

TECHNICAL



the human communication system



NEUROSCIENCE™

TECHNICAL GUIDE

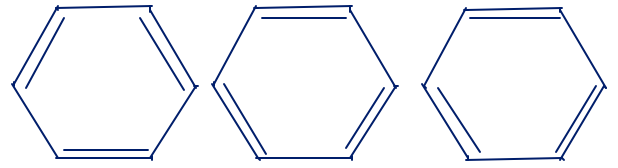


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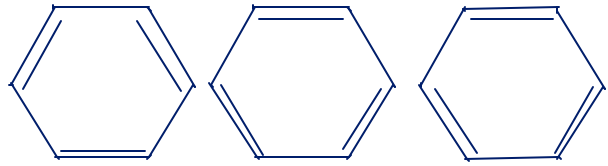
Introduction

“...providing the building blocks necessary

Neurotransmitters along with billions of neurons and trillions of synapses make up the human communication system. The synapses and neurotransmitters serve as the communication channels that determine how we think and act and how our body functions.

If neurons lose the ability to properly relay signals, impaired organ function, metabolic processes and ultimately disease will result. The exact cause is unknown, but it is influenced by several factors that include poor diet, toxic exposure, stress, and certain genetic predispositions.

A compromised communication system is marked by uncontrolled or erratic firing of neurons. Sub-optimal neurotransmitter levels, an imbalance between the inhibitory and excitatory systems, or a combination of the two causes this loss of control. Laboratory measurements of neurotransmitters have shown that insufficient or unbalanced levels are present in patients with conditions such as fatigue, insomnia, anxiety, depression, obesity, and many others. Many of these conditions require aggressive medication and medical attention.



to make more neurotransmitters ..."

There are several options with which to address these issues. Numerous pharmaceutical therapies, like the SSRIs, are available. Another option is the use of targeted Amino Acid Therapy.

Both methods provide relief of clinical symptoms but work in different ways. Medications such as SSRIs work by redistributing the available neurotransmitters. The drawback is that medications generally do not increase the synthesis or production of neurotransmitters. Amino Acid Therapy works by providing the building blocks necessary to make more neurotransmitters and increase supply.

Recent research in the area of neurotransmitter correction and optimization with the use of targeted Amino Acid Therapy has shown great promise in the improvement of the patient's clinical condition. Milestones in this effort include the development of new assays that allow for an accurate assessment of key neurotransmitters, the establishment of "optimal ranges" for neurotransmitters, and the development of the targeted amino acid therapies for neurotransmitter restoration. These are all tools and guidelines available to aid the physician in the correction of neurotransmitter levels.

We are just beginning to understand how this complex communication system works. However, the clinical outcomes of thousands of patients in whom neurotransmitter levels have been corrected and optimized is evidence that this new medical tool is here to stay and will become an essential part of a patient's workup.

Optimization and manipulation of neurotransmitter levels requires an understanding of their regulation and feedback in order to successfully intervene. This technical guide is intended to highlight some of the important aspects of neurotransmitter optimization as well as provide information on NeuroScience products and methods of treatment.

Gottfried Kellermann, PhD

Neurotransmitters and Clinical Conditions

Neurotransmitters are the chemical messengers that relay signals between nerve cells and are present throughout the body. Without adequate neurotransmitter levels, signals can become disrupted, distorted, or stunted. This results in a significantly impaired quality of life because deficient neurotransmission causes patients to suffer from a variety of symptoms. Many apparently dissimilar diseases have a common underlying neurotransmitter imbalance and are addressed with therapies that affect neurotransmitter function. This becomes clear when the vast number of indications for neurotransmitter-effective drugs is examined.

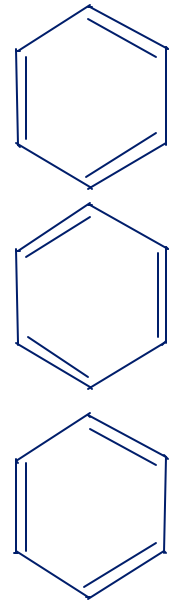
Prozac (fluoxetine) for example is a commonly prescribed antidepressant from the class of neuroactive therapies known as SSRIs and has been recommended or approved for the treatment of the following conditions in addition to depression.

- Alcohol addiction
- Anorexia Nervosa
- Anxiety
- Binge eating
- Bulimia
- Fibromyalgia pain
- Headache pain
- Irritable Bowel Syndrome
- Migraine
- Panic attacks
- Premenstrual Dysphoric Disorder
- Post-traumatic stress disorder
- Sexual dysfunction
- Smoking cessation
- Social anxiety and shyness
- Weight loss

Conclusion:

The symptoms seen in the above conditions may be related to an imbalance in neurotransmitters. Drugs that affect neurotransmitters, like the frequently prescribed Prozac, are used to modify the imbalance and therefore the symptoms seen in many conditions.

The NeuroScience Program is designed to correct the imbalance by optimizing neurotransmitter levels. The process of optimization can provide relief from symptoms.



“few patients may have an imbalance that is limited to a single neurotransmitter”

Neurotransmitter Network: A Delicate Balance

Some reuptake inhibitors, like *Lexapro*, only prevent the reuptake of serotonin while others like *Wellbutrin* only prevent the reuptake of norepinephrine. It is common for a patient to require more than one of these medications to achieve symptom relief due to the balanced serotonin and norepinephrine effect a combination of therapies provides. The need for this combination is well understood and other reuptake inhibitors like *Effexor* have an effect on both serotonin and norepinephrine. There is a complex interaction among the many neurotransmitters.

The NeuroScience Program has found that maintaining the proper ratio and supporting neurotransmitters in the correct sequence is critical to the success of amino acid therapies. A few patients may have an imbalance that is limited to a single neurotransmitter, but the vast majority has imbalances involving multiple neurotransmitters and therefore requires therapies that address multiple neurotransmitters. For this reason, many patients who had their serotonin increased with 5-HTP failed to achieve a positive clinical response. However, if amino acid therapies also

address the catecholamines, a much greater number of patients will show a clinical improvement.

The ratios of serotonin to catecholamine precursors in the NeuroScience formulas are based on this principle. NeuroScience formulas are more effective than general amino acid supplements because general amino acid supplements do not contain the proper ratios of amino acids or address multiple neurotransmitters. Additionally, the modulatory nature and GABA potentiating actions of serotonin dictates that it must be addressed prior to increasing catecholamine levels.

While this is a simplified explanation, it covers the basic theory behind the amino acid therapies used in the NeuroScience neurotransmitter Optimizing Programs. Many other neurotransmitters are involved in the regulation of neurotransmission. Some like GABA can be tested and are known to cause a predictable attenuation of neurotransmission and along with serotonin regulate catecholamine activity. Others like phenylethylamine (PEA) have roles that are clearly defined but were not measured until recently. Others still wait to be discovered.

The Frequency of Neurotransmitter-Related Symptoms

Many conditions, which patients seek relief from, can be worsened due to a neurotransmitter imbalance. Consider the following frequency of neurotransmitter-related diseases in the US:

Depression	10-12%	Migraine	5%
Anxiety	10-30%	Obesity/ Overweight	50-60%
Insomnia	10%	PMS	15%
Irritable Bowel Syndrome	15%	ADD/ADHD	20-22%
Hypertension	10%	Fibromyalgia	5%

These numbers demonstrate that a majority of patients seeking healthcare suffer from symptoms that have been related to neurotransmitter function. The NeuroScience Program works to address the underlying neurotransmitter imbalances responsible for the symptoms frequently seen in these disorders.

Neurotransmitter Related Symptoms

Fatigue	Chronic muscle/joint pain
Inappropriate hunger/food cravings	Irritability/hostility
Inability to focus/concentrate	Depression or agitation
Excessive body fat	Obsessive/compulsive behaviors
Sleep disturbances	Physical or emotional stress
Recurrent diarrhea /Constipation	Headaches

Many apparently unrelated symptoms are influenced by the effects of neurotransmitters and optimizing neurotransmitters can improve many patient symptoms.

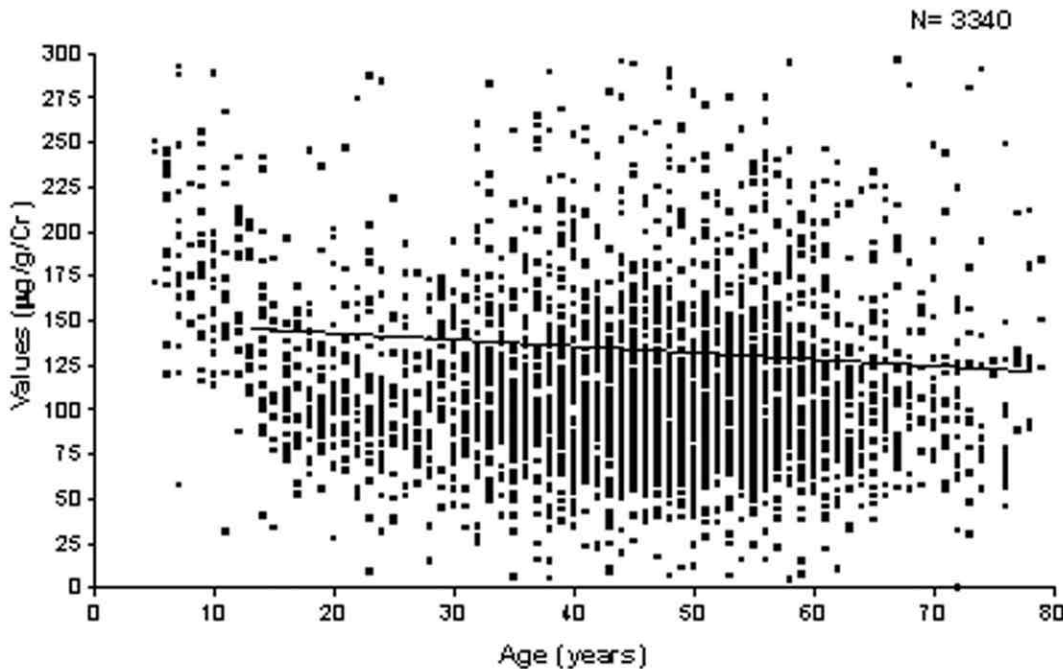
The NeuroScience Program and therapies has been successfully applied to the neurotransmitter imbalances that can cause these symptoms.

Optimization of Neurotransmitter Levels

The laboratory evaluation of neurotransmitter levels has shown that approximately 70% of the population has some degree of neurotransmitter imbalance. An alarming figure confirmed by the increase in the number of patient visits regarding these conditions, as well as the number of prescriptions written for antidepressants and the growing number of obese people who cannot combat their weight due to a lack of appetite control. Figure 1 represents the nature of this variability by displaying the serotonin levels measured in patients.

Serotonin Levels in the Average Patient Population

Figure 1. This graph shows the wide variation seen in baseline urinary serotonin levels seen in unselected patients with neurotransmitter-related symptoms. Other neurotransmitters display a similar variability.



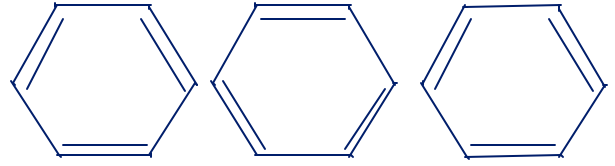
A laboratory assessment of neurotransmitter levels is the first step toward successfully treating patients with these symptoms. Unpublished data from NeuroScience.

Neurotransmitter Testing

“Neurotransmitter testing is used to establish baseline values and to identify the neurotransmitter imbalance ...”

Neurotransmitter testing is an important part of the NeuroScience Optimizing Program. Testing is used to determine which therapies are needed and to set a benchmark from which patient progress can be monitored. Neurotransmitter levels are affected by stress, lifestyle, genetics, and diet. Neurotransmitter testing is used to establish baseline values and to identify the neurotransmitter imbalance that is contributing to the patient's symptoms. While specific neurotransmitter patterns are seen in some conditions/symptoms, neurotransmitter imbalances may also result in symptoms unique to the patient. This is due to the unique genetic makeup and environmental factors that influence the patient as well as influences of unmeasured neurotransmitters.

For example, one patient with low serotonin and high norepinephrine may suffer from hypertension while another may suffer from anxiety. This could be due to either a biochemical differences in the patients themselves or differences in the level of another neurotransmitter. In this case, a low



GABA level in the hypertensive patient and a high GABA level in the anxiety patient would provide an explanation for the differences in clinical presentation and result in the selection of different therapies.

Another example of how testing influences therapy choice can be seen in catecholamine treatment. Low catecholamine levels may be addressed with therapies that contain phenylalanine, tyrosine, or L-dopa. If the patient has low catecholamines and requires more PEA, phenylalanine would be the appropriate therapy choice. If the patient has low catecholamine and requires less PEA, tyrosine or L-dopa would be a better therapy choice.

Baseline Testing

Because apparently similar test results can accompany different clinical presentations, the patient baseline test is an important benchmark. Basing the therapy protocol on symptoms alone will not

provide the information needed to address the underlying neurotransmitter imbalance. The baseline test also provides an important reference point to monitor the effects of therapy.

Not only is testing used to verify the need for a specific dose, laboratory assessments are also used to indicate a need to change a patient's dosing. Due to the close interaction between serotonin, dopamine, epinephrine, norepinephrine, and GABA, all should be included in general patient assessments.

Another test to consider is the neurotransmitter PEA, which is involved in depression, ADD/ADHD, and autism. The adrenal hormones and the sex hormones also influence neurotransmitter function. Therefore, hormone levels should be included when a more comprehensive clinical picture is desired and when changing hormone levels are a part of the clinical presentation.

Specimen Types

Neurotransmitters are present throughout the body and can be measured in a number of specimen types. Those measured most frequently are Urine, Plasma, Saliva, and Cerebral spinal fluid. The resources of the healthcare provider and the risk-benefit ratio are factors used to determine the type of specimen. Information on cerebral spinal fluid is included for reference because it has been used in some medical studies and rare developmental diseases.

Cerebral Spinal Fluid

Cerebral Spinal Fluid is generally collected by lumbar puncture to identify an infection, meningitis, of the brain or spinal cord. This procedure has also been used to collect specimens for neurotransmitter studies. The risks of this procedure are significant and this is not a recommended method of assessing neurotransmitters.

Risks associated with Lumbar puncture

- Allergic reaction to the anesthetic.
- Headache after the test is relatively common and minimized by keeping the patient lying down for 6-8 hours after the procedure.
- Bleeding into the spinal canal.
- Damage to the spinal cord if the needle is inserted too far, the patient moves, or the pressure is high.
- The test should not be performed if raised intracranial pressure is suspected, as there is a risk of brain herniation under pressure, brain damage, or death.

Plasma

While absent of significant patient risks, neurotransmitter levels change rapidly in plasma and are affected by patient posture and the stress of venipuncture. A plasma specimen for neurotransmitter testing is collected by indwelling catheter and after the patient has remained in a supine position for 30 minutes. Specimens must be chilled on ice, centrifuged under refrigeration, and delivered frozen.

Platelet

Platelet serotonin is considered to represent a reserve pool of peripheral serotonin. Platelets have a specific serotonin binding capacity. Differences in this capacity may influence mood and coagulation. Chronic treatment with fluvoxamine (Luvox) decreases platelet serotonin. Levels are not influenced by food or venipuncture. Requires a frozen acid-citrate dextrose (ACD) tube (yellow-stopper), platelet-rich-plasma specimen and ACD whole blood.

Saliva

Saliva specimens are noninvasive and collection procedures do not carry any patient risk. The level of neurotransmitter in saliva fluctuates much less rapidly than plasma. Saliva analysis provides an integrated measurement representing the average neurotransmitter levels over 10-30 minutes.

Urine, 24 hour

Neurotransmitters and their metabolites are excreted in the urine. Collection of a 24-hour urine specimen provides a risk free way of assessing the total output of neurotransmitters. There are however significant variations in the level of a neurotransmitter depending on time of day. These differences are important in determining symptoms but are obscured in a 24-hour urine specimen.

Urine, Timed

A 2-3 hour timed urine collection beginning after the first morning void, provides an integrated measurement representing the average neurotransmitter activity during this period. This time period accurately represents neurotransmitter activity and avoids fluctuations that occur later in the day due to stress, meals, or therapies. Patients that are using prescription neurotransmitter acting therapies are asked to list the medication and doses they are taking. Patients taking amino acid therapies are instructed to take their therapies normally the day prior to but not the morning of their urine specimen collection.

The timed urine specimen has been used for the vast majority of neurotransmitter tests performed by NeuroScience. This specimen is recommended as the primary test for screening patients with neurotransmitter-related symptoms and for monitoring neurotransmitter precursor therapy.

Diurnal Variation of Neurotransmitters

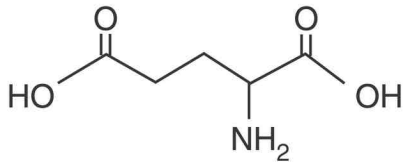
$\mu\text{g}/\text{grCr}$	6am	9am	Noon	3pm	6pm	9pm
Epinephrine	1.5	10.1	11.6	7.0	4.6	3.5
Norepinephrine	10.3	41.9	52.0	34.1	28.7	16.6
Dopamine	131.3	141.4	115.2	108.8	99.7	113.7
Serotonin	111.4	88.4	80.6	74.3	75.4	78.4
GABA	5.5	8.0	4.2	4.3	3.1	4.4
PEA	216.7	355.1	534.4	300.1	341.0	280.9

Table I. This table lists the levels of neurotransmitter in urine specimens collected from a single patient during the course of one day. The 6am specimen is the first morning void. While the absolute values will differ from patient to patient, the trends are preserved.

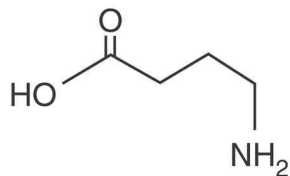
Epi, NE, GABA, and PEA rise and fall during the course of a day.

Dopamine and Serotonin values are relatively stable throughout the day.

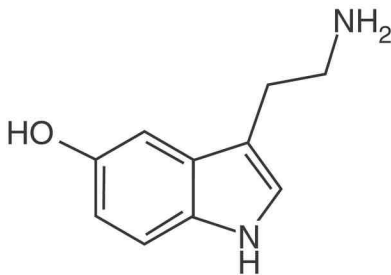
Neurotransmitters Available for Diagnostic Testing



Glutamate



GABA



Serotonin

Glutamate (available soon)

Glutamate is the major excitatory neurotransmitter in the brain. In fact it is believed that 70% of the fast excitatory CNS synapses utilize glutamate as a transmitter. Excitatory neurotransmitters increase the activity of signal-receiving neurons and play a major role in controlling brain function. Glutamate exerts its effects on cells in part through three types of receptors that, when activated, allow the flow of positively charged ions into the cell. Of these, the N-methyl-D-aspartate (NMDA) receptor plays a particularly important role in controlling the brain's ability to adapt to environmental and genetic influences.

An event or process that dramatically increases the function glutamate often induces the death neurons. Such a scenario is believed to take place in e.g. ischemia, trauma, hypoxia, hypoglycemia, and hepatic encephalopathy. More mild but chronic malfunctioning of glutamatergic systems may be involved in many neurodegenerative diseases such as Huntington's disease, Parkinson's disease, Alzheimer's disease, vascular dementia, amyotrophic lateral sclerosis, AIDS-neurodegeneration, Tourette's syndrome, and Korsakoff syndrome. It is unlikely that a disturbance of glutamate homeostasis is the sole initiator of these neurodegenerative diseases, but rather that excitotoxicity plays a pivotal executive role in events triggered by other processes such as energy deficits that facilitate the neurotoxic potential of endogenous glutamate.

GABA

GABA is a true neurotransmitter and is the major inhibitory neurotransmitter of the brain, occurring in 30-40% of all synapses. GABA is second only to glutamate the brain's major excitatory neurotransmitter. The GABA concentration in the brain is 200-1000 times greater than that of the monoamines or acetylcholine.

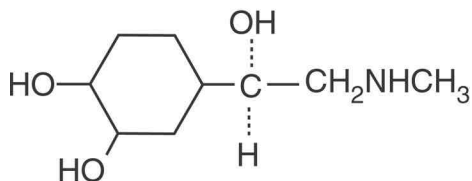
GABA is somewhat unique among neurotransmitters insofar as it is commonly inactivated (after release into the synapse) by active transport into the astrocyte glial cells that are closely associated with synapses—most neurotransmitters are subject to reuptake by the presynaptic neuron. Significant quantities of glutamine are normally present in the brain to support the complex process of GABA synthesis. GABA, as well as glutamate are synthesized from the amino acid glutamine. Glutamine is transported into the presynaptic terminals of inhibitory neurons by the glutamine transporter (GlnT) and is catalyzed by the actions of the enzyme glutamine deaminase to form glutamate. Glutamate in turn is converted into GABA through the actions of glutamic acid decarboxylase (GAD). (NOTE: This biosynthetic route is somewhat more complex than originally thought. Some studies have demonstrated that the glutamate formed from glutamine may enter the tricarboxylic acid (TCA) cycle before being converted to GABA.) The vitamin B6 derivative pyridoxal phosphate is a cofactor in the synthesis of GABA, which is why seizures occur in Vitamin B6 deficiency.

Like glycine, the GABA receptor form a chloride ion channel, allowing more chloride ions to enter the cell and thus making the membrane less likely to depolarize. By potentiating the effects of GABA, the benzodiazepines function as so-called “minor tranquilizers” (to be distinguished from the anti-psychotic “major tranquilizers”). Anxiety is the most frequently diagnosed psychiatric disorder — affecting 10-30% of people — that is why diazepam (Valium) was for many years the most frequently prescribed drug in North America. Alcohol & barbiturates have similar effects on the GABA receptor. In fact, potentiation of chloride influx into neurons is a major mechanism in the effect of alcohol on the brain. Some of the effects of benzodiazepines are probably due to GABA synapses on monoamine-producing neurons.

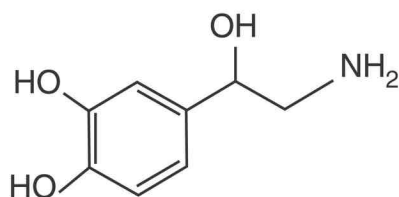
Serotonin

Serotonin is an amine neurotransmitter synthesized by enzymes that act on tryptophan and/or 5-HTP. Serotonin is stored in presynaptic vesicles and released to transmit electrochemical signals across the synapse. Serotonin has been extensively studied and is a therapeutic target for diseases like depression, compulsive disorders, anxiety, and migraines.

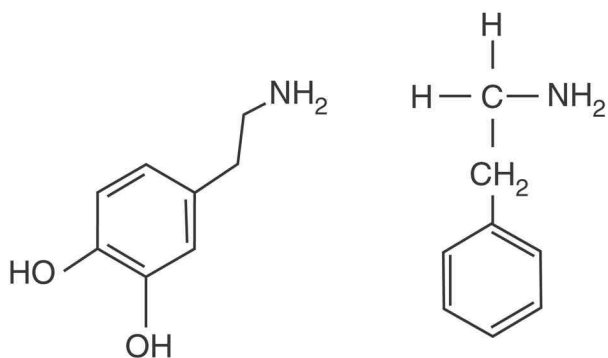
Serotonin acts, in most cases, as an inhibitory neurotransmitter and like GABA modulates neuron voltage potentials to inhibit glutamate activity and neurotransmitter firing.



Epinephrine

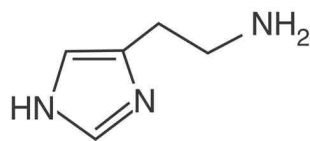


Norepinephrine



Dopamine

PEA



Histamine

Epinephrine

Epinephrine is a neurotransmitter and hormone essential to the body's metabolism and is also known as adrenaline. As a neurotransmitter epinephrine regulates attentiveness and mental focus. Epinephrine is synthesized from norepinephrine. Epinephrine as a hormone is secreted along with norepinephrine principally by the medulla of the adrenal gland. Heightened secretion can occur in response to fear or anger and will result in increased heart rate and the hydrolysis of glycogen to glucose. This reaction, often called the "fight or flight" response, prepares the body for strenuous activity. Epinephrine is used medicinally as a stimulant in cardiac arrest, as a vasoconstrictor in shock, as a bronchodilator and antispasmodic in bronchial asthma, and to lower intra-ocular pressure in the treatment of glaucoma.

Epinephrine acts as an excitatory neurotransmitter and modulates neuron voltage potentials to favor glutamate activity and neurotransmitter firing.

Norepinephrine

Norepinephrine is synthesized from dopamine by means of the enzyme *dopamine beta-hydroxylase*, with oxygen, copper, and vitamin C as co-factors. Dopamine is synthesized in the cytoplasm, but norepinephrine is synthesized in the neurotransmitter storage vesicles. Cells that use norepinephrine for formation of epinephrine use SAME as a methyl group donor. Levels of epinephrine in the CNS are only about 10% of the levels of norepinephrine.

Electrical stimulation of the locus ceruleus produces a state of heightened arousal. The noradrenergic system is most active in the awake state, and it

Neurotransmitters Available for Diagnostic Testing

seems to be important for focused attention, in contrast to the motor arousal of dopamine. Although the locus ceruleus has been identified as a pleasure center, it also seems to contribute to anxiety. Increased neuronal activity of the locus ceruleus is seen upon the occurrence of unexpected sensory events. Brain norepinephrine turnover is increased in conditions of stress. Benzodiazepines, the primary antianxiety drugs, decrease firing in the locus ceruleus, thus reducing distribution of norepinephrine to the forebrain. This may also be part of the explanation for the use of benzodiazepines for inducing sleep.

Norepinephrine acts as an excitatory neurotransmitter and modulates neuron voltage potentials to favor glutamate activity and neurotransmitter firing.

Dopamine

Dopamine is an amine neurotransmitter derived from the amino acid tyrosine. Dopamine serves as a precursor to norepinephrine and epinephrine. Dopamine, like norepinephrine and epinephrine, is stored in vesicles in the axon terminal. Dopamine plays a significant role in the cardiovascular, renal, hormonal, and central nervous systems. It is thought to control processes as diverse as movement to drug addiction. Dopamine dendrites extend into various regions of the brain, controlling different functions through the stimulation of adrenergic and dopaminergic receptors (D1 –D5.)

Dopamine acts, in most cases, as an excitatory neurotransmitter and modulates neuron voltage potentials to favor glutamate activity and neurotransmitter firing.

Beta-phenylethylamine (PEA)

Beta-phenylethylamine (PEA) is an amine neurotransmitter derived from the amino acid L-phenylalanine. Studies of PEA have found that it promotes energy and elevates mood. PEA also functions as a synaptic neuromodulator inhibiting the reuptake of dopamine and norepinephrine. PEA is lipid soluble and readily crosses the blood-brain-barrier. Studies have discovered that patients with depression and those with ADD/ADHD have decreased PEA levels while levels are increased in schizophrenic and psychotic subjects. It has also been implicated in migraines and the antidepressant effects of exercise. One of the biochemical abnormalities resulting from phenylketonuria is an increased production of PEA and hence a greatly elevated urine level of PEA. The administration of PEA or of its precursor L-phenylalanine has been found to improve therapy outcome with some antidepressants and to be an indicator of how well ADD/ADHD patients are responding to therapy.

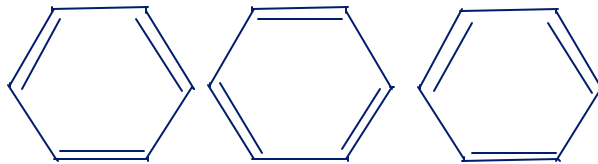
PEA acts as an excitatory neurotransmitter and modulates neuron voltage potentials to favor glutamate activity and neurotransmitter firing.

Histamine

Histamine is the neurotransmitter responsible for the effects of an allergic reaction. Normally present at low levels, high levels can occur during anaphylaxis and cause death. Epinephrine is the only chemical that can quickly reduce histamine levels and is used immediately in severe allergic reactions. Long-term elevations in histamine can deplete epinephrine levels.

Testing

Testing neurotransmitter levels provides a baseline from which the effects of therapy can be monitored. The optimal levels provided in the test reports also provide a biochemical endpoint or target for therapeutic intervention. NeuroScience has assembled a number of panels that include neurotransmitter tests. The profiles shown are suggestions for useful combinations in the investigation of certain clinical conditions or syndromes. These are designed to provide the information needed to assess the neurotransmitter imbalance in the patient while minimizing costs but are by no means exhaustive. The choice of a specific test or profile and its interpretation will depend upon the clinical findings in the patient. In addition to the suggested profiles, healthcare providers can also design their own profiles to meet the specific needs of their patients.



Test Profiles

NeuroBalance Profile # 9012

Neurotransmitter evaluation (urine) - Epinephrine, Norepinephrine, Dopamine, Serotonin, GABA

Indications:

General neurotransmitter assessment
Monitoring amino acid therapy

NeuroendoSupport Profile # 9011

Neurotransmitter and adrenal hormone evaluation (urine and saliva) - Epinephrine, Norepinephrine, Dopamine, Serotonin, GABA, Cortisol x 4, DHEA

Indications:

Stress
Anxiety
Adrenal exhaustion
Fatigue

Neuroendocrine Profile # 9502

Neurotransmitter and adrenal hormone and sex hormone evaluation (urine and saliva)
Epinephrine, Norepinephrine, Dopamine, Serotonin, GABA, PEA, Estradiol, Estrone, Progesterone, Testosterone, Dihydrotestosterone (DHT), Cortisol x 4, DHEA

Indications:

General malaise
Chronic Fatigue Syndrome
Adrenal dysfunction
Lack of motivation
Abnormal hormone function

NeuroFocus Profile # 9019

Neurotransmitter evaluation (urine) - Epinephrine, Norepinephrine, Dopamine, Serotonin, Histamine, GABA, PEA

Indications:

ADD/ADHD
Autism
Mood
Mental focus
General neurotransmitter assessment

NeuroHealth Profile # 9020

Neurotransmitter evaluation (urine) - Epinephrine, Norepinephrine, Dopamine, Serotonin, GABA, PEA,

Indications:

General neurotransmitter assessment
Mood
Mental focus

Insomnia Profile #9021

Neurotransmitter and hormone evaluation (urine and saliva) - Norepinephrine x2, Epinephrine x2, GABA x2, Cortisol x3, Melatonin x3, Creatine x2

Indications:

Insomnia
Sleep disturbances

Testing

Basic Testing Procedure

The following is a summary of the testing procedure and reporting timeframe for neurotransmitter analysis.

Step 1

Patient is given a test kit. Patient collects their specimen and mails it directly to the laboratory for analysis. The laboratory usually receives specimen in 4-7 days. For faster delivery expedited couriers may be used. (Urine transport tubes contain a small preservative pellet that ensures sample integrity during shipment. Specimens are stable at ambient temperatures for up to one month.)

Step 2

Laboratory receives specimen and performs analysis. Patient's results are reviewed and any needed recommendations are included. Turn-around-time is usually 5-7 business days.

Step 3

Reports are forwarded to the healthcare provider through a number of options including, fax, mail and email. Reports are also available through our website at www.neuroscienceinc.com

Step 4

Review the test report and recommended therapies. Based on the clinical presentation and the therapy recommendations, choose the appropriate products, if needed. Any questions regarding test results, should be directed to Technical Support. Technical Support can also help interpret results, provide consultation about dosing options, and offer strategies for handling any special concerns at no cost.

Step 5

Therapeutic recommendations generally include two products to be used in combination during the first two to three weeks of therapy called the Conditioning Phase. Two other products are also generally recommended for the three to six month Therapy Phase that follows. The exact recommendation will depend on the test results and clinical presentation.

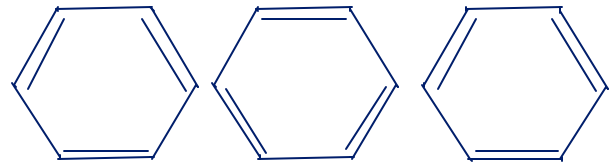
Step 6

Retest. If a patient proceeds as expected, a retest is recommended after six to eight weeks of therapy. This test will verify that appropriate levels of neurotransmitters have been attained. If the patient experiences any difficulty or fails to achieve the desired outcome, earlier testing may be recommended to determine a patient's current neurotransmitter levels and to guide changes in the therapeutic regimen.

Step 7

Maintenance. After neurotransmitter levels have been restored, it may be recommended that therapy be reduced to the minimum effective dose. At this point, doses would be slowly titrated down.

Optimum Ranges & Reference Ranges



There is significant variation in neurotransmitter levels in the general population. We believe this reflects the widespread nature of neurotransmitter imbalances seen in the “apparently healthy” population and that this is also a factor in many of the chronic subclinical symptoms or complaints.

As a matter of comparison, all laboratory reports include what is called an Observed or Reference Range. The observed range is a reflection of the

standard deviation above and below the mean neurotransmitter level seen in an “apparently healthy” population. This population excludes individuals currently diagnosed with clinical conditions that significantly effect neurotransmitter levels, but does not exclude individuals that have subclinical complaints or symptoms.

Within the apparently healthy population there are “high functioning” individuals that are free

from all subclinical complaints and this population is the basis for Optimal Ranges.

The realization that high functioning individuals had neurotransmitter levels that were different from the general population was the first step in

establishing Optimal Ranges. This meant that it was possible for individuals with neurotransmitter levels outside the optimal range to improve their well being if their neuro-

transmitter levels were optimized. This Optimal Range is a benchmark for determining the need for therapy as well as the goal for the therapeutic outcome.

The Optimal Range has been refined and in present form is also based on the review of medical literature and the opinions of the NeuroScience medical advisors regarding what values would be most desirable to avoid neurotransmitter-related symptoms.

Optimal Range is a benchmark ... as well as the goal for the therapeutic outcome

NeuroScience has realized that the goal of successful amino acid therapy is to optimize a patient’s neurotransmitter levels. Achieving this goal will improve the clinical outcome of the patient. Clinically, these values have proven to be very useful and achieving Optimal Levels of neurotransmitters has successfully eliminated many neurotransmitter-related symptoms.

Interpretation of Urinary Neurotransmitters

The interpretation of urinary neurotransmitters is not always straightforward. A high neurotransmitter level represents high activity or turnover. This, however, may not necessarily relate to high levels within the presynaptic neuron since high turnover can lead to over-excretion and a resulting depletion of the releasable neurotransmitter pools.

Neurotransmitters are synthesized at a constant rate when all components necessary for synthesis are present in adequate amounts. They are then released into the synapse in discreet bursts. When the size and number of these bursts are sufficient, the postsynaptic neuron will fire. If neurotransmitters are released in a disorganized stream, the postsynaptic neuron will fail to fire. There is a critical threshold of neurotransmitter levels required for neurotransmission that is only reached by the synchronized release of neurotransmitters from their presynaptic vesicles. Even if the total amount of neurotransmitter released is enough to trigger the neuron, if it is not released in an organized manner, the neuron will not fire.

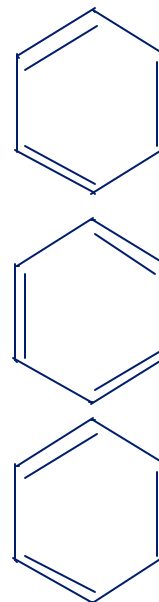
After binding to its receptor, a neurotransmitter be released back into the synapse. There are a number of possible fates for the neurotransmitter after this dissociation. The majority of monoamine neurotransmitters are taken back into the presynaptic neurons where they will be degraded by enzymes or repacked into storage vesicles for reuse. Most of the remaining neurotransmitters are lost to diffusion or degradation by enzymes.

As neurotransmitter activity or turnover increases, the relative amount of a neurotransmitter that is lost to diffusion increases. Unless there is an increase in the availability of amino acid precursors to balance this increased loss of neurotransmitters, high turnover can, overtime, result in depletion of the presynaptic pool. The net result is a deficit in neurotransmitters and symptoms of low neurotransmitter levels.

High excretion may also be due to an error in neurotransmitter metabolism; a poorly understood phenomenon, that leads to a low level of neurotransmitters in the CNS and symptoms associated with low neurotransmitters function. Current research suggests that a deficit, either acquired or genetic, in neurotransmitter transport can increase the urinary excretion of neurotransmitters. Despite these limitations, neurotransmitter testing is clinically useful in establishing a therapeutic protocol, assessing the outcome of ongoing therapy, as well as examining the underlying biochemical imbalance that may be affecting the patient.

Hormones interact with numerous receptors in the central nervous system. Through this interaction, sex hormones and stress adaptation hormones control the severity and incidence of many neurotransmitter-related disorders. As such, including an assessment of hormones along with neurotransmitters can provide a more detailed clinical picture and refine therapy regimens to improve patient outcome.

The Neuroendocrine Connection



The role of sex hormones in brain function is multifaceted and influences the actions of multiple neurotransmitters. It is well known that some diseases are more likely to affect a particular gender. Anxiety disorders and depression, for example, are more common in women while substance abuse, compulsive disorders, and antisocial behavior are more prevalent in men.

These differences may be due to the antidopamine effects of estrogen, which also explains why Parkinson's disease is more severe in women. Estrogens are neuroprotective by inducing the formation of new synapses. In contrast, progesterone inhibits this formation. Progesterone potentiates GABA receptors and reduces neurotransmitter activity. This is important for patients with premenstrual syndrome, epileptics, or compulsive disorders. Estradiol also decreases the level of monoamine oxidase (MAO) the enzyme responsible for the inactivation of amine neurotransmitters like serotonin and dopamine. In contrast, progesterone increases MAO synthesis.

The adrenal hormones, DHEA and Cortisol, in addition to regulating metabolism and body weight, are an active part of the stress response and influence cognitive function. Like the sex

hormones adrenal hormones influence neurotransmitter actions and disease in multiple ways. Norepinephrine is secreted in response to stress and repeated stress increases this response as well as increasing the level of the rate limiting enzyme tyrosine hydroxylase required for the synthesis of the catecholamines.

In contrast, cortisol inhibits the release of catecholamines and reduces the post-synaptic response to norepinephrine. In addition to reducing the effects of norepinephrine, cortisol, like progesterone, potentiates GABA receptors. These effects of cortisol explain its ability to reduce anxiety.

DHEA is another hormone of the adrenal gland with effects on neurotransmitter function and disorders. DHEA enhances the neurotransmission of both serotonin and norepinephrine. This may explain its ability to enhance cognitive function, reduce depression, and its inverse association with pain in Fibromyalgia.

An integrated approach to neurotransmitter-related disease takes into account the important role of hormones. With this understanding, more options are available to either augment existing or create new therapeutic regimens.

Neurotransmitter Patterns and Associated Symptoms

While no neurotransmitter test will diagnose a particular disease, a number of general patterns are commonly seen in some patient populations. Good examples include the high PEA levels seen in autism patients and the elevated dopamine seen in ADD/ADHD pediatric patients.

Common Associations of Test Results and Patient Conditions

Epinephrine

Epinephrine levels above the optimum range are frequently observed in patients with:

- Anxiety
- Hyperactivity
- Stress

Epinephrine levels below the optimum range are frequently seen in patients with:

- Fatigue
- Poor concentration
- Low cortisol levels due to adrenal insufficiency
- Adrenal burnout

Norepinephrine

Norepinephrine levels above the optimum range are frequently observed in patients with:

- High blood pressure
- Insulin resistance
- Stress
- Errors in neurotransmitter metabolism
- Obesity (Generally these patients have high blood pressure and/or insulin resistance.)

Norepinephrine levels below the optimum range are frequently seen in patients with:

- Fibromyalgia and other pain disorders
- Patients who regularly engage in very strenuous exercise
- Mood disorders

Dopamine

Dopamine levels above the optimum range are frequently observed in patients with:

- Autism
- Hyperactivity/ ADD
- Abuse victims
- Use of therapies that contain L-DOPA or Mucuna pruriens
- Errors in neurotransmitter metabolism
- Parkinson's Syndrome
- High carbohydrate diet

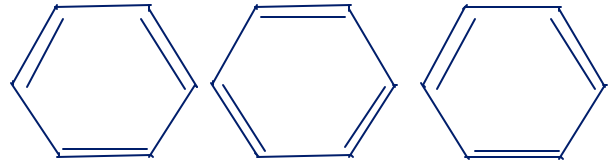
Dopamine levels below the optimum range are frequently seen in patients with:

- Drug/alcohol abuse
- Sleep disorders
- Neurotoxicity

Serotonin

Serotonin levels above the optimum range are frequently observed in patients with:

- Therapies that contain 5-HTP
- Errors in neurotransmitter metabolism



Serotonin levels below the optimum range are frequently seen in patients with:

- Depression
- Drug/alcohol abuse
- Poor Diet
- Insomnia
- Stress

GABA

GABA levels above the optimum range are frequently observed in patients with:

- Anxiety
- Insomnia
- Autism
- Elevated catecholamines
- Compulsive eaters

GABA levels below the optimum range are frequently observed in patients with:

- Schizophrenia
- Epilepsy
- Errors in neurotransmitter metabolism

PEA

PEA levels above the optimum range are frequently observed in patients with:

- Schizophrenia
- Psychotic disorders
- Phenylketonuria
- ADD/ADHD
- Autism

PEA levels below the optimum range are frequently observed in patients with:

- Depression
- Chocolate cravings (suggested)
- Fatigue

Histamine

Histamine levels above the optimum range are frequently observed in patients with:

- Active allergy or inflammation
- UTIs
- Cigarette use
- Restlessness/ Inability to relax

Histamine levels below the optimum range are frequently observed in patients with:

- Antihistamine use
- L-dopa therapy

What Causes Neurotransmitter Disorders?

Neurotransmitter-related disorders occur when the current levels of neurotransmitters are unable to properly relay the electrical signal from one neuron to the next. The following situations are likely to result in neurotransmitter-related symptoms.

Low neurotransmitters levels If neurotransmitters are low, they will be unable to simultaneously engage enough of the postsynaptic receptor sites and cause membrane depolarization. This disrupts signal transduction by causing the postsynaptic nerve to fire ineffectively or not at all. Low neurotransmitter levels can result from prolonged stress, genetic predisposition, and diets low in the amino acids from which neurotransmitters are made.

Low postsynaptic receptor levels The postsynaptic neuron fires when sufficient numbers of its receptors are engaged by the neurotransmitters. If the number of receptors is low, increased levels of the neurotransmitters are required to cause the neuron to fire and relay a signal. Neurotoxic substances like heavy metals, pesticides, illicit amphetamines, and some prescription drugs can cause permanent damage to the nervous system by reducing the number of active receptors.

High neurotransmitters levels If the levels of neurotransmitters are high, the frequency of inappropriate signals that are relayed increases. This increased “static” can cause neurotransmitter related symptoms.

Modulation of neurotransmitters function A number of molecules modulate the release of neurotransmitters or the permeability of ion channels by altering intracellular calcium levels. These changes can effectively alter the efficiency of neurotransmission. Other biogenic amines, peptides, or neurosteroids can potentiate or attenuate the effects of neurotransmitters and the resulting signaling mechanisms and alter the physiological response. The molecules that cause these effects are called neuromodulators.

In contrast to glutamate and GABA which are the fast-acting true neurotransmitters and directly responsible for the transfer of information, neuromodulators have slower longer-lasting effects that enhance or inhibit the true neurotransmitters. There are several classes of neuromodulators: most prominent are peptides such as the endorphins and enkephalins, biogenic amines such as epinephrine, norepinephrine, dopamine, and serotonin, and hormones such as the estrogens, androgens, and corticosteroids. The changes these neuromodulators cause effectively alter the efficiency of neurotransmission. If the efficiency of neurotransmission is decreased, higher levels of neurotransmitters are required.

Unbalanced Network There are many neurotransmitters that work together to ensure proper neuron signaling and function. Regulatory feedback among neurotransmitters maintains balance within this network. If the levels of certain neurotransmitters are either too high or too low, it will affect the levels of other neurotransmitters and ultimately the patient’s health. Serotonin is an important modulator of catecholamine activity.

The effects of this regulation are commonly observed in patients that have high dopamine activity and low serotonin. Increasing serotonin in these patients through the implementation of 5-HTP containing therapies will decrease the dopamine activity in the vast majority of these patients.

High doses of a number of antidepressant drugs can adversely affect neurotransmitter signaling. These drugs act by temporarily increasing synaptic neurotransmitter levels or imitating a neurotransmitter function. Chronic use can lead to a depletion of the vesicle pool available for secretion, or alter the number of post-synaptic receptors available for signaling.

Amino Acids

The Precursors of Important Neurotransmitters

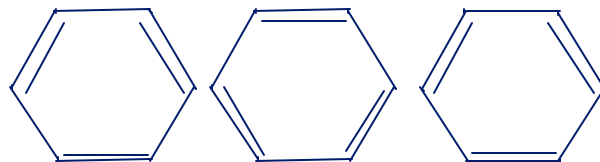
Amine neurotransmitters are formed from amino acid precursors by the action of specific enzymes. Serotonin is synthesized through the conversion of tryptophan. The catecholamines and PEA are synthesized through the conversion of phenylalanine. (See Neurotransmitter Biochemistry) Whole food protein sources like eggs, meat, or cheese contain many amino acids including tryptophan and phenylalanine but the amount of precursors that cross the blood-brain-barrier after eating these foods is relatively small. Diets that are restrictive in either the amount or variety of the foods they include, such as vegetarian, low calorie, or low carbohydrate, are the most likely to limit neurotransmitter production. By enriching the diet with these specific amino acids in the absence of other dietary amino acids (taking them on an empty stomach) the amounts that cross the blood-brain-barrier are increased and the production of the neurotransmitters is increased.

The conversion of tryptophan to serotonin and phenylalanine to dopamine is a multi-step process. The rate-limiting enzymatic step in this conversion prevents therapeutic levels of the neurotransmitters

from being achieved. If however, the amino acid intermediaries 5-HTP and/or 3, 4-dihydroxy-phenylalanine (L-dopa) are included, this rate-limiting enzymatic step is bypassed and neurotransmitter levels can be increased rapidly and to therapeutic levels.

The enzymes that form neurotransmitters require a number of vitamin and mineral cofactors to function properly. NeuroScience products contain sufficient levels of these cofactors along with the amino acids to ensure increased neurotransmitter levels.

Laboratory tests confirm that 5-HTP will increase serotonin and *Mucuna pruriens*, due to its L-dopa content, will increase dopamine. Phenylalanine will increase PEA as well as dopamine. Other amino acids modulate amino transport and are useful for regulating neurotransmitters. Theanine for example can be used to increase GABA. Most importantly, clinical outcomes have demonstrated that neurotransmitter precursor therapy has a significant effect in many clinical conditions including fatigue, insomnia, pain, and depression.



The success of any therapeutic regimen requires that the therapies be appropriately chosen. This is also true for NeuroScience in preparing the products used to correct neurotransmitter imbalances. NeuroScience guarantees that all its products meet label claims and an independent laboratory has verified that all 5-HTP is free of Peak X. The following ingredients are included in the NeuroScience formulas and an explanation of their role is provided.

Explanation of Ingredients

5-HTP

While the amino acid tryptophan is converted to serotonin, 5-HTP, an intermediary in this process, is also converted to serotonin but without regulatory feedback. Therefore therapeutic serotonin levels can readily be attained.

Tyrosine

Tyrosine (N-acetyltirosine) is converted to the catecholamines following these steps. Tyrosine - L-dopa - Dopamine – Norepinephrine - Epinephrine.

Phenylalanine

L-Phenylalanine is an essential amino acid and is converted to the catecholamines following these steps. Phenylalanine - Tyrosine - L-dopa - Dopamine – Norepinephrine - Epinephrine. Phenylalanine may also be converted to the neurotransmitter PEA through the actions of *aromatic amino acid decarboxylase*. The D-phenylalanine isomer enhances endorphin based pain relief by inhibiting enkephalinase, the enzyme that metabolizes endorphins. D-phenylalanine can be converted to L-phenylalanine within the body.

Vitamin B6 and Folic acid

Tyrosine is converted to L-dopa by *tyrosine hydroxylase*, an enzyme, which requires tetrahydrobiopterin (a product of folic acid) as a cofactor. These vitamins are also methyl donors and prevent the depletion of SAME, which is a required cofactor in the enzymatic conversion of norepinephrine to epinephrine and the conversion of 3, 4-dihydroxyphenylalanine to dopamine.

Cysteine

Cysteine has an important three-part role in the NeuroScience program. First, cysteine is a key component of glutathione, the body's toxin neutralizing powerhouse. Second, cysteine is a component of *tyrosine hydroxylase*, the enzyme responsible for the rate-limiting step in the conversion of tyrosine to the catecholamines. Adequate cysteine supports *tyrosine hydroxylase* enzyme levels. Third, cysteine supports sulfur containing amino acid pathways and spares SAME, which is required for methylation in the synthesis of neurotransmitters.

Vitamin C

Dopamine monoxygenase, which converts dopamine to norepinephrine, is Vitamin C dependent. While vitamin C is required for the conversion of 5-HTP to serotonin, it inhibits the peripheral conversion of 5-HTP in the GI tract.

Calcium Citrate

Intracellular Ca^{2+} stimulates cellular processes that cause catecholamine (epinephrine) release and an increase in tyrosine hydroxylase gene expression.

Selenium

A number of selenium containing compounds are involved in detoxification mechanisms. Selenocysteine, for example, is a normal component of glutathione peroxidase, an antioxidant enzyme that may behave like other antioxidants, such as vitamin E, protecting tissues against methylmercury toxicity. Cysteine has been reported to have the potential to increase CNS methylmercury levels. Selenium prevents this increase.

Mucuna Pruriens

The amino acid tyrosine is enzymatically converted to dopamine in a rate-limited multi-step process. The amino acid 3, 4-dihydroxyphenylalanine (L-dopa) is an intermediary in this process and is also converted to dopamine but without regulatory feedback. Therefore therapeutic dopamine levels can readily be attained. Mucuna Pruriens is a nutrient dense bean that contains significant amounts of this amino acid intermediary. Supplementation with Mucuna can help establish serotonergic/catecholaminergic balance. Mucuna is also used to reduce the excretion of serotonin.

Theanine

Theanine is an amino acid that increases GABA levels. It acts by modulating the excretion of serotonin and the catecholamines and reducing the uptake of the stimulatory amino acid glutamate. Theanine is an amino acid naturally found in green tea. The ability of theanine to reduce the stimulatory effects of caffeine and increase the effectiveness of some anti-tumor drugs has been well studied. Theanine also has an important neuroprotective effect and has been found to prevent the death of neurons exposed to oxidative stress or glutamic acid overstimulation. These latter effects may be responsible for its ability to prevent brain damage in models of ischemic stroke.

Taurine

Taurine is an inhibitory amino acid. Taurine increases the effects of GABA by enhancing its interaction with its receptor. Additionally, taurine decreases the effects of the stimulatory amino acid, N-methyl-D-aspartate, which is involved in stress and anxiety.

Glutamine

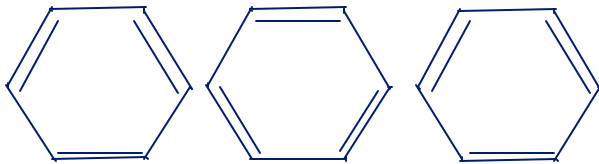
Glutamine is a conditionally essential amino acid and contributes to GABA synthesis.

Boswellia serrata

Boswellia blocks the production of the inflammatory compounds known as leukotrienes by inhibiting the enzyme *5-lipoxygenase* (5-LOX). Unlike aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs) boswellia has a broader range of use and none of the NSAID side effects or safety limitations. The conversion of arachidonic acid by 5-LOX to leukotrienes, a particularly important factor in inflammation, is not affected by nonselective or COX2 selective NSAIDs. Leukotrienes are proinflammatory, recruit proinflammatory immune cells, increase vascular permeability, are powerful bronchoconstrictor agents, and are damaging to the gastro-intestinal tract.

Explanation of Products

When products are provided to increase neurotransmitter levels, it is very important that the amino acids that support excitatory and inhibitory neurotransmitter systems are in the proper ratio. The quantity and ratio of amino acids in these products vary. This determines the extent to which a product will affect the levels of the neurotransmitters that enhance either the inhibitory effects of GABA or the excitatory effects of Glutamate. The following NeuroScience products are frequently included in the recommendations. They have been divided into categories based on the degree to which they support the inhibitory or excitatory neurotransmitter system.



Serene is an amino acid formula that raises serotonin via 5-hydroxytryptophan (5-HTP). This formulation of 5-HTP and specific cofactors supports serotonin levels in preparation to using amino acid therapies that have catecholamine support. This two-step process addresses the low serotonin levels commonly seen in neurotransmitter test results as well as prevents catecholamine overstimulation. Neurotransmitter testing has shown that individuals can have significant differences in their serotonin levels and that a large portion of the population has serotonin levels below the NeuroScience Optimal Range. Serene is used extensively during the Conditioning Phase of neurotransmitter optimization.

GABAMAX is a formula designed to address neurotransmitter overstimulation and is used in patients with high catecholamine turnover or increased GABA excretion. GABA is the primary inhibitory neurotransmitter in the brain and regulates neurotransmitter activity to prevent overstimulation. GABAMAX contains the amino acid theanine, which has been widely studied for its ability to provide a calming effect and prevent the neurotransmitter stimulatory effects induced by caffeine. These studies match observations by NeuroScience that theanine reduces catecholamine activity/turnover and urinary excretion. Taurine is another inhibitory amino acid in the GABAMAX formula. Taurine acts by enhancing the effects of GABA. Together these amino acids can quickly reduce high neurotransmitter excretion. Glutamine is a conditionally essential amino acid and contributes to GABA synthesis.

N-acetytyrosine and 5-hydroxytryptophan are included at low levels to maintain neurotransmitter balance. Other ingredients are vitamin and mineral

Products to Support the Inhibitory System

cofactors of the enzymes required for the synthesis of neurotransmitters. GABAMAX has been used successfully during the initial phase of neurotransmitter therapy to reduce catecholamine excretion prior to using Optimum-C, Optimum-S, TransLean, and TransLean Plus.

CeroLox is a formula designed to address neurotransmitter overstimulation and is used in patients with high catecholamine turnover or increased GABA excretion. While very similar, CeroLox differs from GABAMAX in that CeroLox substitutes L-phenylalanine for N-acetyltirosine. This will provide support for PEA. CeroLox also includes magnesium instead of calcium. Magnesium stimulates GABA production. GABA is the primary inhibitory neurotransmitter in the brain and regulates neurotransmitter activity to prevent over stimulation. CeroLox contains the amino acid theanine, which has been widely studied for its ability to provide a calming effect and prevent the neurotransmitter stimulatory effects induced by caffeine. These studies match observations by NeuroScience that theanine reduces norepinephrine and epinephrine activity/turnover and urinary excretion. Taurine is another inhibitory amino acid in the CeroLox formula. Taurine acts by enhancing the effect of GABA. Together these amino acids can quickly reduce high neurotransmitter excretion. 5-hydroxytryptophan is included to increase serotonin levels. Phenylalanine is included at low levels to maintain neurotransmitter balance. Other ingredients are vitamin and mineral cofactors of the enzymes required for the synthesis of neurotransmitters.

Optimum-S is an amino acid formula that preferentially supports serotonin neurotransmission via 5-hydroxy-tryptophan (5-HTP). Optimum-S also includes a combination of the D- and L-

forms of phenylalanine. This formulation of a small amount of L-phenylalanine combined with 5-HTP preferentially supports serotonin levels in preparation to using amino acid therapies that have more catecholamine support. This two-step process addresses the low serotonin levels commonly seen in neurotransmitter test results as well as prevents catecholamine overstimulation. Phenylalanine is also included to support the formation of the neurotransmitter phenylethylamine (PEA). These neurotransmitters are associated with increased attentiveness and reduced depression. Optimum-S has been used successfully to optimize neurotransmitter levels. Optimum-S is used extensively during the Conditioning Phase of neurotransmitter optimization.

EndoTrex is an easy to administer oral spray containing theanine. This formula is designed to address neurotransmitter overstimulation and is used in young patients with high catecholamine turnover or increased GABA excretion. GABA is the primary inhibitory neurotransmitter in the brain and regulates neurotransmitter activity to prevent overstimulation. EndoTrex contains the amino acid theanine, which has been widely studied for its ability to provide a calming effect and prevent overstimulation. These studies match observations by NeuroScience that theanine reduces dopamine, norepinephrine, and epinephrine activity/turnover and urinary excretion. EndoTrex can quickly reduce high neurotransmitter excretion. EndoTrex has been prepared in an advanced liposomal liquid formula and has a pleasant root beer flavor. EndoTrex is used during the initial phase of neurotransmitter therapy to reduce catecholamine excretion prior to using Optimum-C. EndoTrex is prepared without additional amino acids, vitamins, or minerals so it may be easily combined with other therapies.

Products to Support the Excitatory System

Optimum-C is a balanced amino acid formula to support serotonin and catecholamine neurotransmission via 5-hydroxytryptophan (5-HTP) and L-Phenylalanine. Phenylalanine also supports the formation of the neurotransmitter phenylethylamine (PEA). These neurotransmitters are associated with increased attentiveness and reduced depression. Optimum-C is generally used to address imbalances observed in laboratory neurotransmitter assessments, and after a conditioning phase that has a higher level of serotonin support. This process of tailoring therapies and first addressing the low serotonin levels commonly seen in neurotransmitter test results in improved patient outcome and prevents catecholamine overstimulation. Theanine is included to provide ongoing support of GABA. Optimum-C has been used successfully to optimize neurotransmitter levels. Optimum-C is used extensively during the Therapy Phase of neurotransmitter optimization.

Balance-D is an amino acid formula that contains a standardized extract of the nutrient dense bean *Mucuna pruriens*, a source of 3,4-dihydroxyphenylalanine (L-dopa), to support dopamine levels. Balance-D is also used during the conditioning phase of neurotransmitter optimizing therapy to address serotonin/ dopamine imbalances observed in laboratory neurotransmitter assessments. Serotonin excretion can also be down regulated with Balance-D and is frequently used in conjunction with 5-HTP containing therapies like Optimum-S or Serene.

TransLean is an amino acid formula that supports neurotransmission via 5-hydroxytryptophan (5-HTP), N-acetytyrosine, and D, L-phenylalanine. This formulation can be used to address neurotransmitter imbalances accompanied by reduced adrenal function as well as for appetite suppression when combined with Balance-D. Phenylalanine, which supports catecholamine production along with tyrosine, also supports the formation of the anti-fatigue neurotransmitter phenylethylamine (PEA) and the production of the appetite suppressing peptide cholecystokinin (CCK). TransLean also includes a combination of vitamins intended to support adrenal function and metabolism.

TransLean Plus is an amino acid formula designed to address food craving and control appetite. It includes *Mucuna pruriens* and N-acetylcysteine along with the neurotransmitter support ingredients of TransLean. This all-in-one product greatly simplifies dosing and reduces cost. Phenylalanine, which supports catecholamine production along with tyrosine, also supports the formation of the anti-fatigue neurotransmitter phenylethylamine (PEA) and the production of the appetite suppressing peptide cholecystokinin (CCK). *Mucuna Pruriens* increases dopamine to suppress appetite and N-acetylcysteine is neuroprotective and supports sulfur containing amino acid pathways for detoxification and methylation. TransLean Plus also includes a combination of vitamins intended to support adrenal function and metabolism.

Products Supporting Both the Excitatory and Inhibitory Systems

NeuroSupport is an amino acid formula that supports serotonin neurotransmission via 5-hydroxytryptophan (5-HTP). NeuroSupport also includes a combination of the D- and L- forms of phenylalanine. This formulation combines 5-HTP with D-L-phenylalanine at doses that support neurotransmitters at maintenance levels. Phenylalanine is also included to support the formation of the neurotransmitter phenylethylamine (PEA). This neurotransmitter is associated with increased attentiveness and reduced depression. NeuroSupport has been used successfully to maintain neurotransmitter levels after the optimizing phase of the NeuroScience neurotransmitter program.

SanoX (Migraine Relief) provides a balanced amino acid formula to support serotonin and catecholamine neurotransmission via 5-hydroxytryptophan (5-HTP) and N-acetytyrosine. SanoX is generally used to address imbalances observed in laboratory neurotransmitter assessments of patients with migraine symptoms. SanoX may follow a conditioning phase that has a higher level of serotonin support. Brain hyperexcitability is viewed as an underlying pathology in migraine sufferers. Normalizing fluctuations in neurotransmitter levels and preventing overstimulation can prevent migraines from being triggered. Serotonin constricts blood vessels and reduces brain swelling and migraine pain. Theanine is included to provide ongoing support of GABA, the major inhibitory neurotransmitter. Magnesium is important for reducing calcium channel activity and reducing vascular spasms.

Other Products

CysNAC contains N-acetylcysteine, which plays an important role in the NeuroScience neurotransmitter optimizing programs. First, cysteine is a component of tyrosine hydroxylase, the enzyme responsible for the rate-limiting step in the conversion of tyrosine to the catecholamines. Adequate cysteine supports tyrosine hydroxylase levels.

Second, and most importantly, cysteine is a key component of glutathione, the body's toxin neutralizing powerhouse. Glutathione inhibits the apoptosis of neurons by preventing the oxidation of neurotransmitters. Oxidized neurotransmitters can cause the apoptosis of neurons. CysNAC is used in patients that are also using Mucuna-containing therapies. Mucuna contains 3,4-dihydroxyphenylalanine (L-dopa), which can increase neurotransmitter oxidation. CysNAC is also used in patients with low epinephrine levels to support the conversion of norepinephrine to epinephrine.

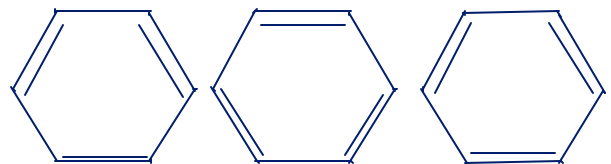
FlamX is a gelcap containing a standardized preparation of boswellia serrata. Boswellia inhibits the formation of the proinflammatory leukotrienes and is useful in patients with inflammatory disorders and does not cause any of the gastrointestinal side effects seen with NSAID use. FlamX may actually reduce these symptoms when taken with NSAIDs. The Boswellia preparation in FlamX has been used in numerous clinical studies and has been shown to reduce patient pain and inflammation and increase the levels of active components five times higher than equivalent doses of other Boswellia preparation. This preparation has also been approved by the European Agency for the Evaluation of Medical Products, EMEA to treat inflammation associated edema. FlamX contains the only commercially available Boswellia preparation that has shown to be effective in double-blind placebo-controlled studies.

Neurotransmitter Optimizing Protocols

'...addressing this imbalance will lead to an improvement in neurotransmitter related symptoms...'

Amino acids that are neurotransmitter precursors or modulators can be used to address a neurotransmitter imbalance. NeuroScience believes that addressing this imbalance will lead to an improvement in neurotransmitter related symptoms and clinical response to additional treatments. The levels of neurotransmitters can increase quickly following the implementation of neurotransmitter precursor therapies. If not done properly, this can cause adverse side effects. Most frequently the side effects are manifested as symptoms of "excitatory excess."

Excitatory excess occurs when there is predominance of excitatory neurotransmitters such as epinephrine, norepinephrine, dopamine, or PEA that is not adequately held in check by the inhibitory system. The increased agitation, anxiety, or jittery feelings often limits patient progress or causes disenchantment with the optimizing approach. Through the feedback gained from physicians using the NeuroScience protocols, we have been able to study the occurrence of these side effects and have developed new therapies and a three-phase protocol that avoids these problems and improves patient outcome.



Introduction

Since there is a subtle balance in the body between the excitatory and the inhibitory neuronal system, the first phase of the Optimization Program called the Conditioning Phase addresses the inhibitory system.

GABA is the primary inhibitory neurotransmitter. It is potentiated and modulated by serotonin and taurine. Consequently, the Conditioning Phase products will be used to increase the inhibitory system. A list of these products can be found on pages 28-29. They differ in the composition, strength, and ratios of the amino acids to provide therapeutic options to meet the needs of the treating physician.

Conditioning (Phase I Addressing the Inhibitory System)

During the conditioning phase, therapies are used that have a lower ratio of catecholamine support compared to the amount of serotonin support. Therapies may also be included to enhance GABA levels. In addition to their function to reduce anxious and depressive symptoms, serotonin and GABA also have important roles in regulating the stimulatory effects of the catecholamines. By first increasing serotonin and GABA high catecholamine activity and turnover can be reduced and symptoms of “excitatory excess” can be prevented. After the conditioning phase, the patient may begin therapies with a higher ratio of catecholamine support.

Therapy (Phase 2 Addressing the Excitatory System)

Once serotonin and GABA levels have been addressed, therapies that have a higher level of catecholamine precursors are implemented. The products used during this phase move from the serotonin weighted therapies of the conditioning phase and increase catecholamines while maintaining the proper balance in the neurotransmitter network.

Because neurotransmitter-related symptoms are most commonly the result of imbalances in more than one neurotransmitter, the therapies in this phase include multiple amino acids. During this phase, neurotransmitter levels are raised above the optimal range in order to replenish depleted neurotransmitter pools.

During the Therapy Phase, amino acid doses may be increased or changed if the desired clinical response is not seen. Dose adjustments, if needed, during the therapy are made at one-week intervals to prevent delays in achieving a positive clinical outcome. Neurotransmitter testing during this phase verifies that appropriate neurotransmitter levels have been achieved. If this has not occurred, the test results will be used to guide changes in either the dose or the specific therapy used. This phase continues until neurotransmitters are in the appropriate therapeutic ranges and have been maintained for 2-6 months.

Neurotransmitter Optimizing Protocols

Maintenance

(Phase 3 Addressing Therapeutic Levels)

After the therapy phase, depleted neurotransmitter pools are replenished and the level of therapy is slowly reduced or is changed to maintenance formulas. At this point testing is used to maintain neurotransmitter levels in the optimal range. This phase of therapy may last as long as needed. For some patients this may mean lifelong therapy.

Therapy Duration

The levels of some neurotransmitters can be changed very rapidly. Serotonin levels, as measured in a urine specimen, can be increased with 5-HTP in less than an hour. Likewise, L-dopa will increase dopamine very rapidly. This increase however is not paralleled in the presynaptic vesicle pool unless levels are maintained for an extended, months long, period of time.

The time it takes to restore presynaptic vesicles depends on the level of neurotransmitters available. For this reason, neurotransmitter levels are increased to what are called “therapeutic values” during the Therapy Phase of treatment. Therapeutic values are five to ten-fold higher than the normal reference range. This increases that rate of repletion, shortens the therapy phase, and hastens patient improvement. The length of therapy is designed to provide the prolonged increase in neurotransmitter levels required to completely restore presynaptic vesicle pools. While the length of therapy will vary by patient, the Therapy Phase in most patients lasts 3-4 months.

A Maintenance Phase that includes a much lower dose of the amino acid precursors follows the Therapy Phase. At this point, the goal is to maintain neurotransmitters levels in the Optimal Range. Follow-up testing is used to confirm that neurotransmitter levels are appropriate. The maintenance phase may be continued indefinitely.

Note - To best use our program, testing should occur throughout treatment so that you can adjust formulations and dosing for individual patients as they progress toward optimal health.

Medications

During Testing

Some medications may affect the levels of neurotransmitters in the urine. In most cases it is sufficient to include information about the therapies the patient is using and not necessary for the patients to interrupt their therapy to perform neurotransmitter testing.

During Therapy

During the conditioning phase, patients who are using prescription medications in addition to amino acid therapies and patients perceived to be “sensitive” may be started on a lower dose than is recommended for the general patient. These patients may then increase their dosing after 2-5 days of therapy at a particular dose if there are no adverse side effects. Generally, no attempts at altering prescription medication regimens are made. If, however; the patient has a desire to decrease either the number or dosage of medications they are taking and the healthcare provider determines it is clinically prudent, dosages may be reduced after the first eight weeks of the program.

Low doses of selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) have been taken along with the neurotransmitter precursor therapies and provide an effective combination for alleviating many neurotransmitter-related symptoms. Tricyclic antidepressants are more likely to adversely influence the outcome of neurotransmitter precursor therapy and require careful patient monitoring. Monoamine Oxidase inhibitors e.g. Nardil or Parnate significantly affect the outcome of neurotransmitter precursor therapy and are not recommended. Many other medications may be incorporated into a successful amino acid therapy protocol.

Case Studies

The following sample case studies are included to help guide the choice of products used to address neurotransmitter deficiencies and related symptoms. This is only a guide and has limitations. Individual treatments and dosage requirements will depend on the patient symptoms, laboratory test results, the clinical assessment of the patient, and the resources available to the healthcare provider.

Example #1

Sex: Female

DOB: 2-15-54

Patient Complaints: Anxiety & Insomnia

Current medications: None

Baseline Test: **Neuroendo Support Profile #901 I (URINE: Serotonin, Epinephrine, Norepinephrine, Dopamine, GABA, SALIVA: DHEA, Cortisol x4)**

Neurotransmitter	Patient Results:	Optimal Ranges	Therapeutic Range
Ug/grCr			
Epinephrine	18.3	8-12	8-13
Norepinephrine	72.5	30-55	35-70
NE:Epi ratio	3.96	3.0-6.0	NA
Dopamine	288.4	125-175	200-500
Serotonin	98.9	175-225	250-1200
GABA	16.7	1.0-3.5	15-30
DHEA	950 pg/ml (7am)		
Cortisol	14.2 ng/ml (7am)		
	8.7 ng/ml (11am)		
	5.4 ng/ml (3pm)		
	4.5 ng/ml (7pm)		

Comments

The patient's complaints of anxiety and insomnia correspond well with the laboratory results. All of the "excitatory" neurotransmitters are elevated (epinephrine, norepinephrine, dopamine)

GABA, the primary inhibitory neurotransmitter, is also elevated indicating that the regulatory feedback is still intact. However, the GABA response is insufficient to bring epinephrine, norepinephrine, and dopamine under control. The reason the GABA response is insufficient is most likely due to the low level of serotonin. Serotonin is a major potentiator of GABA function.

The elevated cortisol and DHEA levels indicate high patient stress. High stress can contribute to increases in catecholamine levels through the up-regulation of the enzymes that make epinephrine and norepinephrine.

Conclusion: The patient's nervous system is in an unbalanced excitatory state. This leads to a condition of anxiety and insomnia. The therapeutic approach will be to strengthen the inhibitory (GABA) system by first addressing serotonin levels followed by therapies that support the GABA system. This will bring the excitatory system under control.

Therapy Objective

Balance the excitatory and inhibitory neurotransmitter systems

Conditioning Phase (Addressing the Inhibitory System): Week 1

The first objective of this phase is to increase serotonin and decrease the high turnover seen in epinephrine, norepinephrine, and dopamine. Serotonin is involved in the regulation of catecholamine turnover, especially dopamine. Increasing serotonin with the 5-HTP containing product Serene is the first step toward accomplishing this objective.

Conditioning Phase Protocol:

Serene (2 capsules) twice a day (morning, bedtime)

Conditioning Phase (Addressing the Inhibitory System): Week 2

The second objective of the conditioning phase is to increase GABA; this begins in week two. GABA is the major inhibitory neurotransmitter and will function in conjunction with serotonin to reduce catecholamine turnover. GabaMAX contains the amino acids theanine and taurine. These amino acids increase GABA levels and enhance its function, respectively

Conditioning Phase Protocol:

Serene (2 capsules) twice a day (morning, bedtime)

GabaMAX (2 capsules) twice a day (morning, bedtime)

Therapy Phase: Week 3

The objective of this phase is to replenish the releasable pool of neurotransmitters contained in the presynaptic vesicles. Optimum-S is recommended for this objective. Optimum-S contains D,L-phenylalanine a precursor to dopamine, norepinephrine, epinephrine, and PEA as well as 5-HTP the precursor to serotonin. Because this patient has significant elevations in her catecholamine levels, Optimum-S, which has a low ratio of excitatory to inhibitory amino acids, was chosen over other products. Cysteine is included to support to the sulfur containing amino acid pathways involved in the synthesis neurotransmitters including the conversion of norepinephrine to epinephrine.

Therapy Phase Protocol:

GabaMAX (2 capsules) twice a day (morning, bedtime) until finished

Optimum-S (2 capsules) twice a day (morning, bedtime)

CysNAC (1 capsule) twice a day (morning, bedtime)

Results of First Retest

Performed after 6 weeks in the therapy phase

Neurotransmitter	Baseline	Retest #1	Optimal	Therapeutic
ug/grCr	Results:	Results:	Range	Range
Epinephrine	18.3	8.2	8-12	8-13
Norepinephrine	72.5	5.7	30-55	35-70
NE:Epi ratio	3.96	6.55	3.0-6.0	NA
Dopamine	288.4	177.4	125-175	200-500
Serotonin	98.9	1256.6	175-225	250-1200
GABA	16.7	7.7	1.0-3.5	15-30

Interpretation

The results of the retest reveal significant improvements in the patient's neurotransmitter values. GABA is still somewhat elevated but is much closer to the expected reference range. This indicates that anxiety has not completely come under control. Serotonin levels have increased dramatically and are in the "Therapeutic Range." A value this high is desirable during this phase of therapy and will help to replenish depleted presynaptic vesicles. The laboratory values also indicate that the high catecholamine activity observed in the baseline test is being brought under control.

Clinical Presentation

Patient reports that anxiety is significantly improved and that sleep seems somewhat more restful.

Recommendation

Current therapy with Optimum-S and CysNAC should continue for another 1-2 months.

Results of Second Retest

Performed after 10 weeks in the therapy phase.

Neurotransmitter	Baseline	Retest	Retest	Optimal	Therapeutic
	Results:	results #1	Results #2	Range	Range
Epinephrine	18.3	8.2	7.5	8-12	8-13
Norepinephrine	72.5	53.7	51.4	30-55	35-70
NE:Epi ratio	3.96	6.55	6.85	3.0-6.0	NA
Dopamine	288.4	177.4	165.3	125-175	200-500
Serotonin	98.9	1256.6	1186.4	175-225	250-1200
GABA	16.7	7.7	4.8	N/A	15-30

Interpretation

Most results are essentially unchanged from first retest. The exception is GABA. The further reduction in GABA levels, indicate that the patients anxiety is coming under control.

Presentation

Anxiety is under better control now than prior to starting therapy.

Recommendation

Current therapy with Optimum-S and CysNAC should continue for another month and then Optimum-S may be reduced, CysNAC can be discontinued. The goal at this point is to reduce therapy so that serotonin levels return to optimal ranges for maintenance. If symptoms return, dosage of Optimum-S may be increased. Retesting after minimum effective dose is found will determine if neurotransmitters are at optimal levels.

Results of Last Retest

Performed 8 weeks after discontinuing CysNAC and Reducing Optimum-S to 1 capsule BID

Neurotransmitter Ug/grCr	Baseline Results:	Retest #1 Results	Retest #2 Results	Retest #3 Results	Optimal Range	Therapeutic Range
Epinephrine	18.3	8.2	7.5	7.0	8-12	8-13
Norepinephrine	72.5	53.7	51.4	55.1	30-55	35-70
NE:Epi ratio	3.96	6.55	6.85	6.19	3.0-6.0	NA
Dopamine	288.4	177.4	165.3	162.3	125-175	200-500
Serotonin	98.9	1256.6	1186.4	176.0	175-225	250-1200
GABA	16.7	7.7	4.8	4.0	2.0-3.5	15-30

Interpretation

Good maintenance neurotransmitter levels.

Presentation

Insomnia is infrequent. Anxiety is much less frequent and less severe. Patient indicates that she takes an extra dose of Optimum-S at bedtime for occasional insomnia and gets some relief.

Recommendation

Continue Optimum-S. Use GabaMAX 1-2 capsules as needed for occasional insomnia. Retest annually.

Final Comments

This patient initially presented with low serotonin and high catecholamine levels. The catecholamine turnover was reduced by strengthening the inhibitory neurotransmitter system with the combination of Serene and GabaMAX. Therapeutic levels of neurotransmitter levels were attained with Optimum-S and maintained for 3 months. After this period, the dose of Optimum-S was reduced to 1 capsule BID and neurotransmitter levels dropped from the Therapeutic Range to the Optimal Range.

Serotonin levels are stable and much improved over those observed in the baseline test. Likewise, catecholamine levels are significantly lower than observed in the baseline test. The GABA levels have also decreased and reflect the reduction in patient's anxiety.

Patient reports significant improvement and will continue on this maintenance level of dosing.

Example #2**Sex:** Male**DOB:** 5-18-67**Patient Complaints:** Fatigue & Depression**Current medications:** None**Baseline Test: NeuroBalance Profile #9012 (URINE: Serotonin, Epinephrine, Norepinephrine, Dopamine, GABA)**

Neurotransmitter	Baseline	Optimal	Therapeutic
Ug/grCr	Results:	Range	Range
Epinephrine	2.3	8-12	8-13
Norepinephrine	26.8	30-55	35-70
NE:Epi ratio	11.65	3.0-6.0	NA
Dopamine	100.2	125-175	200-500
Serotonin	111.5	175-225	250-1200
GABA	7.3	2.0-3.5	15-30

Comment

The patient complains of Fatigue and Depression. All of the “excitatory” neurotransmitters are decreased (epinephrine, norepinephrine, dopamine) and the level of GABA is elevated.

GABA the primary inhibitory neurotransmitter is elevated indicating that the regulatory feedback is overcompensating. The GABA response is sufficient to reduce epinephrine, norepinephrine, and dopamine and decrease wakefulness and motivation.

Conclusion: The patient’s nervous system is in a depleted excitatory state. This leads to a condition of fatigue. The fatigue, from reduced catecholamine levels, combined with the reduced serotonin level is likely to be a factor in the patient’s depression.

The therapeutic approach will be to first address serotonin levels followed by therapies that support the catecholamine system. Raising the serotonin levels first will help ensure that the therapies that increase the excitatory system won’t over stimulate the patient.

Therapy Objective

Increase the excitatory neurotransmitter system and preserve and strengthen the inhibitory neurotransmitter system.

Conditioning Phase (Addressing the Inhibitory System): Week 1 & 2

The first objective of this phase is to increase serotonin. Serotonin regulates catecholamine turnover, especially dopamine. Increasing serotonin with the 5-HTP containing product Optimum-S, is the first step toward accomplishing this objective. Optimum-S contains D, L-phenylalanine a precursor to dopamine, norepinephrine, epinephrine, and PEA as well as 5-HTP the precursor to serotonin. Optimum-S is chosen here because it contains a small amount of catecholamine and PEA support in order to prevent further fatigue.

Conditioning Phase protocol :

Optimum-S (2 capsules) twice a day (morning, bedtime)

Conditioning Phase (Addressing the Excitatory System): Week 3

The second objective of the conditioning phase is to increase dopamine; this begins in week three. Dopamine is the precursor to norepinephrine and epinephrine and will function to increase catecholamine levels and stimulate the excitatory system. Balance-D contains a highly purified preparation of Mucuna pruriens. Mucuna is a bean that naturally contains significant amounts of L-dopa.

Conditioning Phase Protocol:

- Optimum-S (2 capsules) twice a day (morning, bedtime)
- Balance-D (1 capsules) once a day (bedtime)

Therapy Phase: Week 4

The objective of this phase is to replenish the releasable pool of neurotransmitters contained in the presynaptic vesicles. Because this patient has significant deficits in their catecholamine levels Optimum-C, which has a high ratio of excitatory to inhibitory amino acids, was chosen over other therapies.

The ratio of catecholamine precursors to serotonin precursors in Optimum-C is increased in order to preferentially raise the catecholamines and PEA. Cysteine is included to support to the sulfur containing amino acid pathways involved in the synthesis neurotransmitters including the conversion of norepinephrine to epinephrine.

Therapy Phase Protocol:

- Optimum-S (2 capsules) once a day (bedtime) until bottle is finished
- Balance-D (1 capsule) once a day (bedtime) until bottle is finished
- Optimum-C (3 capsules) twice a day (morning and noon)
- CysNAC (1 capsule) twice a day (morning and noon)

Results of First Retest

Performed after 5 weeks in the Therapy Phase

Neurotransmitter	Baseline	Retest #1	Optimal	Therapeutic
ug/grCr	Results	Results:	Range	Range
Epinephrine	2.3	3.5	8-12	8-13
Norepinephrine	26.8	51.9	30-55	35-70
NE:Epi ratio	11.65	14.8	3.0-6.0	NA
Dopamine	100.2	468.6	125-175	200-500
Serotonin	111.5	901.0	175-225	250-1200
GABA	7.3	8.0	2.0-3.5	15-30

Interpretation

The results of the retest reveal significant improvements in the patient's neurotransmitter values. GABA stays somewhat elevated in response to Balance-D therapy. Serotonin and dopamine levels have increased dramatically and are in the "Therapeutic Range." A value this high is desirable during this phase of therapy and will help to replenish depleted presynaptic vesicles. The laboratory values also indicate that the low catecholamine levels observed in the baseline have increased.

Clinical Presentation

Patient reports that he is feeling much better. Fatigue and depression are significantly reduced.

Recommendation

Current therapy with Optimum-C and CysNAC should continue for another 2-3 months. A neurotransmitter retest should be performed at that time.

Results of Second Retest

Performed after 15 weeks in the therapy phase. The dose of Optimum-C was reduced from 3 capsules BID to 2 capsules BID during this phase.

Neurotransmitter	Baseline	Retest #1	Retest #2	Optimal	Therapeutic
ug/grCr	Results	Results	Results	Range	Range
Epinephrine	2.3	3.5	4.8	8-12	8-13
Norepinephrine	26.8	51.9	48.6	30-55	35-70
NE:Epi ratio	11.65	14.8	2.8	3.0-6.0	NA
Dopamine	100.2	468.6	203.8	125-175	200-500
Serotonin	111.5	901.0	187.1	175-225	250-1200
GABA	7.3	8.0	5.0	2.0-3.5	15-30

Interpretation

Neurotransmitter levels have decreased from the therapeutic levels seen early in therapy to more maintenance values.

Note: The following changes occurred in the patient's therapy since the previous test. The patient reduced dose of Optimum-C from 3 capsules BID to 2 capsules BID. The Balance-D started in week 3 of the patient's therapy lasted for 60 days. This test was taken about 8 weeks after the Balance-D was discontinued.

Presentation

Progress maintained. Patient reports still feeling improvement at a lower dose of Optimum-C.

Recommendation

Current therapy with Optimum-C and CysNAC should continue.

Final Comments

Initially the patient presented with an elevated GABA and low excitatory neurotransmitter levels. Through Neurotransmitter Optimization, the level of GABA has been decreased and the level of the excitatory catecholamines increased. This change significantly reduced the level of fatigue and depression in the patient.

The therapeutic levels of neurotransmitters observed during the therapy phase can restore the depleted presynaptic vesicles.

Increasing serotonin and the catecholamines also enhances neurotransmission. The reduced depression reported by the patient is likely a result of the improved neurotransmitter balance.

Example #3

Sex: Female

DOB: 1-13-77

Patient Complaints: Weight Gain, Fatigue, and Irritable Bowel

Current Medications: None

Baseline Test: NeuroRegulatory Profile #9001 (Serotonin, Epinephrine, Norepinephrine, Dopamine)

Results:

Neurotransmitter	Baseline	Optimal	Therapeutic Ranges
ug/grCr	Results:	Range	Ranges
Epinephrine	2.3	8-12	8-13
Norepinephrine	26.8	30-55	35-70
NE:Epi ratio	4.53	3.0-6.0	NA
Dopamine	186.3	125-175	200-500
Serotonin	109.5	175-225	250-1200
GABA	7.3	1.5-4.0	15-30

Comments

Epinephrine Norepinephrine, and Serotonin are low. Dopamine is above the optimal range this is most likely due to the low serotonin. In the absence of appropriate serotonin levels, dopamine turnover increases and results in higher dopamine excretion.

Therapy Objective

Conditioning Phase Objective

Support the inhibitory neurotransmitter prior to providing increased excitatory neurotransmitter support.

Conditioning Phase Protocol

Optimum-S (3 capsules) at bedtime

Balance-D (1 capsule) at bedtime

Therapy Phase Objective

Increase serotonin and dopamine in to help regulate the the brains appetite control center.

Therapy Phase Protocol

Optimum-S (3 capsules) at bedtime until bottle is finished.

Balance-D (1 capsule) at bedtime until bottle is finished.

TransLean (3 capsules) twice a day (30 min before morning and evening meal)

CysNAC (1 capsules) twice a day (30 min before morning and evening meal)

* If appetite suppression is not achieved, add Balance-D (1-3 capsules) with TransLean

Results of First Retest

Specimen collected after 4 weeks in the Therapy Phase

Neurotransmitter ug/grCr	Baseline Results	Retest #1 Results	Optimal Range	Therapeutic Range
Epinephrine	2.3	8.4	8-12	8-13
Norepinephrine	26.8	59.4	30-55	35-70
NE:Epi ratio	11.7	7.3	3.0-6.0	NA
Dopamine	186.3	405.1	125-175	200-500
Serotonin	109.5	650.6	175-225	250-1200
GABA	7.4	4.2	1.5-4.0	15-30

Interpretation

The catecholamine system shows significant response. Patient's serotonin also increased. GABA level have declined despite the increase catecholamine levels due to the increase in serotonin levels.

Clinical Presentation

Patient's fatigue and GI have improved and reports that there has been a significant reduction in her appetite. Patient is taking one additional cap of Balance-D with each dose of TransLean and continues with Optimum-S and Balance-D at bedtime.

Recommendation

Continue on current regimen until the bottle of Optimum-S is finished and then continue with:

Balance-D (1 capsule) at bedtime until bottle is finished.

TransLean (3 capsules) twice a day (30 min before morning and evening meal)

CysNAC (1 capsules) twice a day (30 min before morning and evening meal)

Retest in 2-3 months

Results Second retest

Specimen Collected after a total of 4 months in the program.

Neurotransmitter ug/grCr	Baseline Results	Retest #1 Results	Retest #2 Results	Optimal Range	Therapeutic Range
Epinephrine	2.3	8.4	9.2	8-12	8-13
Norepinephrine	26.8	59.4	63.7	30-55	35-70
NE:Epi ratio	11.7	7.3	8.0	3.0-6.0	NA
Dopamine	186.3	405.1	420.9	125-175	200-500
Serotonin	109.5	650.6	343.5	175-225	250-1200
GABA	7.4	4.2	4.6	1.5-4.0	15-30

Interpretation

Patient's dopamine levels increased, serotonin levels decreased with the discontinuation of the Optimum-S. Epinephrine and norepinephrine increased slightly since the last test.

Clinical presentation

Patient feels very good and reports an improved libido. Appetite control is solid and patient is pleased with her weight loss.

Recommendation

Continue on current protocol as long as appetite suppression is required. Reevaluate once weight loss goals have been achieved.

Example #4

Sex: Male

DOB: 12-20-96

Patient Complaints: Autism, ADD/ADHD, and Anxiety

Current medications: None

Baseline Test: **NeuroFocus Profile #9019 (URINE: Serotonin, Epinephrine, Norepinephrine, Dopamine, GABA, PEA)**

Neurotransmitter	Baseline Results:	Optimal Range	Therapeutic Ranges
Ug/grCr			
Epinephrine	15.7	8-12	8-13
Norepinephrine	80.5	30-55	35-70
NE:Epi ratio	11.65	3.0-6.0	NA
Dopamine	380.5	125-175	200-500
Serotonin	288.7	175-225	250-1200
GABA	9.3	1.0-3.5	15.30
PEA	1272	150-250	400-1000

Interpretation

Patient is in a high excitatory state. The levels of the excitatory neurotransmitters (epinephrine, norepinephrine, dopamine, PEA) are all elevated.

Clinical Presentation

Patient displays hyperactivity and high anxiety in response to any changes in their environment. Speech and communication skills delayed, typical of mild-moderate autism spectrum.

Recommendation

Epinephrine, norepinephrine, dopamine, and PEA are high and should be decreased through a therapy program that enhances the inhibitory (serotonin and GABA) neurotransmitter system. The therapies that might be chosen include: EndoTrex, which contains theanine, GabaMAX, which contains theanine, taurine, and glutamine, Serene, which contains 5-HTP, or CeroLox, which is a combination of Serene and GabaMAX.

Comments

The high level of PEA reflects the symptoms in this patient. Neurotransmitter tests of Autistic patients, as well as those with anxiety symptoms, frequently display high levels of PEA.

Interpretation

Patient is in a high excitatory state. The levels of the excitatory neurotransmitters (epinephrine, norepinephrine, dopamine, PEA) are all elevated and should be decreased through a therapy program that enhances the inhibitory (serotonin and GABA) neurotransmitter system.

Clinical Presentation

Patient displays hyperactivity and high anxiety in response to any changes in their environment. Speech and communication skills delayed, typical of mild-moderate autism spectrum.

Recommendation

Conditioning Phase: Weeks 1 & 2

CeroLox (1-2 capsule) twice a day (morning and bedtime)

EndoTrex (theanine) (2 sprays) 3-5 times daily (morning, noon, and bedtime)

Therapy Phase: Week 3

CeroLox (1-2 capsule) twice daily (morning and evening meal)

Optimum-S (1 capsule) twice a day (morning and evening meal)

EndoTrex (theanine) (2 sprays) as needed symptomatically

Note: The above-recommended dosage is for patients age 2-5 years. Increase dosage for older patients accordingly.

Retest in 4-6 weeks or sooner if needed

Optimum-S contains precursors for the catecholamine and serotonin system with emphasis on the serotonin system. It is used to raise serotonin and to a lesser degree the catecholamines.

CeroLox is a combination of ingredients designed to raise GABA and modulate dopamine activity. It is used as an adjunct therapy in patients with insufficient GABA function and those with symptoms of anxiety and insomnia.

EndoTrex (theanine) is a neurotransmitter modulator that reduces epinephrine, norepinephrine, and dopamine activity. Theanine is used symptomatically as an anti-anxiety and anti-hyperactivity amino acid.

Comments

The high level of PEA reflects the symptoms in this patient. Neurotransmitter tests of Autistic patients, as well as those with anxiety symptoms, frequently display high levels of PEA and GABA. Optimum-S is included in the therapy recommendation because it contains D, L-, phenylalanine, which provides greater support for PEA than L-phenylalanine. PEA enhances cognitive function. Recommend retesting neurotransmitter levels in 6-8 weeks.

Results of first retest.

Performed after 4 weeks in the therapy phase.

Neurotransmitter	Baseline	Retest #1	Optimal	Therapeutic
Ug/grCr	Results:	Results	Range	Range
Epinephrine	15.7	10.4	8-12	8-13
Norepinephrine	80.5	50.4	30-55	35-70
NE:Epi ratio	5.13	4.85	3.0-6.0	NA
Dopamine	480.5	211.8	125-175	200-500
Serotonin	188.7	175.6	175-225	250-1200
GABA	9.3	14.3	1.0-3.5	15-30
PEA	2272	1150	150-250	400-1000

Interpretation

Current regimen targeting the inhibitory neurotransmitter system has decreased the levels of the excitatory neurotransmitters. The level of the inhibitory neurotransmitter serotonin has remained stable and GABA has increased. The increased GABA is desired during this phase of therapy to modulate the excitatory neurotransmitters.

Clinical Presentation

Patient anxiety is lessened and ADD/ADHD behavior has been significantly reduced. EndoTrex use has declined from 4-5 times per day initially to 2-3 times per day during the past two weeks. Speech and communication skills have made small improvements. Patient's parents are pleased with current progress.

Recommendation

Continue on current therapy (1 Cerolox BID, 1 Optimum-S BID, & Endotrex PRN). The objective of therapy during the next 3-4 months will be to make further gains in the excitatory:inhibitory balance.

Results of Second retest.

Performed after 16 weeks in the therapy phase.

Neurotransmitter	Baseline	Retest #1	Retest #2	Optimal	Therapeutic
Ug/grCr	Results:	Results	Results	Range	Range
Epinephrine	15.7	10.4	8.5	8-12	8-13
Norepinephrine	80.5	50.4	42.1	30-55	35-70
NE:Epi ratio	5.13	4.85	4.95	3.0-6.0	NA
Dopamine	480.5	211.8	180.3	125-175	200-500
Serotonin	188.7	175.6	230.5	175-225	250-1200
GABA	9.3	14.3	5.3	1.0-3.5	15-30
PEA	2272	1150	475.6	150-250	400-1000

Interpretation

The levels of the excitatory neurotransmitters have continued to decline serotonin has increased slightly. GABA levels, which were initially elevated, have declined. This is expected since the levels of excitatory neurotransmitters have continued to decrease. This occurrence often coincides with a reduction in anxiety symptoms. The neurotransmitter levels seen in this test are quite good. PEA is still slightly elevated.

Clinical Presentation

Patient anxiety is lessened and ADD/ADHD behavior has been significantly reduced. EndoTrex use continues but is needed only a couple times a week. Small but noticeable improvements have been seen in speech and communication.

Recommendation

Continue on Cerolox and Endotrex. The Optimum-S may be reduced to 1 cap HS and then removed from regimen if symptoms do not worsen.

Comments

Patient has responded well and shown significant improvement during this neurotransmitter-optimizing program.

A Review of Neurotransmitter Biochemistry

Biosynthesis of Amino Acid-Derived Compounds

Phenylalanine is an essential amino acid and is a precursor in the biosynthesis of several biologically important compounds including PEA and the catecholamines. Each of the three closely related catecholamines—dopamine, norepinephrine, and epinephrine — has a specific function as a neurotransmitter or hormone.

Dopamine Synthesis

a. Formation of Tyrosine

L-Phenylalanine is hydroxylated to tyrosine by *phenylalanine hydroxylase* (also called “*phenylalanine-4-monooxygenase*”) a mixed function hydroxylase, which requires tetrahydrobiopterin and molecular oxygen as cofactors.

b. Formation of L-dopa

(1) Tyrosine is hydroxylated to 3,4-dihydroxyphenylalanine (L-dopa) by *tyrosine hydroxylase*, a mixed-function oxidase, which requires tetrahydrobiopterin as a cofactor.

(2) Tyrosine hydroxylation is the rate-limiting step in catecholamine biosynthesis; the enzyme is allosteric, with dopamine, norepinephrine, and epinephrine acting as negative effectors.

c. Formation of Dopamine

Aromatic amino acid decarboxylase, a pyridoxal phosphate-dependent enzyme, forms 3,4-dihydroxyphenylethylamine (dopamine) from L-dopa.

d. Formation of Norepinephrine

(1) Another mixed-function oxidase, dopamine β-hydroxylase, hydroxylates dopamine on the side chain to yield norepinephrine.

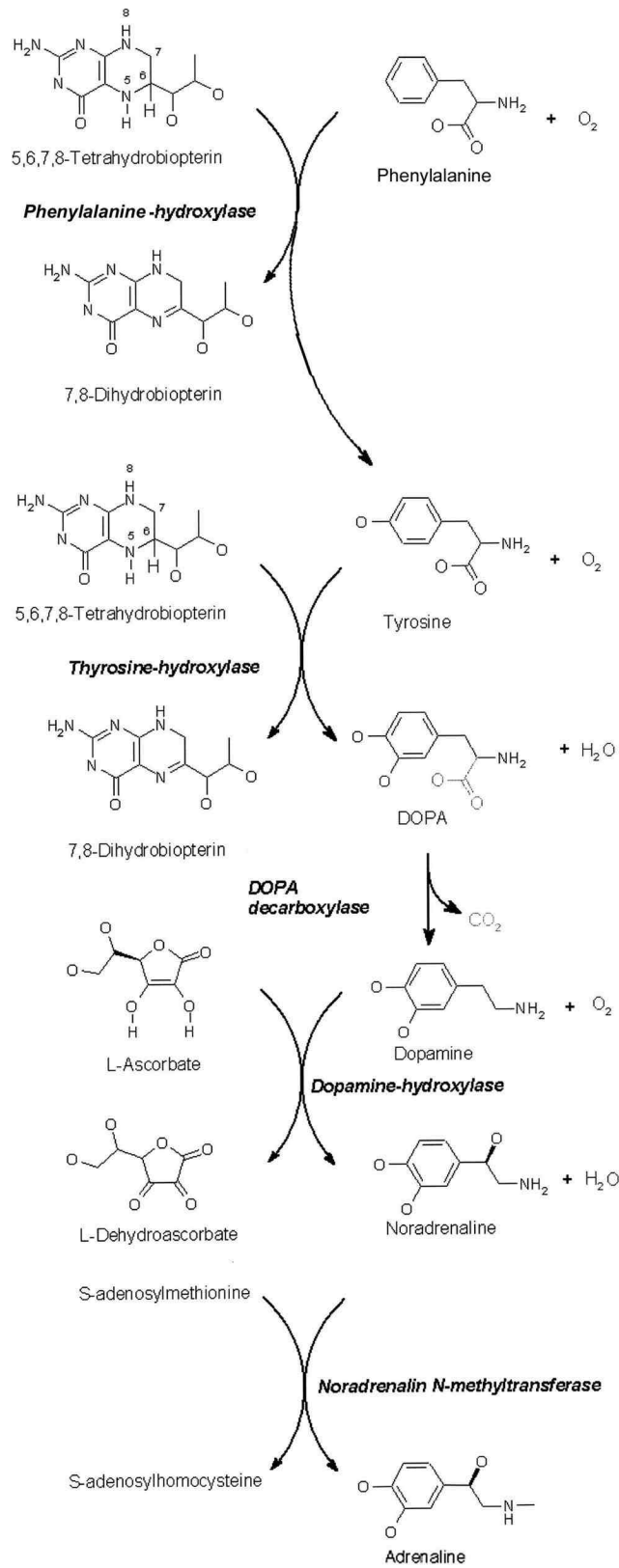
(2) The enzyme contains copper and requires ascorbate (vitamin C) and molecular oxygen.

(3) Norepinephrine is the major neural transmitter of the sympathetic nervous system.

e. Formation of Epinephrine

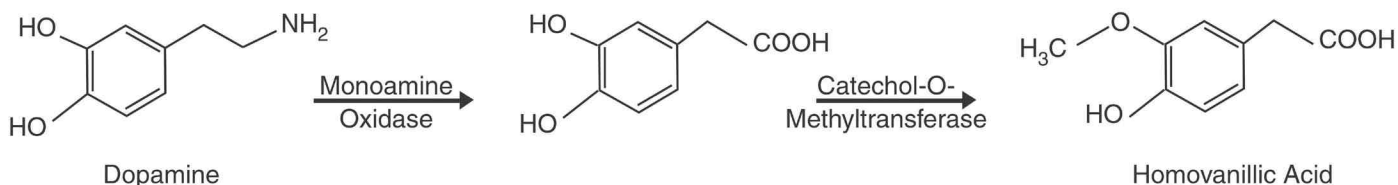
Norepinephrine is methylated by phenylethanolamine N-methyltransferase to form epinephrine, using SAMe as the methyl donor. Catecholamines can be taken back up into neurons after release via the dopamine transporter, or metabolized by monoamine oxidase (to 3,4,-dihydroxyphenylacetic acid) or catechol-O-methyltransferase (to 3-methoxytyramine). These enzymes are major mechanisms for inactivation of catecholamines (and monoamines). Action by both enzymes results in the formation of homovanillic acid (3-methoxy-4hydroxy-phenylacetic acid).

Catecholamine Pathway



Serotonin Biosynthesis

Serotonin is present at highest concentrations in platelets and in the gastrointestinal tract. Lesser amounts are found in the brain and the retina. Serotonin containing neurons have their cell bodies in the midline raphe nuclei of the brain stem and project to portions of the hypothalamus, the limbic system, the neocortex, and the spinal cord. After release from serotonergic neurons, most of the released serotonin is recaptured by an active reuptake mechanism.



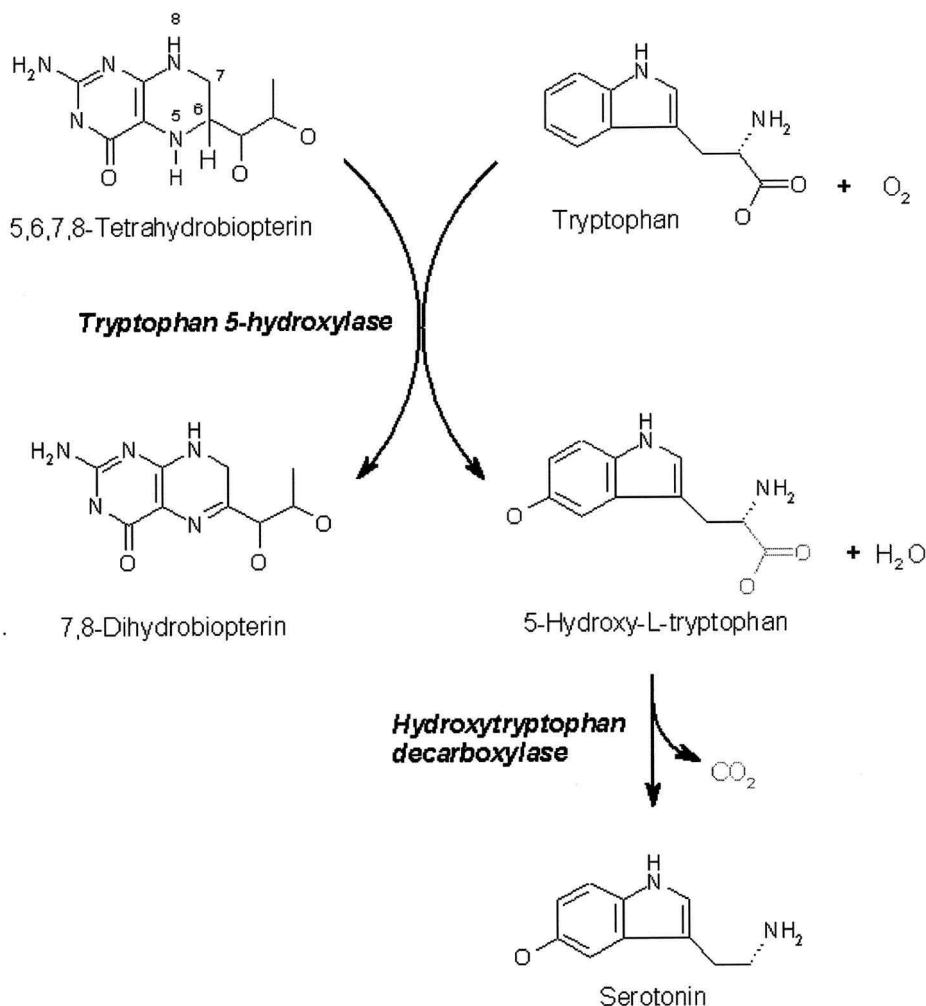
a. Formation of 5-HTP

(1) Tryptophan is hydroxylated to (5-HTP) by *tryptophan hydroxylase*, a mixed-function oxidase, which requires tetrahydrobiopterin as a cofactor (catalyzed by *tryptophan-5-monoxygenase*).

(2) Tryptophan hydroxylation is the rate-limiting step in serotonin biosynthesis; the enzyme is allosteric, with serotonin acting as a negative effector. The hydroxylase is normally not saturated and as a result, an increased uptake of tryptophan in the diet will lead to increased brain serotonin content.

b. Formation of Serotonin

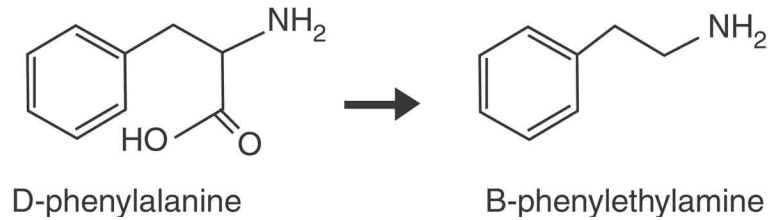
Aromatic L-amino acid decarboxylase then catalyzes 5-HTP to serotonin.



Phenylethylamine (PEA) Synthesis

Formation of PEA

Phenylalanine is decarboxylated to beta-phenylethylamine by phenylalanine decarboxylase a pyridoxyl phosphate dependent enzyme.



GABA Synthesis

Formation of GABA

GABA is directly biosynthesized from L-glutamate by the action of glutamic acid decarboxylase (GAD) which requires pyridoxal 5'-phosphate as a cofactor. L-glutamate is available from α -ketoglutarate, a product of glucose metabolism. Glucose is a normal nutrient supplied to the CNS via the blood via active transport. Glutamate can also be synthesized from glutamine by the enzyme glutaminase.

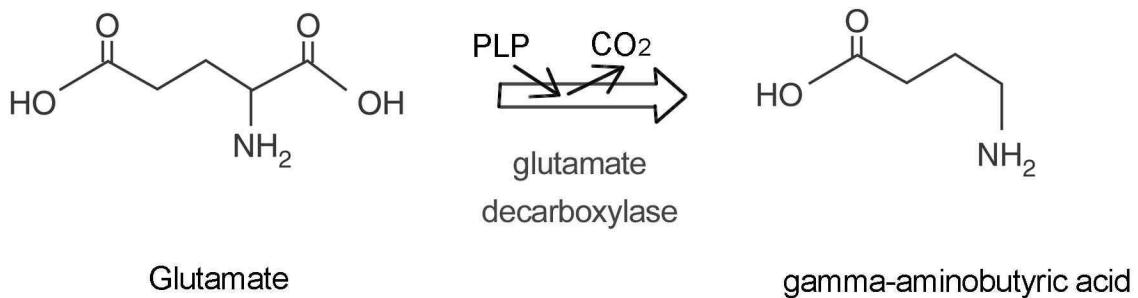


Figure 2: Synthesis of GABA

Suggested Reading

Books

Synaptic Self: How Our Brains Become Who We Are. LeDoux, Joseph. Viking. Jan. 2002. ISBN 0-670-03028-7.

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