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors.[5] Within 1 week of this dosing value change, the patient became asymptomatic, indicating that adequate OCT balance of the serotonin–dopamine system had occurred. The patient's response and remission with amino acid treatment was very impressive and relatively abrupt compared with the 22-year course of his disease. This profound resolution of symptoms was achieved within 6 weeks of the first clinic visit.

The patient noted the return of solid stools, no further vomiting, restored energy, increased motivation, and resolution of depression symptoms. All prescription medications that the patient had been taking since the start of amino acid treatment were discontinued after 6 weeks of amino acid treatment, including mesalamine and naltrexone, with no return of symptoms. The amino acid dosing values that had induced relief of symptoms were continued.

Following remission of symptoms, the patient's sedimentation rate returned to the normal range. His weight stabilized at approximately 20 pounds above the lowest weight attained while disease symptoms were present. The patient reported that he was very comfortable at that weight. The patient found that if he missed a dose of the amino acids, some of the Crohn's disease symptoms would return.

A third OCT assay interpretation was obtained 5 months later with amino acid dosing values that induced relief of symptoms. Urinary serotonin was reported as 9019.5 µg of serotonin per 1 g of creatinine and urinary dopamine was 604.3 µg of dopamine per 1 g of creatinine; both were in Phase 3 (Table 2). At this point, the patient was still asymptomatic. The recommendation was to decrease the daily 5-HTP dosage to 300 mg, decrease L-tyrosine dosing by 1000 mg per day, and continue other amino acids as before. After this dosing value change, the patient was then taking the following in divided daily doses: 300 mg 5-HTP, 6000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors. Following this change in amino acid dosing values, the patient continued to be asymptomatic, a state that exists to this day as long as he is compliant with the prescribed amino acid dosing values.

Endoscopy subsequent to remission of symptoms was performed in March 2010. This was 26 months after starting the amino acid protocol guided by OCT assay interpretation and 24 months after achieving relief of symptoms. This endoscopy was performed by the same gastroenterologist that performed endoscopy prior to remission of symptoms. At this endoscopy, the patient was taking his amino acids daily with no prescription medications. He was taking no insulin or oral hypoglycemic agents, and his HbA_{1c} had returned to normal. There were no signs of diabetes or other illnesses. He had returned to full-time gainful employment, after a period of over 4 years during which he was fully disabled.

The gastroenterologist reported that for the first time in 10 years of caring for the patient, the Crohn's disease was in complete remission. This finding was verified by the pathologist after review of tissue samples submitted.

As of the time of writing this paper, the patient continues to do well with no infections or adverse reactions. He is gainfully employed and living a normal life. All follow-up testing, including sedimentation rates, have been normal.

Discussion

Scientific basis

The authors have documented a number of patients with Crohn's disease who experienced similar remission of symptoms with this approach. This case was selected for this paper due to the severity of disease in the patient.

Serotonin and dopamine levels inside and outside of the cell structures containing them are primarily a function of

transporter status.[5] The question raised is how OCT assay interpretation of renal transporters relates to the OCTs of the gastrointestinal (GI) tract. The hypothesis is that performing OCT assay interpretation on one set of OCTs will give insight into transport of serotonin, dopamine, and their precursors at other OCTs throughout the body. Within 3–5 days of starting or changing amino acid precursor dosing values, serotonin, dopamine, and their precursors reach equilibrium throughout the body.[3,5–7] At equilibrium, amino acid precursors, serotonin, and dopamine exert similar effects at cation transporters throughout the body.

In the competitive inhibition state, the serotonin and dopamine systems function as one system in transport, synthesis, and metabolism. Affecting change to one system will affect both systems in their functions. Serotonin, dopamine, and their amino acid precursors compete for transport at the OCTs. Significant increases in one monoamine will decrease monoamine and precursor transport of the other system through competitive inhibition. Transport of precursors into the cells is required in order to place them in an environment where synthesis takes place. The same enzyme, the L-aromatic amino acid decarboxylase enzyme (AAAD), is responsible for synthesis of serotonin and dopamine. Creating an environment where precursors of one system are significantly increased without significantly increasing the precursors of the other system leads to decreased access to the AAAD by precursors of the other system, with associated decreased synthesis or depletion due to competitive inhibition. Both serotonin and dopamine are metabolized by the monoamine oxidase (MAO) enzyme system. A significant increase in levels of one system will increase MAO activity, leading to increased metabolism and depletion of the other system.[2,5,6]

In the intestinal tract of Crohn's patients there is excessive synthesis with associated increased tissue levels of serotonin.[8,9] In Crohn's disease, high levels of serotonin dominate synthesis, metabolism, and transport, leading to dopamine and catecholamine levels that are low relative to the balance needed to function properly with the serotonin levels present.[3,5]

OCT assay interpretation

As noted in previous peer-reviewed research by the authors, OCT phase determination defines the status of the serotonin and dopamine gates at the entrance to the basolateral monoamine OCT (open or partially closed) of the proximal convoluted renal tubule cells of the kidneys and the status of serotonin and dopamine saturation in these transporters (see Table 2).[5]

Proper interpretation of the findings requires the following explanation. Serotonin and dopamine both need to be in the competitive inhibition state when OCT assay interpretation is performed. This means that significant dosing values of both serotonin and dopamine need to be administered simultaneously. When in the competitive inhibition state, serotonin and dopamine are in full competition for transport, synthesis, and metabolism.[3,5] Testing of the urine is only done after amino acid precursors of the monoamines are started in accordance with the protocol, placing the serotonin–dopamine system in the competitive inhibition state. Baseline testing in the endogenous state prior to administration of amino acid precursors is of no value, as these assay levels correlate with nothing. As noted in previous peer-reviewed literature, baseline testing of urinary serotonin and dopamine does not correlate with baseline assays performed on subsequent days in the same individual.[6]

Simply giving the patient one or more amino acid precursors is not the key to optimal outcomes. The OCT needs to be challenged with serotonin and dopamine precursors in significant amounts to place transport in the competitive inhibition state so that proper OCT assay interpretation can be realized.[5]

The OCTN

There is a known genetic defect of OCTN1 and OCTN2 in the colon of patients suffering from Crohn's diease.[9] All OCT and OCTN transporters are capable of transporting organic cations, including serotonin, dopamine, and their precursors.[8] In Crohn's disease, the serotonin content of the mucosa and submucosa of the proximal and distal colon is increased.[10] Increased synthesis of serotonin is known to be associated with Crohn's disease.[11] No reasonable explanation of the etiology of serotonin elevation in the colon tissue of Crohn's disease patients has been put forth previously.

It is postulated that the known OCTN1 and OCTN2 genetic deficit may be tied to the increased synthesis and tissue levels of serotonin seen with Crohn's disease. Based on OCT assay interpretation, it appears that a severe imbalance between serotonin and dopamine transport, synthesis, and metabolism is at the heart of Crohn's disease.

An imbalance of the serotonin–dopamine transport system has been linked to numerous diseases.[3,5–7] It is proposed that much of the clinical constellation found with Crohn's disease may be induced by a serotonin toxicity of the colon exacerbated by relatively low levels of dopamine resulting from defective OCTN transport.

In the GI tract, serotonin is contained primarily in the enteroendocrine cells (ECs). The serotonin–dopamine transporter balance of the ECs controls paracrine–autocrine and/or endocrine mediators that modulate GI function.[12] It is asserted that proper treatment needs to include correct management of the serotonin and dopamine imbalance in transport, synthesis, and metabolism. The only definitive way to address these problems optimally is with OCT analysis interpretation in the competitive inhibition state that is established with proper amino acid precursor administration.

It is postulated that the patient's Crohn's disease was impacted in a positive manner as follows. It is known that there is increased synthesis of serotonin with increased serotonin levels in the proximal and distal colon.[11] Levels of the serotonin–dopamine system are impacted primarily by synthesis, uptake, and metabolism. For serotonin and dopamine to be synthesized, their amino acid precursors need to be transported into the structures where this occurs. There appears to be a defect in transport of serotonin precursors of the colon. Serotonin precursors are transported preferentially at the exclusion of dopamine precursors, leading to high levels of synthesis, high levels of serotonin in portions of the colon, and compromise of catecholamine synthesis. Properly balancing the serotonin and dopamine precursor transport leads to a decrease in serotonin synthesis, less serotonin in the tissue of the proximal and distal colon, and an increase in synthesis of dopamine, norepinephrine, and epinephrine. Increased serotonin levels of Crohn's disease lead to increased MAO activity, which without reciprocal increases of the catecholamines leads to increased metabolism of the catecholamines, further exacerbating the imbalance.

Other implications

With a case study such as this there is always the possibility that remission was coincidental to treatment. This patient had a 22-year history of progressively worsening Crohn's with no remissions and has been free of Crohn's disease symptoms clinically and on biopsy for 2.5 years since the appropriate dosing values of serotonin and dopamine amino acids were established. We leave it to the reader to speculate as to the odds of this being a spontaneous coincidental remission versus a response to properly balanced amino acids.

One other aspect of the patient's treatment needs to be discussed. The patient was suffering from depression. Previously published peer-reviewed literature by the authors indicates that this same approach with OCT assay interpretation for treatment of depression is effective.[3,7] In this case study, the patient's depression resolved when the serotonin and dopamine were balanced to the degree needed for relief of Crohn's disease symptoms. It is asserted that it was no coincidence that the patient's depression resolved simultaneously with the resolution of the symptoms of Crohn's disease.

Conclusion

In recent years, a genetic defect of the OCTN1 and OCTN2 of the colon has been identified in patients with Crohn's disease. The OCTN1 and OCTN2 are responsible for transport of cations, including the monoamines of the serotonin–dopamine system and their precursors. It is known with Crohn's disease patients that there is a marked increased in serotonin levels of the proximal and distal colon associated with a defect in serotonin synthesis. It remains to be proven whether a transport problem exists in the serotonin–dopamine system induced by the OCTN1 and OCTN2 genetic defect found in Crohn's disease. For now, these observations cannot be overlooked. Clearly, further studies relating to OCT analysis interpretation and the OCTN transporters of the colon as they relate to other abnormal findings associated with Crohn's disease are indicated.

This paper potentially opens the door to a new area of treatment and study in Crohn's disease patients. The goal of the paper is to stimulate further interest in these findings in order to duplicate, confirm, and invite scrutiny of these results.

Disclosure

Dr Marty Hinz is President of Clinical Research, Neuro-Research Clinics, Inc., Cape Coral, Florida, USA. Dr Thomas Uncini is Medical Director of DBS Labs, Duluth, Minnesota, USA. Dr Alvin Stein reports no disclosures.

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