Neuro-Biogenic Amines

Presented by Antony Haynes

10\textsuperscript{th} March 2016
At
The Royal Society of Medicine
Here’s what you get

By attending this evening, you will have access to these documents

1. This powerpoint presentation (which is slightly different to the hard copy you have).

2. The Neurotransmitter Questionnaire The single sheet portraying NeuroBiogenic Amine metabolism.

3. The nutritional suggestions for specific therapeutic intervention to address NeuroBiogenic Amine imbalances.

4. The nutritional suggestions for supporting the BBB.

5. Happiness Questionnaire
Introducing NeuroBioGenic Amines
Gentle Reminders

This is an introduction to the subject

No single aspect of an individual’s health is necessarily going to be the sole key to well-being

No single functional lab test should be taken in isolation without being folded into the context of the case history and individual (n=1) in front of you.

Nutritional therapy can be a mighty powerful tool in restoring and improving good health, but it is not everything.
What is a NeuroBiogenic Amine (neurotransmitter)?

• A neuro-biogenic amine is a molecule (chemical) that carries a signal between nerve cells.

• A *neuromodulator* is a molecule that alters a nerve cells’ response to a neurotransmitter signal.

• Neuro-biogenic amines and neuromodulators have effect when they bind to specialised receptors on other cells, or inside a cell.

• Neurotransmitters are necessary because all nerve cells are separated by minute spaces called *synapses*.
Summary of Information Provided
• Happiness Questionnaire
• Neurotransmitters (brief intro)
• 21st Century Living
• Neurotransmitters (more info)
• NZT (!)
• The Pursuit of Happiness
• Intro to key neurotransmitters
• Symptoms of specific neurotransmitter imbalances
• A word about oxytocin
• A word about serotonin syndrome
• A word about NMDA receptor
• Functional Lab tests to consider
• The Gut Connection
• Microbiome & Neurotransmitter Connection
• A word about Kynurenic Acid & Quinolinic Acid
• Neuro-Biogenic Amines
• Example urine test results with detailed explanations
• Catecholamine NeuroBiogenic Amines
• Blood Brain Barrier
• What nutritional and non-nutritional action to take to address imbalances in neurotransmitters / neurobiogenic amines.
THC

• Molecule of tetrahydrocannabinol, or THC, the main mind-altering ingredient found in the Cannabis plant.
Happiness Questionnaire

• The Oxford Happiness Questionnaire was developed by psychologists Michael Argyle and Peter Hills at Oxford Brookes University.

• This is a good way to get a snapshot of your current level of happiness. You can even use your score to compare to your happiness level at some point in the future by taking the survey again. If you are using some of the interventions presented on this site to raise your happiness level, you can see whether your score on the Oxford Happiness Questionnaire goes up as a result.
Instructions

• Below are a number of statements about happiness. Please indicate how much you agree or disagree with each by entering a number in the blank after each statement, according to the following scale:

• 1 = strongly disagree
• 2 = moderately disagree
• 3 = slightly disagree
• 4 = slightly agree
• 5 = moderately agree
• 6 = strongly agree

• Please read the statements carefully, because some are phrased positively and others negatively. Don’t take too long over individual questions; there are no “right” or “wrong” answers (and no trick questions). The first answer that comes into your head is probably the right one for you. If you find some of the questions difficult, please give the answer that is true for you in general or for most of the time.
Happiness - The Questionnaire

• 1. I don’t feel particularly pleased with the way I am. (R) _____
• 2. I am intensely interested in other people. _____
• 3. I feel that life is very rewarding. _____
• 4. I have very warm feelings towards almost everyone. _____
• 5. I rarely wake up feeling rested. (R) _____
• 6. I am not particularly optimistic about the future. (R) _____
• 7. I find most things amusing. _____
• 8. I am always committed and involved. _____
• 9. Life is good. _____
• 10. I do not think that the world is a good place. (R) _____
Happiness - The Questionnaire

• 11. I laugh a lot. _____
• 12. I am well satisfied about everything in my life. _____
• 13. I don’t think I look attractive. (R) _____
• 14. There is a gap between what I would like to do and what I have done. (R) _____
• 15. I am very happy. _____
• 16. I find beauty in some things. _____
• 17. I always have a cheerful effect on others. _____
• 18. I can fit in (find time for) everything I want to. _____
• 19. I feel that I am not especially in control of my life. (R) _____
• 20. I feel able to take anything on. _____
Happiness - The Questionnaire

• 21. I feel fully mentally alert. _____
• 22. I often experience joy and elation. _____
• 23. I don’t find it easy to make decisions. (R) _____
• 24. I don’t have a particular sense of meaning and purpose in my life. (R) _____
• 25. I feel I have a great deal of energy. _____
• 26. I usually have a good influence on events. _____
• 27. I don’t have fun with other people. (R) _____
• 28. I don’t feel particularly healthy. (R) _____
• 29. I don’t have particularly happy memories of the past. (R) _____
Calculate your score

• Step 1. Items marked (R) should be scored in reverse:

- If you gave yourself a “1,” cross it out and change it to a “6.”
  - Change “2” to a “5”
  - Change “3” to a “4”
  - Change “4” to a “3”
  - Change “5” to a “2”
  - Change “6” to a “1”

• Step 2. Add the numbers for all 29 questions. (Use the converted numbers for the 12 items that are reverse scored.)

• Step 3. Divide by 29. So your happiness score = the total (from step 2) divided by 29.
Happiness - The Questionnaire

• It is recommended to record your score and the date. Then you’ll have the option to compare your score now with your score at a later date. This can be especially helpful if you are trying some of the exercises, and actively working on increasing your happiness.

• The average is 4.

Reference
Happiness - The Questionnaire

• **Between one and two**
  
  Not happy. You may be seeing yourself and your situation as worse than it really is. Try taking the depression symptoms test (CES-D Questionnaire) at the University of Pennsylvania’s “Authentic Happiness” Testing Centre. You’ll have to register, but this is beneficial because there are a lot of good tests there and you can re-take them later and see how your scores have changed.

• **Between two and three**
  
  Somewhat unhappy. Try starting a gratitude journal or gratitude list, or make a gratitude visit. Or take a look at the “Authentic Happiness” site mentioned above.
Happiness - The Questionnaire

• Between three and four
  • Neutral – not really happy or unhappy. A score of 3.5 would reflect an equal number of happy and unhappy responses. Exercises designed to increase happiness have been tested in scientific studies and have been shown to make people lastingly happier.

• Four
  • Somewhat happy or moderately happy - satisfied. This is what the average person scores.

• Between four and five
  • Rather happy; pretty happy. Check other score ranges for suggestions and information.
Happiness - The Questionnaire

• Between five and six

• Very happy. Being happy has benefits beyond simply feeling good. It’s correlated with advantages in health, with better marriages, and with attaining your goals. A base of happiness allows you to broaden and build toward greater success.

• Six

• Too happy. That’s right – it’s possible to be too happy. Research seems to indicate that there’s an ideal level of happiness to do well at work or school, or for your health, and that being too happy may be associated with poorer performance in these areas.
Happiness - The Questionnaire

• If your score was 4 or less and you want to improve it ... perhaps you could do worse than to aim to improve your levels of brain messengers (i.e. neurotransmitters).
Neurotransmitters
Living in the 21st Century

What is it doing to us?
21st Century Living

No TRACE Homo Sapiens? NO Evidence
The Missing Link

Australopithecus  Sahelanthropus tchadensis  Homo habilis  Homo erectus  Neanderthal  Human?

5 million years ago  3 million years ago  2 million years ago  1 million years ago  100k years ago  80k years ago  6k years ago

Poof!  Poof Gone!  Uhmm...?

extinct  extinct

MISSING LINK  PRESTO!

Civilization Present Day
21st Century Living

- Big Bang
- 3 billion
- Life begins?
- 6 billion
- Cambrian explosion
- 9 billion
- First eukaryote
- 12 billion
- Colonization of galaxy completed
- 15 billion
21st Century Living

The Meaning of the 21st Century
21st Century Living

• 21st Century Living can place huge demands on us. Long hours, high stress, 24 hour opening, the internet and emails, multiple tasks to do, lack of sleep, and too little or too much exercise, all can erode well-being on many levels.

• One of the first, most important and most sensitive aspects of human biochemistry that we need to keep in balanced harmony in order to thrive in this environment is that of our neurotransmitters.
Students' Ideas about Learning, Working, and Living in the Future!

Fast Forward French Curriculum

Relationships: The Basis of Future Education

Students as Partners in Their Education

Teaching Financial Literacy: The Importance of Finance & Money Management

International Focus: Teaching & Learning

Collaboration

Inclusive
Stressful Living in the 21st Century

• NUTS, in this case, is an acronym which stands for the four broad reasons that we develop stress:
  • **N: Novelty** – New things make us stress out
  • **U: Unpredictability** – things that change frequently stress us out
  • **T: Threats to ego or self** – things that make us lose face, embarrass us, or threaten us physically stress us out
  • **S: Sense of control** – feeling like we have no control over a situation stresses us out.

• Dr Sonia Lupien, McGill University in Montreal, Quebec, Canada.
Stressful Living in the 21st Century

• So, the more NUTS you go, the greater the threat to the healthy balance of your neurotransmitters!
Neurotransmitters & Syllabus

• Neurotransmitters play key roles in cognitive function, behaviour and in general well-being.
• You will learn about neuro-biogenic amines, neuromodulators, and the blood brain barrier.
• You will also be shown the means to assess neurotransmitter status by both symptomatic questionnaires (you don’t have to rely solely on the Happiness Questionnaire).
• As well as a newly available accurate urine lab test.
• Then you will be shown how to support a balanced neurotransmitter status (both with and without the use of the lab test), as well as how to support the blood brain barrier, with specific nutritional therapy intervention.
Therapeutic Opportunity

• Information gained through neuro-biogenic amine testing may provide therapeutic opportunities that improve clinical success and patient health outcomes.

• Associations between urinary neurotransmitter levels and health conditions have been documented in scientific literature and may provide valuable insights as part of a comprehensive health assessment.
Neurotransmitters
Potato Not Prozac!
Welcome to NZT

• NZT is thallanylzirconio-methyl-tetrahydro-triazatriphenylene, a powerful new class of psychotropic medication that merges various features of NDRI’s, NaSSA’s and SSRI’s.

• NZT works, in part, by maintaining higher levels of 5-HT in the synapse while increasing norepinephrine and serotonin neurotransmission by blocking presynaptic alpha-2 adrenergic receptors while at the same time blocking certain serotonin receptors.
How does NZT work?

• NZT is a nitrogen-based psychotropic that impacts specific brain activity in several ways but most significantly by elevating receptivity and synaptic sharing between the hippocampus, the amygdale and the striatum.

• In controlled doses, taken over the course of a relatively short period of time, NZT significantly improves both short-term and long-term memory, memory capacity, and the analytical purposing of memory. Because it also impacts the sympathetic and parasympathetic nervous systems, NZT can improve higher brain function, hand-eye coordination, muscle memory and even the body’s immune system.

• In some people, NZT can even induce lucid dreaming and what is sometimes called ‘fugue state’.
Is NZT effective?

• When taken as directed (one pill per day for seven consecutive days), NZT has been shown to be 97.3% effective in improving memory, hand-eye coordination and a host of cognitive abilities.

• In those cases where NZT was not effective, subjects did not finish the full therapeutic regimen.

• NZT was studied in men and women 18 to 45 weighing 95 to 270 pounds.
Who can take NZT?

• Men and women who are considered to be in good health – who have no known history of cardiopathy, cardiomyopathy, cerebral ischemia or intracranial haemorrhage, kidney or liver problems, a history of mania or seizure disorders are generally speaking good candidates for NZT.
Hang on, before we get too side-tracked ... 

Let’s Get back to the Pursuit of Happiness !
Happiness is ....

- Serotonin: the self-esteem & sleep chemical
- Oxytocin: the trust chemical
- Melatonin: the R&R chemical
- Norepinephrine: the excitement chemical
- Phenylethylamine: the bliss & infatuation chemical
- Acetylcholine: the alertness chemical
- Endorphins: the pain killer chemical
- Dopamine: the reward chemical
Symptoms of Neurotransmitter Imbalance

There are also symptom checkers for specific neurotransmitters:

- Glutamate
- GABA
- Dopamine
- AcetylCholine
- Serotonin
- Noradrenaline
Glutamate Imbalances
Glutamate Imbalances (too high)

- Neuro-degenerative diseases
- Paroxysmal symptoms
- Hyperactivity
- Migraines
- Poor attention
- Irritability
- Explosive behaviours
- Anger attacks
- Aggression
- Poor mood / mood swings
- Bipolar disease
GABA Imbalances
GABA Imbalances (too low)

- Anxiety
- Depression
- Panic attacks
- Poor attention & focus
- Phobias
- Feel stressed / pressured / overwhelmed
- Sweaty, clammy hands
- Butterflies in stomach
- Lump in throat
- Have trouble relaxing / loosening up
- Low stress tolerance

- Body tends to be tense/stiff/uptight
- Trembling/twitching/shaking
- Anxious/nervous/jumpy/‘on edge’
- Feel panicky/panic attacks
- Heart palpitations or fast resting heart rate (over 85bpm)
- Sleep problems or chronic pain
- Use alcohol/food/cigarettes to relax
- Valium/Xanax/Avitan/GABA reduce above symptoms
- Family history of anxiety or panic attacks
Cortical GABA Concentrations in Healthy and Depressed Subjects

Dopamine Imbalances
Dopamine Imbalances (too low)

• Inability to concentrate
• Poor attention & poor attention to detail
• Poor memory
• Reduced ability to feel pleasure
• Flat, bored, apathetic and low enthusiasm
• Depressed
• Low drive and motivation
• Restless
• Impatient
• Difficulty getting through a task even when interesting

• Crave uppers (e.g. caffeine/nicotine/diet soft drinks)
• Prone to addictions (e.g. alcohol, cigarettes)/addictive personality
• Shy/introvert
• Low libido or impotence
• Mentally fatigued easily and physically fatigued easily
• Put on weight easily
• Procrastinator/little urgency
• Sleep too much and trouble getting out of bed
• Family history of alcoholism/ADD/ADHD
Dopamine Imbalances (too high)

- Psychosis
- OCD
- Anxiety
- Aggression
- Poor impulse control
- Low pain threshold
Dopamine Pathways
Principal “Pleasure” System of the Brain

Natural Rewards Elevate Dopamine Levels

Effects of Drugs on Dopamine Levels

Source: Di Chiara and Imperato
DOPAMINE RECEPTOR AVAILABILITY (NMS) AND DEPRESSIVE SYMPTOMATOLOGY (BECK)

![Graph showing the relationship between Beck Depression Inventory and Ratio Index (NMS). The correlation coefficient r = 0.67 (n=24).]
Serotonin Imbalances
Serotonin Imbalances (too low)

- Depression
- Anxiety
- Melancholic
- Insomnia / Sleep problems / Light sleeper
- Nervous
- Worrier
- Poor response to stress
- Negative / Pessimistic
- Irritable / impatient/edgy
- Self destructive, masochistic or suicidal thoughts / plans

- Think about the same things over & over again
- Low self esteem / confidence
- Feel worse in and dislike dark weather
- Anger / rage / explosive behaviour / assaultive
- Inflammation / chronic pain
- PMS
- Anti-depressants / 5HTP improve mood
- Family history of depression / anxiety / OCD / eating disorders
Noradrenaline Imbalances
Noradrenaline Imbalances (too low & too high)

• Too Low
  • Depression
  • Anxiety
  • Panic Attacks

• Too high
  • Cardiovascular disease
Acetylcholine Imbalances
Acetylcholine Functions

• Acetylcholine synthesis occurs in the hippocampus
• Acetylcholine facilitates communication between neurons and mediates release of other neurotransmitters
• Acetylcholine function is critical for cognitive processing, memory, arousal, and attention
• Diminished Acetylcholine correlates with severity of cognitive dysfunction
Acetylcholine Imbalances (too low)

- Poor concentration
- Poor memory
- Difficulty remembering names and faces after meeting people
- Trouble understanding spoken or written language
- Forget where you put things (e.g. keys)
- Slowed and/or confused thinking
- Making simple mistakes at work
- Difficulty finding the right words before speaking
- Prefer to do things alone than in groups / social withdrawal
- Rarely feel passionate
- Feel despair and lack joy
- Lost some of my creativity / lack imagination
- Dry mouth
- Increased risk of dementia
Oxytocin

• Oxytocin activates orexin.
• The structure of oxytocin is very similar to that of vasopressin. Due to its similarity to vasopressin, it can reduce the excretion of urine slightly.
• In several species, oxytocin can stimulate sodium excretion from the kidneys (natriuresis), and, in humans, high doses can result in hyponatremia.
• Falling in love, having sex, nursing and positive social encounters all of these lead to increased oxytocin.
A Word About
Serotonin Syndrome
Serotonin Syndrome

• Serotonin syndrome is not an idiopathic drug reaction; it is a predictable consequence of excess serotonin on the CNS and/or peripheral nervous system.

• For this reason, some experts strongly prefer the terms serotonin toxicity or serotonin toxidrome which more accurately reflect that it is a form of poisoning. Other names include serotonin sickness, serotonin storm, serotonin poisoning, hyperserotonaemia, or serotonergic syndrome.

• Excessive levels of serotonin produce a spectrum of specific symptoms including cognitive, autonomic, and somatic effects. Symptoms may range from barely perceptible to fatal. Numerous drugs and drug combinations have been reported to produce serotonin syndrome, though the exact mechanism is not well understood in many instances.

• Diagnosis includes observing symptoms and investigating patient history for causal factors (interacting drugs).
Serotonin Syndrome

• The syndrome has a characteristic picture but can be mistaken for other illnesses in some people, particularly those with neuroleptic malignant syndrome, a condition characterised by excessive blockade of the dopamine receptors (usually the result of anti-nausea / vomiting or antipsychotic drugs), leading to movement disorders, changes in temperature, and other problems.

• No laboratory tests can currently confirm the diagnosis. Hence it is diagnosed based on symptoms, disease course (that is, the progression of the disease) and the exclusion of other possible causes of the presenting symptoms.

• Treatment consists of discontinuing medications which may contribute and in moderate to severe cases administering a serotonin antagonist. An important adjunct treatment includes controlling agitation with benzodiazepine sedation.
Serotonin Syndrome

Has anyone here ever come across a single case of Serotonin Syndrome?
A Word About
The NMDA Receptor
The N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR), is a glutamate receptor and ion channel protein found in nerve cells.

It is activated when glutamate and glycine (or D-serine) bind to it, and when activated it allows positively charged ions to flow through the cell membrane.

The binding of a neurotransmitter to its receptor activates a receptor function, in this example, opening an ion channel.
NMDA Receptor

• The NMDA receptor is very important for controlling synaptic plasticity and memory function.


• Calcium flux through NMDARs is thought to be critical in synaptic plasticity, a cellular mechanism for learning and memory.
NMDA Receptor

• “Synaptic plasticity is the cellular mechanism underlying learning and memory.”

• “Recently, we identified Girdin as a key molecule involved in regulating long-term memory. It was demonstrated that phosphorylation of Girdin by Akt contributed to the maintenance of LTP by linking the BDNF/TrkB signaling pathway with NMDA receptor activity. These findings indicate that Girdin plays a pivotal role in a variety of processes in the CNS. Here, we review recent advances in our understanding about the roles of Girdin in the CNS and focus particularly on neuronal migration and memory.”

Figure 3.

The binding of a neurotransmitter to its receptor activates a receptor function, in this example, opening an ion channel.
Glutamate Receptors

Increases phospholipase A2

Free radicals/oxidative stress
Mitochondrial dysfunction
Activation of caspases/apoptosis
DNA-damage
Cell membrane degradation

NMDA-receptor
Mg$$^{2+}$$
Ca$$^{2+}$$
Excitatory amino acids, such as glutamate, homocysteine, homocysteic acid

Cell death

Vitamin D buffers against hyperactivation of intracellular calcium. Increases calcium binding protein = Calbindin, natural glutamate antagonist.
NMDA Receptor Inhibition

• Therefore, a central goal is often to calm, reduce, inhibit & antagonise the NMDA receptor activity, in the majority of cases.
Other than case history information & questionnaires ... ... how else can we measure happiness?
Measuring Happiness?

• Let’s Take A Step Back ...

• Is Happiness Biological?

• If there is a connection, what other ways are there to measure it?
Functional Lab Tests

• Adrenal Hormones?
• Thyroid Hormones?
• Glucose Tolerance Test?
• Heavy Metal Tests?
• Stool Test ? Happy Gut - Happy Bugs – Happy Brain - Happy Person?
• Haematology & Biochemistry?
• Cholesterol testing?

or

• Neurotransmitters & Biogenic Amines?
Gut-Neurotransmitter Connection
Gut – Neurotransmitter Connection

• The gut microbiota has the capacity to produce a diverse range of compounds that play a major role in regulating the activity of distal organs and the liver is strategically positioned downstream of the gut.

• Gut microbiota linked compounds such as short chain fatty acids, bile acids, choline metabolites, indole derivatives, vitamins, polyamines, lipids, neurotransmitters and neuroactive compounds, and hypothalamic-pituitary-adrenal axis hormones have many biological functions.

Gut – Neurotransmitter Connection

• “The gut microbiome influences immunological, endocrine, and neural pathways and plays an important role in infant development. Several factors influence colonization of the infant gut microbiome.

• Different microbial colonization patterns are associated with vaginal versus surgical birth, exposure to antibiotics, and infant-feeding patterns. Because of extensive physiological influence, infant microbial colonization patterns have the potential to impact physical and neurocognitive development and life course disease risk.

• Understanding these influences will inform newborn care and parental education.”

Gut – Neurotransmitter Connection

• “Up-regulation of the serotonin transporter level in the midbrain and thalamus may underlie the pathogenesis of FD such as abdominal and psychological symptoms via a brain-gut interaction.”

Gut – Neurotransmitter Connection

• The human gut microbiome impacts human brain health in numerous ways:

• (1) Structural bacterial components such as lipopolysaccharides provide low-grade tonic stimulation of the innate immune system. Excessive stimulation due to bacterial dysbiosis, small intestinal bacterial overgrowth, or increased intestinal permeability may produce systemic and/or central nervous system inflammation.

• (2) Bacterial proteins may cross-react with human antigens to stimulate dysfunctional responses of the adaptive immune system.

Gut – Neurotransmitter Connection

• (3) Bacterial enzymes may produce neurotoxic metabolites such as D-lactic acid and ammonia. Even beneficial metabolites such as short-chain fatty acids may exert neurotoxicity.

• (4) Gut microbes can produce hormones and neurotransmitters that are identical to those produced by humans. Bacterial receptors for these hormones influence microbial growth and virulence.

• (5) Gut bacteria directly stimulate afferent neurons of the enteric nervous system to send signals to the brain via the vagus nerve.

Gut – Neurotransmitter Connection

• “Through these varied mechanisms, gut microbes shape the architecture of sleep and stress reactivity of the hypothalamic-pituitary-adrenal axis. They influence memory, mood, and cognition and are clinically and therapeutically relevant to a range of disorders, including alcoholism, chronic fatigue syndrome, fibromyalgia, and restless legs syndrome.”

“Changes in gut microbiota can modulate the peripheral and central nervous systems, resulting in altered brain functioning, and suggesting the existence of a microbiota gut-brain axis. Diet can also change the profile of gut microbiota and, thereby, behaviour.”

A Word about Kynurenic acid (KYNA)
Kynurenic acid

• Tryptophan may also be converted into kynurenine by another enzymatic pathway.

• The shift of tryptophan metabolism away from serotonin towards kynureneine may be promoted by increased cortisol, inflammation or bacterial lipopolysaccharide ("endotoxin").

• Aging and oxidative stress may also upregulate the kynurenine pathway.

• Accumulation of kynurenic acid, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been associated with symptoms of schizophrenia and cognitive degeneration.
Kynurenic acid

• Kynurenic acid (KYNA or KYN) is a product of the normal metabolism of amino acid L-tryptophan.

• It has been shown that kynurenic acid possesses neuroactive activity.

• At normal levels it acts as an anti-excitotoxic and anti-convulsant, most likely through acting as an antagonist at excitatory amino acid receptors. Because of this activity, it may influence important neurophysiological and neuropathological processes.

• As a result, kynurenic acid has been considered for use in therapy in certain neurobiological disorders. Conversely, increased levels of kynurenic acid have also been linked to certain pathological conditions.
Quinolinic Acid

• Quinolinic acid is a downstream product of the kynurenine pathway, which metabolises the amino acid tryptophan. It acts as an NMDA receptor agonist.

• Quinolinic acid has a potent neurotoxic effect. Studies have demonstrated that quinolinic acid may be involved in many psychiatric disorders, neurodegenerative processes in the brain, as well as other disorders.

• Within the brain, quinolinic acid is only produced by activated microglia and macrophages.
### Kynurenic Acid : Quinolinic Acid Ratio

**Malabsorption and Dysbiosis Markers**

<table>
<thead>
<tr>
<th>Malabsorption Markers</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>Indoleacetic Acid (IAA)</td>
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<td>Phenylacetic Acid (PAA)</td>
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**Bacterial Dysbiosis Markers**

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<tr>
<td>Dihydroxyphenylacetic Acid (DHPA)</td>
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<td>3-Hydroxyphenylacetic Acid</td>
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<td>4-Hydroxyphenylacetic Acid</td>
<td>&lt;= 4.4</td>
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<tr>
<td>Benzoic Acid</td>
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<td>Hippuric Acid</td>
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**Yeast / Fungal Dysbiosis Markers**

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**Cellular Energy & Mitochondrial Metabolites**

**Carbohydrate Metabolism**

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<td>Pyruvic Acid</td>
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<td>β-OH-Butyric Acid (BHBA)</td>
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**Energy Metabolism**

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<td>C6-Cr-Acetonic Acid</td>
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<td>α-Ketoglutaric Acid (AKG)</td>
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<td>Malic Acid</td>
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<tr>
<td>β-OH-β-Methylglutaric Acid (HMG)</td>
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**Fatty Acid Metabolism**

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**Creatinine Concentration**

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<tr>
<th>Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>12.0</td>
</tr>
</tbody>
</table>

### Neurotransmitter Metabolites

<table>
<thead>
<tr>
<th>Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanillylmandelic Acid</td>
<td>5.1 - 15.0</td>
</tr>
<tr>
<td>Homovanillic Acid</td>
<td>1.8 - 18.8</td>
</tr>
<tr>
<td>5-Hydroxyindoleacetic Acid</td>
<td>&lt;= 13.9</td>
</tr>
<tr>
<td>3-Methyl-4-Phenylglycol</td>
<td>&lt;= 0.07</td>
</tr>
<tr>
<td>Kynuronic Acid</td>
<td>&lt;= 4.8</td>
</tr>
<tr>
<td>Quinolinic Acid</td>
<td>&lt;= 19.2</td>
</tr>
<tr>
<td>Kynuric / Quinolinic Ratio</td>
<td>&lt;= 0.25</td>
</tr>
</tbody>
</table>

### Neurotransmitter Metabolites

<table>
<thead>
<tr>
<th>Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Ketoacidic Acid</td>
<td>&lt;= 1.6</td>
</tr>
<tr>
<td>o-Ketosaccharic Acid</td>
<td>&lt;= 0.37</td>
</tr>
<tr>
<td>o-Ketosaccharic Acid</td>
<td>&lt;= 0.06</td>
</tr>
<tr>
<td>o-Keto-B-Methyvaleric Acid</td>
<td>&lt;= 0.8</td>
</tr>
<tr>
<td>Formiminoglycic Acid (FIGlu)</td>
<td>&lt;= 1.0</td>
</tr>
<tr>
<td>Glutaric Acid</td>
<td>&lt;= 0.29</td>
</tr>
<tr>
<td>Isocitrylic Acid</td>
<td>&lt;= 1.4</td>
</tr>
<tr>
<td>Methylmalonic Acid</td>
<td>&lt;= 1.3</td>
</tr>
<tr>
<td>Xanthurenic Acid</td>
<td>&lt;= 0.39</td>
</tr>
<tr>
<td>3-Hydroxypyroolactic Acid</td>
<td>&lt;= 0.30</td>
</tr>
<tr>
<td>3-Hydroxyisovaleric Acid</td>
<td>&lt;= 0.17</td>
</tr>
</tbody>
</table>

### Toxin & Detoxification Markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>o-Ketopiperic Acid (from Strychnine)</td>
<td>&lt;= 0.74</td>
</tr>
<tr>
<td>o-Hydroxycocutolutylic Acid (from MTBE)</td>
<td>&lt;= 14.9</td>
</tr>
<tr>
<td>Orotic Acid</td>
<td>&lt;= 0.35</td>
</tr>
<tr>
<td>Pyroglutamic Acid</td>
<td>&lt;= 36.0</td>
</tr>
</tbody>
</table>

### Tyrosine Metabolism

<table>
<thead>
<tr>
<th>Markers</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogentisic Acid</td>
<td>&lt;= 0.50</td>
</tr>
<tr>
<td>2-Hydroxyphenylacetic Acid</td>
<td>&lt;= 0.05</td>
</tr>
</tbody>
</table>

**Metabolic Analysis Reference Ranges are Age Specific**
Neuro-Biogenic Amines

Introduction to Urinary Neuro-Biogenic Amines
Neuro-Biogenic Amines

• Urinary neuro-biogenic amines may serve as biomarkers for neurotransmitter status. Biomarkers [such as cholesterol, thyroid stimulating hormone (TSH) or complete blood count (CBC)] are commonly used in medical evaluations. Such measurements indicate biologic function, and may be used in both in patient assessment and to monitor the results of therapy.

• Complex disorders, such as diabetes, are often evaluated and monitored with just a few biomarkers. Urinary neurotransmitter biomarkers may provide additional insights for patients with behavioural, cognitive or neurologic symptoms. Altered patterns of urinary neurotransmitters may highlight the need for precursor amino acids or nutritional cofactors essential for synthesis and metabolism.
Neuro-Biogenic Amines

When might one consider Neuro-Biogenic Amines in clinical practice?
Cognitive Symptoms

- Concentration & Memory
- Mood Disorders
- Behavioural Disorders
- Stress Related Disorders & Conditions

Neuro Biogenic Amines

- Fatigue Related Conditions
- Sleep Disorders
- Some Digestive Disorders (e.g. IBS)
- Adrenal Related Conditions (especially with normal ASI results)
Neuro-Biogenic Amines

• Who do we know who has one or more of those?
# Neuro-Biogenic Amines

<table>
<thead>
<tr>
<th>Comprehensive test analytes</th>
<th>Core test analytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine, free</td>
<td>Dopamine, free</td>
</tr>
<tr>
<td>3,4-Dihydroxyphenylacetic acid (DOPAC)</td>
<td></td>
</tr>
<tr>
<td>3-Methoxytyramine (3-MT)</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine, free</td>
<td>Norepinephrine, free</td>
</tr>
<tr>
<td>Normetanephrine</td>
<td></td>
</tr>
<tr>
<td>Epinephrine, free</td>
<td>Epinephrine, free</td>
</tr>
<tr>
<td>Metanephrine</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Serotonin</td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid (5-HIAA)</td>
<td></td>
</tr>
<tr>
<td>Tryptamine</td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Gamma-aminobutyrate (GABA)</td>
<td>Gamma-aminobutyrate (GABA)</td>
</tr>
<tr>
<td>Tyrosine</td>
<td></td>
</tr>
<tr>
<td>Tyramine</td>
<td></td>
</tr>
<tr>
<td>Phenethylamine (PEA)</td>
<td>Phenethylamine (PEA)</td>
</tr>
<tr>
<td>Taurine</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>Glycine</td>
</tr>
<tr>
<td>Histamine</td>
<td>Histamine</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Creatinine</td>
</tr>
</tbody>
</table>
Neuro-Biogenic Amines

• Here’s a case at hand
# A Functional Medicine Approach To Mental Health
– Dr Jay Lombard

## Summary Symptoms & Signs Associated with Neurotransmitter Imbalances

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Too high a level</td>
</tr>
<tr>
<td></td>
<td>Neuro-degenerative diseases</td>
</tr>
<tr>
<td></td>
<td>Paroxysmal symptoms</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity</td>
</tr>
<tr>
<td></td>
<td>Migraines</td>
</tr>
<tr>
<td></td>
<td>Poor attention</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
</tr>
<tr>
<td></td>
<td>Explosive behaviours</td>
</tr>
<tr>
<td></td>
<td>Anger attacks</td>
</tr>
<tr>
<td></td>
<td>Aggression</td>
</tr>
<tr>
<td></td>
<td>Poor mood / mood swings</td>
</tr>
<tr>
<td></td>
<td>Bipolar disease</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Too low a level</td>
</tr>
<tr>
<td></td>
<td>Inability to concentrate</td>
</tr>
<tr>
<td></td>
<td>Poor attention &amp; poor attention to detail</td>
</tr>
<tr>
<td></td>
<td>Poor memory</td>
</tr>
<tr>
<td></td>
<td>Reduced ability to feel pleasure</td>
</tr>
<tr>
<td></td>
<td>Flat, bored, apathetic and low enthusiasm</td>
</tr>
<tr>
<td></td>
<td>Depressed</td>
</tr>
<tr>
<td></td>
<td>Low drive and motivation</td>
</tr>
<tr>
<td></td>
<td>Restless</td>
</tr>
<tr>
<td></td>
<td>Impatient</td>
</tr>
<tr>
<td></td>
<td>Difficulty getting through a task even when interesting</td>
</tr>
<tr>
<td></td>
<td>Crave uppers (e.g. caffeine/nicotine/diet soft drinks)</td>
</tr>
<tr>
<td></td>
<td>Shy/introvert</td>
</tr>
<tr>
<td></td>
<td>Low libido or impotence</td>
</tr>
<tr>
<td></td>
<td>Mentally fatigued easily and physically fatigued easily</td>
</tr>
<tr>
<td></td>
<td>Put on weight easily</td>
</tr>
<tr>
<td></td>
<td>Procrastinator/little urgency</td>
</tr>
<tr>
<td></td>
<td>Sleep too much and trouble getting out of bed</td>
</tr>
<tr>
<td></td>
<td>Prone to addictions (e.g. alcohol, cigarettes)/addictive personality</td>
</tr>
<tr>
<td></td>
<td>Drug abuse</td>
</tr>
<tr>
<td></td>
<td>Family history of alcoholism/ADD/ADHD</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Symptom</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dopamine</td>
<td><strong>Too high a level</strong></td>
</tr>
<tr>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td>OCD</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Aggression</td>
</tr>
<tr>
<td></td>
<td>Poor impulse control</td>
</tr>
<tr>
<td></td>
<td>Low pain threshold</td>
</tr>
<tr>
<td>GABA</td>
<td><strong>Too low a level</strong></td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Phobias</td>
</tr>
<tr>
<td></td>
<td>Feel stressed/pressured/overwhelmed</td>
</tr>
<tr>
<td></td>
<td>Butterflies in stomach</td>
</tr>
<tr>
<td></td>
<td>Lump in throat</td>
</tr>
<tr>
<td></td>
<td>Have trouble relaxing/loosening up</td>
</tr>
<tr>
<td></td>
<td>Low stress tolerance</td>
</tr>
<tr>
<td></td>
<td>Body tends to be tense/stiff/upright</td>
</tr>
<tr>
<td></td>
<td>Trembling/twitching/shaking</td>
</tr>
<tr>
<td></td>
<td>Anxious/nervous/jumpy/‘on edge’</td>
</tr>
<tr>
<td></td>
<td>Sleep problems or chronic pain</td>
</tr>
<tr>
<td></td>
<td>Use alcohol/food/cigarettes to relax</td>
</tr>
<tr>
<td></td>
<td>Valium/Xanax/Avitan/GABA reduce above symptoms</td>
</tr>
<tr>
<td></td>
<td>Family history of anxiety</td>
</tr>
<tr>
<td>Serotonin</td>
<td><strong>Too low a level</strong></td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Melancholic</td>
</tr>
<tr>
<td></td>
<td>Insomnia / Sleep problems / Light sleeper</td>
</tr>
<tr>
<td></td>
<td>Nervous</td>
</tr>
<tr>
<td></td>
<td>Worrier</td>
</tr>
<tr>
<td></td>
<td>Poor response to stress</td>
</tr>
<tr>
<td></td>
<td>Negative / Pessimistic</td>
</tr>
<tr>
<td></td>
<td>Irritable / impatient/edgy</td>
</tr>
<tr>
<td></td>
<td>Self destructive, masochistic or suicidal thoughts / plans</td>
</tr>
<tr>
<td></td>
<td>Think about the same things over &amp; over again</td>
</tr>
<tr>
<td></td>
<td>Low self esteem / confidence</td>
</tr>
<tr>
<td></td>
<td>Feel worse in and dislike dark weather</td>
</tr>
<tr>
<td></td>
<td>Anger / rage / explosive behaviour / assultive</td>
</tr>
<tr>
<td></td>
<td>Inflammation / chronic pain</td>
</tr>
<tr>
<td></td>
<td>PMS</td>
</tr>
<tr>
<td></td>
<td>Anti-depressants / SHTP improve mood</td>
</tr>
<tr>
<td></td>
<td>Family history of depression / anxiety / OCD / eating disorders</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Symptom</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td><strong>Too low a level</strong></td>
</tr>
<tr>
<td></td>
<td>Poor cognitive function</td>
</tr>
<tr>
<td></td>
<td>Poor concentration</td>
</tr>
<tr>
<td></td>
<td>Panic</td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td>Sweaty</td>
</tr>
<tr>
<td></td>
<td><strong>Too high a level</strong></td>
</tr>
<tr>
<td></td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>Panic</td>
</tr>
<tr>
<td></td>
<td>Sweaty</td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td><strong>Too low a level</strong></td>
</tr>
<tr>
<td></td>
<td>Poor concentration</td>
</tr>
<tr>
<td></td>
<td>Poor memory</td>
</tr>
<tr>
<td></td>
<td>Difficulty remembering names and faces after meeting people</td>
</tr>
<tr>
<td></td>
<td>Trouble understanding spoken or written language</td>
</tr>
<tr>
<td></td>
<td>Forget where you put things (e.g. keys)</td>
</tr>
<tr>
<td></td>
<td>Slowed and/or confused thinking</td>
</tr>
<tr>
<td></td>
<td>Making simple mistakes at work</td>
</tr>
<tr>
<td></td>
<td>Difficulty finding the right words before speaking</td>
</tr>
<tr>
<td></td>
<td>Lost some of my creativity / lack imagination</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td>Increased risk of dementia</td>
</tr>
</tbody>
</table>
### Comprehensive Adrenal Stress Profile

#### Salivary Cortisol and DHEA - Age Group 41 - 50

<table>
<thead>
<tr>
<th>Sample 1 Post Awakening</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample 2 (+ 4 - 5 Hours)</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample 3 (+ 4 - 5 Hours)</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.1</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample 4 (Prior to Sleep)</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Daily Cortisol</th>
<th>Inside Range</th>
<th>Outside Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0</td>
<td>Range 21 - 41 nmol/L</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DHEA Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 2 (am)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>DHEA : Cortisol Ratio</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>0.02 - 0.26</td>
</tr>
<tr>
<td>DHEA : Cortisol Ratio</td>
<td>0.30 - 1.00</td>
</tr>
<tr>
<td>DHEA : Cortisol Ratio</td>
<td>1.0 - 4.00</td>
</tr>
</tbody>
</table>

#### Adrenal Stress Stage

**Cyclic Variation**: Overall this is an indication of normal adaptation to both chronic and acute stressors, however there is some variation in the individual timed readings. (See page 2 for specific indications). In the context of a patient with very long-standing stressors (years) it can indicate either good coping/adaptation methods, or represent hormone levels “dropping through” normal ranges on the way to depleted levels after having been over stimulated for many years. In such a case a follow up test in 2 - 3 months is recommended.
<table>
<thead>
<tr>
<th>Neuro-Biogenic Amines, Comprehensive; urine first morning void</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESULT/UNIT</strong></td>
</tr>
<tr>
<td><strong>per g creatinine</strong></td>
</tr>
<tr>
<td><strong>Dopamine, free</strong></td>
</tr>
<tr>
<td><strong>3,4-Dihydroxyphenylacetic acid (DOPAC)</strong></td>
</tr>
<tr>
<td><strong>3-Methoxytyramine (3-MT)</strong></td>
</tr>
<tr>
<td><strong>Norepinephrine, free</strong></td>
</tr>
<tr>
<td><strong>Normetanephrine</strong></td>
</tr>
<tr>
<td><strong>Epinephrine, free</strong></td>
</tr>
<tr>
<td><strong>Metanephrine</strong></td>
</tr>
<tr>
<td><strong>Serotonin</strong></td>
</tr>
<tr>
<td><strong>5-Hydroxyindolacetic acid (5-HIAA)</strong></td>
</tr>
<tr>
<td><strong>Tryptamine</strong></td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
</tr>
<tr>
<td><strong>Gamma-aminobutyrate (GABA)</strong></td>
</tr>
<tr>
<td><strong>Tyrosine</strong></td>
</tr>
<tr>
<td><strong>Tyramine</strong></td>
</tr>
<tr>
<td><strong>Phenylethylamine (PEA)</strong></td>
</tr>
<tr>
<td><strong>Taurine</strong></td>
</tr>
<tr>
<td><strong>Glycine</strong></td>
</tr>
<tr>
<td><strong>Histamine</strong></td>
</tr>
<tr>
<td><strong>Creatinine</strong></td>
</tr>
</tbody>
</table>
• We’ll come back to the case in a bit
What is a Neuro-biogenic Amine (neurotransmitter)?

• A neuro-biogenic amine is a molecule (chemical) that carries a signal between nerve cells. A *neuromodulator* is a molecule that alters a nerve cells’ response to a neurotransmitter signal.

• Neuro-biogenic amines and neuromodulators have effect when they bind to specialised receptors on other cells, or inside a cell. Neurotransmitters are necessary because all nerve cells are separated by minute spaces called *synapses*.

See Figure 1.
Figure 1.

Nerve synapse

The image demonstrates the components of a single neural synapse. Each nerve cell has many synapses with other neurons:

A: Presynaptic Neuron (Axon)
B: Post-synaptic Neuron (Dendrite)

1. Nerve cell mitochondria
2. Synaptic vesicle full of neuro-biogenic amine
3. Autoreceptor
4. Synapse
5. Neurotransmitter receptor
6. Calcium Channel
7. Fused vesicle releasing neurotransmitter
8. Neurotransmitter re-uptake pump
Neuro-Biogenic Amines

• Neuro-biogenic amines convert the electrical signal that travels within the nerve cell into a chemical signal that is shared with another nerve cell. The receiving, or post-synaptic cell, then generates the electric signal to pass onto the next cell.

• The electrical signals, or action potentials, are generated in the nerve cells by the passage of charged mineral elements, or ions, into and out of the cell. A lack of mineral elements may affect the function of nerve cells, and prevent proper electrical signaling.

• In general, a neurotransmitter is synthesised by the nerve cell, then, stored in a vesicle until it is needed.
Neuro-Biogenic Amines

• There is always a small amount of neuro-biogenic amines leaking out of vesicles into the synapses; in a healthy nervous system this neurotransmitter released is either taken back into the nerve cell and vesicle or metabolised by enzymes in the synapse or nerve cell.

• Some nerve cell metabolites may act like neurobiogenic amines or neuromodulators. Other metabolites have no known function and are simply excreted from the body by the liver and kidneys.

• Normal levels of neurotransmitters are essential for nerve cell function in the central and peripheral nervous system.
The Nervous System

• The central nervous system (CNS) consists of the brain and spinal cord (Figure 2). The peripheral nervous system consists of all the nerve fibers that branch off from the spinal cord and extend to all parts of the body. The CNS is separated from the peripheral nervous system by the blood-brain barrier (BBB), a single cell lining around the brain’s blood vessels and capillaries (Figure 2).

• The semi-permeable membrane barrier limits blood circulation access to the brain and spinal cord. The BBB is meant to protect the brain from foreign substances and infectious agents, to maintain a constant supportive environment for the brain, and to keep out hormones and neurotransmitters released into circulation.
The central nervous system consists of the brain and spinal cord. The *blood-brain barrier* is a single layer of cells that protects the central nervous system from foreign substances in the circulating blood.
Types and Functions of Neuro-biogenic Amines

• There are many types of neuro-active substances. “Classic” neurotransmitters are called small molecule neurotransmitters or biogenic amines. Some amino acids obtained from the diet or synthesised in the body may act as neurotransmitters or neuromodulators.

• Other amino acids serve as precursors for neurotransmitter synthesis.

• Many peptides (proteins formed by linked amino acids) are neuro-active, and many hormones have neuro-active properties.

• The neurotransmitters tested by Doctor’s Data, Inc. include precursor and neuro-active amino acids, “classic” small molecule neurotransmitters and their metabolites:
Neurotransmitters, biogenic amines, metabolites & Amino acids

- **Small molecule neurotransmitters (biogenic amines)**
  - Catecholamines: Dopamine, Epinephrine (Adrenaline), Norepinephrine (Noradrenaline)
  - Histamine, Serotonin

- **Metabolites**
  - 3,4-Dihydroxyphenylacetic acid (DOPAC), 3-Methoxytyramine (3-MT), 5-Hydroxyindolacetic acid (5-HIAA), Metanephrine, Normetanephrine
  - **Trace Amines**: Phenylethylamine (PEA), Tyramine, Tryptamine

- **Amino acids**
  - Gamma aminobutyric acid (GABA), Glutamate, Glycine, Taurine, Tyrosine
Neurotransmitter Function

• Neurotransmitter function is determined by the molecule’s post-synaptic effects. (See Figure 1.) Neurotransmitters act in two ways, they either increase (excitatory) or decrease (inhibitory) the likelihood that a nerve cell will transmit any electrical information.

• Multiple neurotransmitters may be released together into a single synapse. The neurotransmitters released together may serve as “co-transmitters”. As co-transmitters they may further influence a nerve cell or receptor’s response to neuro-active compounds.
Excitation & Inhibition

• Excitatory neurotransmitter synapses have a different conformation (form) and location on the nerve cell from inhibitory synapses.

• Only two neurotransmitters, the amino acids GABA and Glycine, have inhibitory effects.

• The levels of neurotransmitters are determined by their rates of synthesis and metabolism (breakdown), or turnover. The effect of a neurotransmitter is determined, in large part, by the receptor that it binds to.
Neurotransmitter transporters

• Monoamine transporters are located in cell membranes and include specific transporters for dopamine (DAT), norepinephrine (NET) and serotonin (SERT).

• The transporters move monoamines into and out of cells using ion gradients. The transporters function to remove neurotransmitters from the synapse ("reuptake") back into the cell for storage in vesicles.

• The neurotransmitters are removed from the cytoplasm into vesicles by the vesicular monoamine transporter (VMAT).

• Mutations and single nucleotide polymorphisms in monoamine transporters may affect neurotransmitter levels and are being evaluated for their effects in behavioural, mood, attention and neurodegenerative disorders.
Monoamine Transporters

• Inhibition of monoamine transporters by “reuptake inhibitor” medications is used in the treatment of depression, obsessive compulsive disorder (OCD), anxiety, chronic pain syndrome, and attention deficit hyperactivity disorder (ADHD).

• Altered VMAT density in the brain has been associated with neurodegenerative conditions.
Neurotransmitter Receptors

• Neurotransmitter activity occurs when a neuro-active molecule binds to specific receptors on the post-synaptic nerve. (See Figures 1 & 3.)

• Receptor function is as important as neurotransmitter levels; a dysfunctional receptor may affect biochemistry, mood, behavior and learning.

• Receptors are specialised proteins on neurons. Two main types of receptors, excitatory and inhibitory, determine the response of a signal-receiving neuron. A balance between excitatory and inhibitory signaling is necessary for normal function.

• Excessive excitatory signaling may result in symptoms such as seizures, excessive inhibitory signaling may result in sedation, anaesthesia or loss of coordination.
Neurotransmitter Receptors

- The binding of a neurotransmitter to a receptor activates its function. Receptor activation may have direct effects on the nerve cell or activate second messengers.
- Second messengers may have local or systemic effects. The activity of a nerve cell is determined by the balance of excitatory and inhibitory signals it receives. Often, a neurotransmitter may have the ability to bind to several types of receptors.
- Some receptors are “promiscuous” and may bind with multiple neurotransmitters.
- Other compounds, such as hormones and drugs, may also bind to neurotransmitter receptors. At least one receptor type, the N-methyl-D-aspartate receptor (NMDAR), binds two neurotransmitters simultaneously. NMDA receptors bind to Glutamate, but also require a Glycine cofactor. (See Figure 3.)
Figure 3.

The binding of a neurotransmitter to its receptor activates a receptor function, in this example, opening an ion channel.
Definition of Allosteric

• Allosteric regulation (or allosteric control) is the regulation of a protein by binding an effector molecule at a site other than the protein's active site.
Neurotransmitter Receptors

• There are two primary types of neurotransmitter receptors, *ionotropic* and *metabotropic*. Ionotropic receptors open or close channels in the cell membrane to allow ions (such as calcium) to enter or leave the cell.

• Changing the level of ions in a cell affects the cell’s potential to generate electrical signals (see Figure 3).

• Metabotropic receptors affect cell activity indirectly through second messengers. Second messengers may have local or systemic effects. Local second messenger effects might involve changes in nerve cell chemistry or DNA expression to make the cell more or less likely to transmit information.

• Second messenger pathways include the cyclic AMP (adenosine monophosphate) pathway, the inositol triphosphate/diacylglycerol (IP3/DAG) pathway and the arachidonic acid pathway.
Neurotransmitter Receptors

• The number, structure and function of neurotransmitter receptors may be affected by mutations or single nucleotide polymorphisms (SNPs), which may alter the amount of time a neurotransmitter stays bound, and the ease of binding.

• It is possible for neurotransmitter levels to be normal, and still have symptoms, if the receptor is dysfunctional. Neurotransmitter receptor defects have been associated with mood disorders, bipolar disorders, and addictive behaviours.

• Research continues to determine how receptor dysfunctions might contribute to neurodegenerative disorders such as Alzheimer’s, Parkinson’s and Huntington’s disease.
Neuro-biogenic Amine Synthesis and Metabolism

• Urinary neuro-biogenic amines provide an overall assessment of a patient’s ability to synthesise and metabolise neurotransmitters, which must occur in both the peripheral nervous system and behind the blood brain barrier (BBB) in the central nervous system (CNS).

• Altered patterns of urinary neuro-biogenic amines may highlight the need for precursor amino acids or nutritional cofactors essential for synthesis and metabolism.

• The assimilation and absorption of nutrients requires a healthy digestive tract and a healthy microbiome (the presence of expected and beneficial microbes in the gastrointestinal tract).

• Neurotransmitters arise from amino acid precursors (see Figure 4.)
Figure 4. Neuro-Biogenic Amine Metabolism.

Metabolism of neurotransmitters inside nerve cells occurs primarily via a two-step process using MAO-A and various dehydrogenase and reductase enzymes. COMT is not found in sympathetic nerve cells.

**Legend:**
- AADC, aromatic amino acid decarboxylase
- AAT, aspartate amino transferase
- ADH, alcohol dehydrogenase
- ALDH, aldehyde/aldose dehydrogenase
- AR, aldehyde/aldose reductase
- COMT, catechol-O-methyl transferase
- MAO-A, monoamine oxidase A
- DBH, dopamine β hydroxylase
- GAD, glutamate decarboxylase
- PAG, phosphate-activated glutaminase
- PAH, phenylalanine hydroxylase
- PNMT, phenylethanolamine N-methyltransferase
- SULT1A3, sulfotransferase type1A3
- TH, tyrosine 3-hydroxylase
- TPH, tryptophan 5-hydroxylase.
Exploring the Test Results
<table>
<thead>
<tr>
<th>Substance</th>
<th>RESULT/UNIT per g creatinine</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
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<tr>
<td>Dopamine, free</td>
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<tr>
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<td>3-Methoxytyramine (3-MT)</td>
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<td>Serotonin</td>
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<tr>
<td>Creatinine</td>
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Figure 6.

The methylation pathway (as it is commonly known) synthesizes cysteine behind the blood-brain barrier, and is a precursor for the antioxidants taurine and glutathione.

Legend for Methylation Pathway Enzymes: AHCY = adenosylhomocysteinase; BHMT = betaine-homocysteine methyltransferase; CBS; MTR = methionine synthase; MTRR = methionine synthase reductase; MTHFR = methylenetetrahydrofolate reductase; SUOX

Synthesis of Glycine, Histamine and Taurine Nutritional cofactors
Legend: PSP = B6
Test Results Explored – LOW norepinephrine

• Research indicates that norepinephrine signalling may contribute to:

• Maintaining focus and attention (vigilance)
• Filter weak stimuli and enhance moderate stimuli, and enhance responses to strong stimuli (stimuli are detectable changes in internal or external environment)
• Information processing and executive functions (reasoning, learning, problem-solving)
• Memory storage and retrieval (particularly memories associated with strong emotion)
• “Fight or flight” stress responses
Test Results Explored – LOW norepinephrine
Test Results Explored – LOW norepinephrine

• Norepinephrine is a catecholamine hormone and neurotransmitter secreted by the adrenal gland.
• It is the principal neurotransmitter in sympathetic nerve endings.
• Norepinephrine may help regulate vigilant attention, cognition and sleep.
• Studies indicate that the brain contributes at most 20% of circulating norepinephrine levels.
Test Results Explored – LOW norepinephrine

• Low levels of norepinephrine may be associated with conditions such as orthostatic hypotension, dopamine beta-hydroxylase (DBH) enzyme deficiency and Menke’s disease.

• Alpha-2 agonistic pharmaceuticals decrease sympathetic nerve outflow and norepinephrine levels.

• Metyrosine therapy may decrease norepinephrine levels.

• Surgical sympathectomy or medical conditions that disrupt autonomic nerve functions may also decrease norepinephrine levels.

• Low levels of precursor amino acids phenylalanine or tyrosine, or low levels of the precursor neurotransmitter dopamine may result in low norepinephrine levels.
Test Results Explored – LOW norepinephrine

• The synthesis of norepinephrine from dopamine requires Vitamin C and copper.

• About half of all norepinephrine is produced in the gastrointestinal tract, pancreas and spleen.

• Most of the norepinephrine produced by these mesenteric organs is removed from portal vein blood by the liver and converted to vanillylmandelic acid (VMA) for excretion.
Test Results Explored – LOW norepinephrine

• Consider:
  • Tyrosine on an empty stomach may improve transport across BBB; may be contraindicated in hypertension; may induce anxiety in some patients.

• Further evaluations:
  • Essential precursor Amino Acid status (Plasma or Urine Amino Acids)
  • Copper status (RBC Elements)
  • Iron status (RBC Elements)
  • Magnesium levels (RBC elements)
  • Selenium status (RBC Elements)
  • Glutathione status (Glutathione:erythrocytes)
  • Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)
  • Methionine metabolism and methylation pathways (Plasma Methylation Profile, DNA Methylation Pathway)
Test Results Explored – LOW Serotonin (5-hydroxytryptamine)

• Serotonin signalling in the central nervous system (CNS) may influence mood, appetite, sleep, memory and learning, homeostasis, and sexual behaviours.

• There are a great many serotonin receptors with different affinities, expression and function. Decreased serotonin levels have been associated with obsessive-compulsive disorder (OCD), anger, insomnia, and depression.

• Some eating disorders and migraine headaches may also be related to low serotonin levels. Low urinary serotonin levels during pregnancy have been associated with increased risk of premature birth.
Test Results Explored – LOW Serotonin (5-hydroxytryptamine)

• In the peripheral nervous system, low levels of serotonin may affect gastrointestinal motility (constipation), and possibly bone mass. Low serotonin levels have been associated with irritable bowel syndrome. Cyproheptadine is an anti-histamine that decreases serotonin levels.

• Studies indicate that serotonin depletion is more likely to affect mood in those with a family history of mood disorders.

• Mutations or single nucleotide polymorphisms (SNPs) in specific enzymes may affect serotonin synthesis or degradation. Several SNPs have been identified and linked to depression; research continues in this area. Serotonin is unable to cross the blood-brain barrier and must be synthesized in the peripheral and central nervous system.
Test Results Explored – LOW Serotonin (5-hydroxytryptamine)

- Tetrahydrobiopterin, iron and Vitamin B6 are required cofactors for serotonin synthesis. The gastrointestinal (GI) tract produces about 80% of the body’s serotonin. During the ”first pass” through hepatic circulation monoamine oxidase (MAO) metabolises 30-80% of GI-derived serotonin to 5-hydroxyindoleacetic acid (5-HIAA).

- Serotonin may also be converted to 5-HIAA in the lungs. Urine and plasma levels of serotonin may vary with the intake of certain foods rich in serotonin, and medications that alter serotonin levels.
Test Results Explored – LOW Serotonin (5-hydroxytryptamine)

• Serotonin is synthesised from the amino acid L-tryptophan in pre-synaptic neurons. Under physiological conditions only about 5% of L-tryptophan is metabolized to Serotonin.

• The enzyme tryptophan hydroxylase (TPH) produces 5-hydroxytryptophan (5-HTP) which is converted to serotonin by aromatic amino acid decarboxylase (AADC), also called 5-HTP decarboxylase.

• AADC is pyridoxal-phosphate (B6) dependent. Different forms of the TPH enzyme are found in the brain and in the gastrointestinal system.

• Evidence indicates that vitamin D upregulates the expression of TPH2 in the brain and inhibits the expression of TPH1 in the periphery.
Test Results Explored – LOW Serotonin (5-hydroxytryptamine)

• Consider:
  • Essential precursor Tryptophan status (Plasma or Urine Amino Acids)
  • Gastrointestinal function (Comprehensive Stool Analysis)
  • Glutathione status (Glutathione:erythrocytes)
  • Bacterial lipopolysaccharide (LPS) [Intestinal Permeability Test]
  • Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)
  • MAOA or COMT SNPs (DNA Methylation Pathway)

• 5-HTP or L-tryptophan supplementation, with B6
Test Results Explored – HIGH PEA

• The level of Phenylethylamine (B-phenylethylamine or PEA) is higher than expected in this sample.

• PEA is considered a trace amine neuromodulator; it modifies the effect of a neurotransmitter signal on a cell or receptor. Trace amines may be found in both the central and peripheral nervous systems & there are trace amine receptors in vascular and renal tissues. Trace amines and their metabolites are excreted through the kidney into the urine.

• The interaction of trace amines and trace amine-associated receptors (TAARs) in the brain may play a role in psychiatric and neurological disease processes. Elevated PEA has been associated with schizophrenia.

• Experiments in humans and animals have associated PEA elevations with stress or anxiety. Very high levels may have amphetamine-like effects and may induce seizures (animal studies).
Test Results Explored – HIGH PEA
Test Results Explored – HIGH PEA

• Elevations in PEA levels have been reported during the use of monoamine oxidase inhibitors (MAOIs) or anti-psychotic medications.
• PEA may alter a cell’s response to dopamine and norepinephrine. PEA may have endocrine effects and inhibit prolactin secretion.
• Animal studies indicate that PEA may increase glucocorticoid levels and PEA has been shown to stimulate acetylcholine release.
• Levels of PEA are not associated with neuron responses to serotonin, GABA or glutamate.
Test Results Explored – HIGH PEA

• Monoamine oxidase inhibitor (MAOI) medications may increase trace amine levels without affecting levels of other neurotransmitters.

• Trace amines may play a role in the activation or regulation of immune responses.

• PEA excretion may be influenced by diurnal rhythms; larger amounts are excreted during the late evening and early morning hours. Exercise, high protein diets or supplements may also increase PEA levels. High levels of the phenylalanine may result in high PEA levels.

• Trace amines may be generated in the gastrointestinal tract by protein-fermenting gut bacteria after a protein-rich meal, and they may be found in a variety of foods as the result of food spoilage or deliberate fermentation. Dietary trace amines are usually metabolised quickly by MAO enzymes. PEA is primarily oxidised by MAO-B which may require selenium.
Test Results Explored – HIGH PEA

- Consider:
- (for low levels)
- Phenylalanine precursor status (Plasma or Urine Amino Acids)
- Selenium status (RBC Elements)
- Glutathione status (Glutathione:erythrocytes)
- Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)
The methylation pathway (as it is commonly known) synthesizes cysteine behind the blood-brain barrier, and is a precursor for the antioxidants taurine and glutathione.

Legend for Methylation Pathway Enzymes: AHCY = adenosylhomocysteine; BHMT = betaine-homocysteine methyltransferase; CBS = cystathionine synthase; MTR = methionine synthase; MTRR = methionine synthase reductase; MTHFR = methylenetetrahydrofolate reductase; SUOX

Synthesis of Glycine, Histamine and Taurine Nutritional cofactors
Legend: PSP = B6
Test Results Explored – LOW Taurine

• Decreased taurine levels may occur due to dietary insufficiency or digestion and absorption issues in the gastrointestinal tract.

• Taurine acts as a neuromodulator and exerts an inhibitory effect on the firing rate of neurons in the central nervous system (CNS) in vitro. Taurine has been shown in human and animal studies to have mild anti-convulsion effects.

• Taurine promotes neural development in both the embryonic brain and the adult brain. Decreased taurine synthesis has been reported in individuals with autoimmune and neurodegenerative diseases, including rheumatoid arthritis, Parkinson’s disease, Alzheimer’s disease, and motor neuron disease.
Test Results Explored – LOW Taurine

• Low taurine levels may contribute to heart muscle disease (cardiomyopathy), kidney disease, pancreatic beta cell malfunction, and the loss of retinal photoreceptors.

• Taurine in nerve cells inhibits glutamate-induced calcium influx and protects against glutamate-induced excito-toxicity.

• Taurine supplements have been used to treat seizure disorders, autism and attention deficit-hyperactivity disorder (ADHD).
Test Results Explored – LOW Taurine

• Taurine levels may be low due to dietary insufficiency or enzyme deficiencies. Taurine synthesis requires B6 and the precursor amino acid cysteine. Taurine synthesis may be important in the CNS.

• Taurine is excreted via urine and bile. The amount of taurine excreted daily is affected by various factors including genetics, age, gender, diet, renal function and medical conditions.

• A low urinary taurine due to a renal clearance disorder may occasionally mask an elevated plasma taurine level.
Test Results Explored – LOW Taurine

• Consider:
  • Renal function (Creatinine Clearance Test)
  • Serum electrolyte status (Serum Elements)
  • Intracellular electrolyte status (RBC Elements)
  • Methionine metabolism and methylation pathways (Plasma Methylation Profile, DNA Methylation Pathway)
  • Oxidative stress/8OH-dG (DNA Oxidative Damage Assay)

• Taurine supplementation
Test Results Explored – LOW Tryptamine

• The level of tryptamine is lower than expected in this sample. Tryptamine is derived from the essential amino acid tryptophan. Tryptamine levels may affect arterial resistance (vasoconstriction) and serotonin signalling.

• Low tryptamine levels or deficient trace amine functions may be associated with some depressive disorders.

• Low plasma tryptamine levels have been associated with chronic migraine and chronic tension headaches.

• Tryptamine may act as a neuromodulator for serotonin signalling; serotonin affects mood, sleep and appetite.
Test Results Explored – LOW Tryptamine
Urinary tryptamine levels seem to correlate with symptom severity in schizophrenia. Tryptamine levels may affect arterial resistance (vasoconstriction) and serotonin signalling. Methylated tryptamines may also play a role in the development of schizophrenia.

Aromatic L-amino acid decarboxylase (AADC) is the rate-limiting enzyme in the conversion of tryptophan to tryptamine. Altered AADC activity may affect trace amine levels without affecting the levels of monoamine neurotransmitters (catecholamines, histamine, serotonin, etc.).

Reserpine (anti-psychotic drug) decreases AADC activity and trace amine levels.
Test Results Explored – LOW Tryptamine

• Consider:

  • Selenium status (RBC Elements)
  • Glutathione status (Glutathione:erythrocytes)
  • Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)

• 5-HTP or L-tryptophan supplementation
Test Results Explored – LOW Tyramine

• Tyramine is derived from the essential amino acid phenylalanine. Tyramine and the other trace amines are found at low levels in the brain.

• Trace amines are not considered neurotransmitters; they are believed to act as neuromodulators.

• Evidence indicates that tyramine may alter neuronal responsiveness, neuron active transport mechanisms and vesicle dynamics.

• Low levels of the precursor amino acid phenylalanine or its metabolite tyrosine, may contribute to low tyramine levels.

• Reserpine may deplete CNS levels of trace amines. Trace amines and their metabolites are excreted through the kidney into the urine.
Test Results Explored – LOW Tyramine
Test Results Explored – LOW Tyramine

• Multiple studies demonstrate that loss of neurons in specific brain areas or loss of specific types of neurons may result in decreased trace amine levels. Low tyramine levels or deficient trace amine functions may be associated with some depressive disorders.

• Tyramine has been shown to inhibit the responses of gamma-aminobutyric acid (GABA) receptors (in vitro).

• Aromatic L-amino acid decarboxylase (AADC) is the rate-limiting enzyme in tyramine synthesis.
Test Results Explored – LOW Tyramine

• Altered AADC activity may alter trace amine levels which may affect dopamine signalling. Loss of specialised dopamine neurons containing AADC have been associated with some forms of schizophrenia.

• Trace amines are metabolised by monoamine oxidase (MAO A/B).

• L-Tyrosine in supplement form may be required.
Test Results Explored – LOW Tyramine

• Consider

• Selenium status (RBC Elements)
• Glutathione status (Glutathione:erythrocytes)
• Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)
• Methylation pathway activity (Plasma Methylation Profile, DNA Methylation Pathway)

• L-Tyrosine supplementation
Test Results Explored – LOW Epinephrine

• Tyrosine is the precursor for the catecholamine neurotransmitters dopamine, norepinephrine and epinephrine; tyrosine availability may affect the synthesis of these catecholamines.

• Small amounts of epinephrine are constantly secreted to maintain normal blood pressure and metabolic functions. Evidence is accumulating that epinephrine has neurotransmitter-like functions in the CNS that may affect the regulation of blood pressure, respiration, and pituitary hormone secretion.

• Clinically, plasma epinephrine levels have been shown to reflect central nervous system (CNS) neural outflow to the adrenal medulla. Virtually all circulating epinephrine originates from the adrenal medulla.
Test Results Explored – LOW Epinephrine
Test Results Explored – LOW Epinephrine

• Decreased epinephrine levels may occur in conditions such as Addison's disease, diabetic nephropathy, congenital 21- hydroxylase deficiency and Autonomic Failure syndromes.

• Alpha- and beta-blocker medications may reduce the effects of epinephrine, but are not documented to reduce systemic epinephrine levels.

• Metyrosine therapy decreases levels of the precursor neurotransmitters dopamine and norepinephrine, and may reduce epinephrine levels.
Test Results Explored – LOW Epinephrine

• Epinephrine is usually present in the urine in small fluctuating amounts and may be increased during and shortly after stress exposures. Monoamine oxidase inhibitors (MAOIs) may elevate epinephrine and metanephrine levels.

• Drugs that stimulate nicotinic, angiotensin II, or glucagon receptors may also increase plasma epinephrine levels.

• Epinephrine is primarily synthesised in the chromaffin cells of the adrenal medulla; small amounts are synthesised in the Central Nervous System (CNS) and the vagus nerve.

• Epinephrine is derived from norepinephrine.
Test Results Explored – LOW Epinephrine

• Consider:
  • Copper status (RBC Elements)
  • Magnesium status (RBC Elements)
  • Status of neurotransmitter precursor Phenylalanine (Amino Acids)
  • MAOA or COMT SNPs (DNA Methylation Pathway)

• L-Tyrosine supplementation
• Adrenal gland support
Test Results Explored – LOW Metanephrine

• Metanephrine is a metabolite of epinephrine. Clinically, metanephrine levels provide an indication of adrenal medulla metabolism of epinephrine prior to its release into circulation. The metabolites are usually present in the urine in low and fluctuating levels.

• Decreases in epinephrine levels will also decrease metanephrine levels. Pure autonomic failure syndromes decrease adrenomedullar function and may decrease epinephrine and metanephrine levels.

• Metyrosine therapy may lower both epinephrine and metanephrine levels. There is scant literature describing the symptoms of pure epinephrine and/or metanephrine insufficiency. However, conditions that may be associated with low epinephrine levels include Addison’s disease, diabetic nephropathy and autonomic failure syndromes.
Test Results Explored – LOW Metanephrine
Test Results Explored – LOW Metanephrine

• Approximately 93% of circulating metanephrine is derived from catecholamine metabolism through the enzyme catechol-O methyl transferase (COMT) in the adrenal medulla. In the normal population, plasma normetanephrine levels are low. Acquired or inherited deficiencies in COMT may result in low metanephrine levels.

• COMT activity requires S-adenosyl-L-methionine (SAM) and magnesium, and may be suppressed by single nucleotide polymorphisms (SNPs). Phenylethanolamine N-methyltransferase (PNMT) deficiency or 21-dehydroxylase deficiency may decrease epinephrine and metanephrine levels.
Test Results Explored – LOW Metanephrine

- Plasma concentrations of total metanephrine (free plus conjugated metanephrine) largely reflect conjugated gastrointestinal metanephrine). Total urinary metanephrine is more clinically relevant and is reported by Doctor’s Data.
Test Results Explored – LOW Metanephrine

• Consider:

  • Essential precursor Amino Acid status (Plasma or Urine Amino Acids)
  • Magnesium status
  • Selenium status
  • MAOA or COMT SNPs (DNA Methylation Pathway)
  • Methionine metabolism and methylation pathways (Plasma Methylation Profile, DNA Methylation Pathway)
Test Results Explored – LOW Normetanephrine

• Normetanephrine is the 3-methoxy metabolite of norepinephrine. Clinically, normetanephrine provides an index of norepinephrine released due to sympathetic nerve activity.

• Between 25-40% of circulating normetanephrine is derived from catecholamine metabolism in the adrenal medulla.
Test Results Explored – LOW Normetanephrine
Test Results Explored – LOW Normetanephrine

• Normetanephrine inhibits low affinity, high capacity biogenic amine transporters such as the plasma membrane monoamine transporter (PMAT), which is highly expressed in the brain.

• PMAT function has been associated with monoamine-related neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD), depression, anxiety, addiction, narcolepsy, fatigue, obesity, eating disorder, other mood disorders, schizophrenia, bipolar disorder and Parkinson’s disease. Research continues to define these associations.
Test Results Explored – LOW Normetanephrine

• Plasma concentrations of total normetanephrine (free plus conjugated metanephrine) largely reflect conjugated gastrointestinal metanephrine). Total urinary normetanephrine is more clinically relevant and is reported by Doctor’s Data.
Test Results Explored – LOW Normetanephrine

• Consider:
  • Tyrosine on an empty stomach may improve transport across BBB; may be contraindicated in hypertension; may induce anxiety in some patients.

• **Further evaluations:**
  • Essential precursor Amino Acid status (Plasma or Urine Amino Acids)
  • Copper status (RBC Elements)
  • Iron status (RBC Elements)
  • Magnesium levels (RBC elements)
  • Selenium status (RBC Elements)
  • Glutathione status (Glutathione:erythrocytes)
  • Oxidative stress (DNA Oxidative Damage Assay/8-OHdG)
  • Methionine metabolism and methylation pathways (Plasma Methylation Profile, DNA Methylation Pathway)
Test Results Explored – HIGH Creatinine

• The urinary creatinine concentration (CC) presented in this report represents the actual creatinine concentration in the specimen that was submitted. Under normal conditions, the rate of excretion of creatinine is quite constant and highly correlated with lean body mass (muscle).

• However, the CC can vary significantly as a function of urine volume. An unusually high CC most likely indicates poor hydration of the patient at the time of the urine collection. A very low CC most likely indicates unusually high fluid consumption, or perhaps the influence of diuretics.
Test Results Explored – HIGH Creatinine

• If the urine specimen is very dilute (extremely low CC), the accuracy of the neurotransmitter analysis may be compromised due to analytical detection limits.

• It is emphasised that the CC in this specimen should not be utilised to assess renal function or glomerular filtration. For that purpose, one should perform a bona fide creatinine clearance test.

• For a given age and gender, intra-individual variability in daily creatinine excretion can vary by as much as two-fold. Therefore, to more accurately assess neurotransmitter status using a random collection, the reported values for each analyte are expressed per gram “normalised” creatinine.
Test Results Explored – HIGH Creatinine

• Consider:

• More optimal hydration
• Investigate exercise regime
Neuro-Biogenic Amines

The Amino Acid Connection
Neuro-Biogenic Amines

• Some neuro-biogenic amine precursors are essential amino acids that must be obtained from the diet.

• Other neurotransmitters may be synthesised by the body, and are considered non-essential. The essential amino acid precursors are phenylalanine and tryptophan.

• Mutations or single nucleotide polymorphisms (SNPs) may alter enzyme conformation or function and affect the synthesis of neuro-biogenic amines. The enzymes in the synthesis pathway require nutrient cofactors; the nutrients will be reviewed in the specific information for each neurotransmitter.

• However, three important enzymes, phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) begin the synthesis process.
EAAs, NEAAs

• An essential amino acid or indispensable amino acid is an amino acid that cannot be synthesised de novo (from scratch) by the organism, but must be supplied in its diet.

• The nine amino acids humans cannot synthesize are phenylalanine, valine, threonine, tryptophan, methionine, leucine, isoleucine, lysine, and histidine (i.e., F V T W M L I K H)

• Six other amino acids are considered conditionally essential in the human diet, meaning their synthesis can be limited under special pathophysiological conditions, such as prematurity in the infant or individuals in severe catabolic distress.
The 20 Amino Acids

- Alanine - ala - A
- Arginine - arg - R
- Asparagine - asn - N
- Aspartic acid - asp - D
- Cysteine - cys - C
- Glutamine - gln - Q
- Glutamic acid - glu - E
- Glycine - gly - G
- Histidine - his - H
- Isoleucine - ile - I
- Leucine - leu - L
- Lysine - lys - K
- Methionine - met - M
- Phenylalanine - phe - F
- Proline - pro - P
- Serine - ser - S
- Threonine - thr - T
- Tryptophan - trp - W
- Tyrosine - tyr - Y
- Valine - val - V
EAAs, SEAAs, NEAAs

**ESSENTIAL AMINO ACIDS**
- (Histidine)
- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine

**SEMI ESSENTIAL AMINO ACIDS**
- Arginine
- Cysteine
- Glycine
- Glutamine
- Proline
- Tyrosine
NON-ESSENTIAL AMINO ACIDS
(Includes SEAAs)

- Arginine
- Cysteine / Cystine
- Glycine
- Glutamine
- Proline
- Tyrosine

- Alanine
- Asparagine
- Aspartic Acid
- Glutathione
- Proline
- Serine
- Taurine
Amino acid groups according to the characteristics of the side chains:

- **Aliphatic** – alanine, glycine, isoleucine, leucine, proline, valine
- **Aromatic** - phenylalanine, tryptophan, tyrosine
- **Acidic** - aspartic acid, glutamic acid
- **Basic** – arginine, histidine, lysine
- **Hydroxylic** – serine, threonine
- **Sulphur-containing** – cysteine, methionine
- **Amidic (containing amide group)** – asparagine, glutamine
Figure 4

Phenylalanine → Phenylethylamine → Tryptamine → Tryptophan → Glutamine

Tyrosine → Tyramine → Norepinephrine → Epinephrine → Serotonin

L-DOPA → Dopamine → 3-MT

MAO-A/B → COMT → MAO-A/B

DOPAC → DPHG → Metanephrine

MAO-A + AR → Normetanephrine

ADH → SUT1A3

ALDH → HVA

MAHGP-SO₄

NTmet-SO₄

5-HIAA → Succinate semi-aldehyde

AAT → TCA cycle → AAT → (mitochondria)

GABA-T

GABA

GAD

Precursors

Neurotransmitters

Intermediary Metabolites

Final Excretion Products
Tetrahydrobiopterin - BH4

• All three enzymes phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) require a tetrahydrobiopterin (BH4) cofactor, and all incorporate iron into their structures.

• Defects in BH4 synthesis or recycling may affect neurotransmitter synthesis and nitric oxide signaling. BH4 deficiency may present with elevated levels of precursor amino acids and low levels of neurotransmitters.

• Enzymatic defects in methylation capacity (methionine metabolism and trans-sulfuration pathways), may affect BH4 levels and may increase oxidative stress in the CNS.

• Oxidative stress may also alter the level of neurotransmitters and enzyme functions.
Catecholamine Neuro-Biogenic Amines

• The metabolism of catecholamine neuro-biogenic amines (epinephrine & norepinephrine) often takes place in the same cells where the amines are produced.

• This occurs because catecholamines are constantly leaking out of vesicles and then taken up again by the neurons.

• Circulating neurotransmitters may also be metabolised in the liver or kidney.

• The enzymes in the pathway often require nutrient cofactors; the nutrients will be reviewed with their neurotransmitters.
Catecholamine Neuro-Biogenic Amines

• The metabolism of precursors or neurotransmitters results in intermediary metabolites. The metabolites may or may not be biologically active, but may provide important functional clues about certain enzymes, such as catechol-O-methyl transferase (COMT) or monoamine oxidase (MAO).

• Mutations or single nucleotide polymorphisms (SNPs) may alter enzyme conformation (shape) or function and affect the metabolism of neurotransmitters. Different enzymes may be used, and different metabolites generated, if a neurotransmitter is processed within a neuron (intraneuronal) or outside it (extraneuronal). (Figure 5.)
Monoamine oxidase A (MAO-A) is found inside sympathetic nerve cells. Catechol-O-methyltransferase (COMT) is not found in sympathetic nerve cells. A neuro-biogenic amine, norepinephrine (NE) in this example, is actively taken into vesicles within the nerve cell for storage, however, small amounts of neurotransmitter are constantly leaking out of the vesicles. NE metabolised by MAO-A will produce different metabolites than NE metabolised by COMT.

**Legend:**

ALDH = aldehyde dehydrogenase  
AR = aldose/aldehyde reductase  
DPHG = 3,4-dihydroxyphenylglycol  
NM = normetanephrine  
VMA = vanillylmandelic acid
Figure 5.

**Intraneuronal Metabolism**

MAO + AR $\rightarrow$ DPHG $\rightarrow$ VMA

MAO-A + NM + ALDH $\rightarrow$ VMA

COMT + NE $\rightarrow$ NM

**Extraneuronal Metabolism**

NM $\rightarrow$ VMA $\rightarrow$ NE

**Circulation**

NM $\rightarrow$ VMA $\rightarrow$ NE
Intraneuronal & Extraneuronal metabolism

• Intraneuronal metabolism occurs primarily via a two-step process through MAO-A and various dehyrodrogenase and reductase enzymes.

• Extraneuronal metabolism occurs through MAO, COMT and sulfotransferase (SULT) enzymes. COMT is not found in sympathetic nerves, but is abundant outside the neuron in other cells and tissues.

• Mutations or single nucleotide polymorphisms (SNPs) may occur in the dehydrogenase or reductase enzymes, and may affect enzyme function. Some of these secondary enzymes may produce neurologically active metabolites.
Aldehyde dehydrogenase (ALDH)

• Aldehyde dehydrogenase (ALDH) activity contributes to a variety of vital biochemical reactions in the body. Altered ALDH function is associated with a variety of medical conditions such as Sjogren’s syndrome, type II hyperprolinaemia, γ-hydroxybutyric aciduria, and pyridoxine-dependent seizures. ALDH is part of the metabolic pathway for dopamine and serotonin.

• Two dopamine metabolites may elevate and have neurotoxic effects due to increased oxidative stress if ALDH function is compromised. Deficient ALDH activity may contribute to elevations of 3-methoxytyramine and serotonin.

• Environmental aldehydes that must be processed by aldehyde dehydrogenases include cigarette smoke, formaldehyde, polyurethane, polyester plastics, and medications. Aldehyde excess due to enzymatic insufficiency may be associated with symptoms of dizziness, nausea, rapid heartbeat (tachycardia) and “alcohol flush”.

Clinical Education
www.leducation.co.uk
Aldehyde dehydrogenase (ALDH)

• Alcohol dehydrogenase (ADH) converts alcohols into aldehydes or ketones that must then be metabolised by ALDH. ADH may participate in the conversion of Vitamin A into retinoic acid.

• Aldose reductase (AR)/Aldehyde reductase (ALR) – reduces aldehyde metabolites of neurotransmitters, aldehydes, corticosteroids, and xenobiotic aldehydes from environmental exposures. These enzymes are abundant in the liver and kidney.
Neuro-Biogenic Amine Synthesis & Metabolism

• Neuro-biogenic amine synthesis or metabolism may be altered by the presence of other medical conditions. Evaluation of these neurotransmitters should be considered for patients with a history of myocardial infarct (heart attack), diabetes, hypothyroid or adrenal disorders. Rarely, urinary neurotransmitters may confirm the presence of certain tumours.

• Neurotransmitter levels may also be influenced by diet, lifestyle and other factors such as high sodium intake, age, gender, body mass index, kidney function, detoxification capacity, environmental exposures, infection or tobacco use. Final excretion products are the result of liver or kidney detoxification. Urinary Neuro-biogenic Amine testing presumes normal kidney function; urine results may be compromised by kidney disorders.
Neuro-Biogenic Amine Synthesis & Metabolism

• Because metabolic enzymes are expressed differently in various body tissues, circulating levels of the biogenic amine neurotransmitters and their metabolites may have distinctive sources. For example, dopamine and norepinephrine metabolism occurs primarily in the gastrointestinal tract (GIT). Urinary levels of neurotransmitters primarily reflect the activity of the peripheral and GIT enteric nervous systems.

• Up to 20% of some urinary neurotransmitters are estimated to originate in the CNS. However, as the enzymatic machinery for neurotransmitter synthesis and metabolism is often similar, if not identical, on both sides of the blood-brain barrier (BBB), normalising urinary neurotransmitter levels based on test results has been shown to result in the improvement of some mood and behaviour symptoms.
Synthesis of Neurotransmitters

• Not all neurotransmitters are synthesised through the same pathways.

• Glucose metabolism leads to the biosynthesis of neurotransmitters such as glutamate, and gamma-aminobutyric acid (GABA).

• Specialised support cells in the brain, the astroglia (astrocytes) contribute to the synthesis and metabolism of glutamate and GABA (see Figure 6).
The methylation pathway (as it is commonly known) synthesizes cysteine behind the blood-brain barrier, and is a precursor for the antioxidants taurine and glutathione.

Legend for Methylation Pathway Enzymes:
AHCY = adenosylhomocysteinase; BHMT = betaine-homocysteine methyltransferase; CBS; MTR = methionine synthase; MTRR = methionine synthase reductase; MTHFR = methylenetetrahydrofolate reductase; SUOX

Synthesis of Glycine, Histamine and Taurine Nutritional cofactors
Legend:  P5P = B6
Blood-Brain Barrier

• The blood-brain barrier (BBB) is a semi-permeable membrane that separates the central nervous system (CNS) from peripheral blood circulation. (See Figure 2.) Normal BBB function is necessary for normal brain function. The BBB functions to:

• Protect the brain from foreign substances and infectious agents
• Buffer fluctuations of neuro-active compounds, nutrients and elements in the systemic circulation to maintain a constant environment for the brain
• Keep out hormones and neurotransmitters released into systemic circulation; excess that might over-stimulate brain receptors and disrupt central nervous system signaling
• Regulate the migration of circulating immune cells into the brain
Blood Brain Barrier

• The BBB exists as tight junctions between specialized capillary endothelial cells that line the blood vessels and capillaries of the brain. Astroglia (astrocyte) cells surround the blood vessels. Astroglia also act as a partial barrier while providing nutrient support to the capillary endothelial cells and the nerve cells of the brain.

• The endothelial capillary wall further employs efflux pumps, which actively transport unwanted molecules back into blood circulation. In the CNS astroglia may release neuro-active molecules (cross-talk), supply neurons with neurotransmitter precursors, sequester or metabolise extracellular neurotransmitter molecules or respond to neurotransmitter signaling.
Blood Brain Barrier

• Water and lipid (fat)-soluble substances pass through the BBB easily, and a variety of transport mechanisms exist to ensure that the brain receives the nutrients it needs. Other transport mechanisms ensure that CNS wastes are released back into the circulation.

• Large molecules, polar (charged) molecules and charged ions cross the BBB with difficulty unless they are specially transported. In addition to the barrier and efflux pumps, enzymes found on the capillary endothelial cell walls further filter the substances passing into the brain.

• Mutations or single nucleotide polymorphisms may affect the structure or function of these enzymes or transport mechanisms.
Blood Brain Barrier

• There are several areas of the brain where the BBB is more permeable or absent. These areas, called circumventricular organs, allow the brain to monitor the blood composition (feedback) to make adjustments to the body physiology. The BBB may be damaged, which increases its permeability and allows foreign substances into the brain.

• The presence of foreign substances from the circulation, such as bacterial lipopolysaccharides or environmental toxins, may cause inflammatory changes in the brain; these changes may affect mood and behavior.

• Accumulating evidence points to associations between BBB dysfunction and the progression of a variety of CNS diseases, such as stroke, multiple sclerosis, brain tumours or neurodegenerative diseases such as Parkinson’s or Alzheimer’s diseases.
Blood Brain Barrier

- The BBB tight junctions may be damaged by:

- High blood pressure
- Delayed development (the BBB is not fully formed at birth)
- Radiation
- Infection
- Inflammation
- Trauma (injury)
- Oxidative stress
- Low oxygen (hypoxia)
- Post-hypoxia re-oxygenation
Blood Brain Barrier

• The enzymatic machinery for neurotransmitter synthesis and metabolism is often similar, if not identical, on both sides of the BBB, and normalising neurotransmitters has been shown to result in the improvement of some mood and behaviour symptoms.

• Because metabolic enzymes are expressed differently in various body tissues, circulating levels of neurotransmitters and their metabolites may have distinct sources. For example, dopamine and serotonin synthesis and metabolism occurs primarily in the gastrointestinal tract (GIT).
Blood Brain Barrier

• Glia cells are found in the enteric (gut) nervous system and in muscle tissue as well as in the CNS. Glial cells in the enteric nervous system may be part of the gut mucosa, may be associated with enteric ganglia (nerve cell clusters), or may be associated with enteric nerves in the smooth muscle layers of the gut.

• Urinary levels of neurotransmitters primarily reflect the activity of the peripheral and GIT enteric nervous systems.

• Up to 20% of urinary neurotransmitters are estimated to originate in the CNS.
Healing for the Blood Brain Barrier

• There are key nutrients that are or may be helpful for the healing of the BBB.

• These involve glycophospholipids, antioxidants such as tocotrienols, fat-soluble vitamins including vitamin D, & vitamin B1.

• There is a detailed list of potentially supportive supplements to promote healing of the BBB provided to you for online access.
# Nutritional Intervention to support those patients With imbalances in their GI or Blood Brain Barriers

(as identified with the antibody-based Cyrex labs tests)

## Intestinal Gut Healing programme

<table>
<thead>
<tr>
<th>Item</th>
<th>Dosage/Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthred Powder (ARG) - <a href="http://tinyurl.com/387gkpzp">http://tinyurl.com/387gkpzp</a></td>
<td>1 scoop in water 20 mins before breakfast &amp; dinner</td>
</tr>
<tr>
<td>Saccharomyces Boulardii (ARG) - <a href="http://tinyurl.com/35392bw">http://tinyurl.com/35392bw</a></td>
<td>1 with breakfast, 1 with lunch, 1 at bedtime</td>
</tr>
<tr>
<td>NT Factor Advanced Physician’s Formula (NTI) - <a href="http://tinyurl.com/7u24opg">http://tinyurl.com/7u24opg</a></td>
<td>1 with breakfast, 1 with lunch, 3 with dinner</td>
</tr>
<tr>
<td>Vitamin D3 Complete (ARG) - <a href="http://tinyurl.com/5r2ybu8">http://tinyurl.com/5r2ybu8</a></td>
<td>1 with breakfast &amp; dinner</td>
</tr>
</tbody>
</table>

## Blood Brain Barrier Healing programme

<table>
<thead>
<tr>
<th>Item</th>
<th>Dosage/Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP Lipids Powder (NTI) - <a href="http://tinyurl.com/9x4lcte">http://tinyurl.com/9x4lcte</a></td>
<td>2 scoops with breakfast &amp; 2 scoops with dinner</td>
</tr>
<tr>
<td>NT Factor Advanced Physician’s Formula (NTI) - <a href="http://tinyurl.com/7u24opg">http://tinyurl.com/7u24opg</a></td>
<td>3 with breakfast, 2 with lunch</td>
</tr>
<tr>
<td>Immuno-gG (BRC) (colostrum)</td>
<td>4 with breakfast &amp; 4 at bedtime</td>
</tr>
<tr>
<td>Tocomin SupraBio™ Tocotrienols (ARG) - <a href="http://tinyurl.com/b6pgg9e">http://tinyurl.com/b6pgg9e</a></td>
<td>1 softgel with breakfast &amp; 1 with dinner</td>
</tr>
<tr>
<td>Vitamin D3 Complete (ARG) - <a href="http://tinyurl.com/5r2ybu8">http://tinyurl.com/5r2ybu8</a></td>
<td>1 with dinner</td>
</tr>
<tr>
<td>Thiamin 50 (BRC)</td>
<td>1 with each meal</td>
</tr>
<tr>
<td>Stamina Caps (BRC) - <a href="http://tinyurl.com/arx3mqr">http://tinyurl.com/arx3mqr</a></td>
<td>2 with breakfast, 2 with lunch &amp; 2 at 5 pm</td>
</tr>
<tr>
<td>Bio-3BL-G (BRC) (or Bio B 100, by BRC)</td>
<td>4 first thing, then 2 tabs every 3 hours until 9 pm</td>
</tr>
</tbody>
</table>

**Specific Food Recommendations**

- **Coconut oil / butter**: 1 tablespoon three times a day (at start of each meal)
- **Chicken Stock**: 1 cup twice daily
Neurotransmitter Testing

Certain foods should be avoided for at least three days prior to neurotransmitter testing. Different foods may contain neuro-active compounds or affect the synthesis or metabolism of different neurotransmitters. In addition, patients should avoid cold weather conditions before and during testing and ensure proper hydration with water or fluids. Catecholamine (Dopamine, Epinephrine, Norepinephrine) levels may be affected by:

- Alcohol
- Amines
  - Walnuts, avocados, fava beans, cheese, beer, red wine
- Banana
- Chocolate
- Citrus fruits
- Cocoa
- Coffee
- Cola
- Licorice
- Tea
- Vanilla
Serotonin levels may be affected by

- Avocado
- Bananas
- Eggplant
- Fruit (especially those listed)
- Kiwi fruit
- Nuts (especially those listed)
- Pineapple
- Plums and prunes
- Tomato products
- Walnuts
Medications & Neurotransmitters

• Medications may alter neurotransmitter levels by binding to or blocking neurotransmitter receptors. No medication should ever be discontinued without the permission of the prescribing physician. Sudden discontinuation of certain medications may be hazardous to health.

• Neuro-active medications are designed to alter neurotransmission; used according to prescription and under medical supervision, such drugs may provide relief for a variety of behavioural, mood and psychiatric disorders. These drugs may act by:
  
  • Altering the rate of neurotransmitter clearance from the synapse  
  • Altering the rate of release of neurotransmitter from a neuron  
  • Binding with a receptor the same as a neurotransmitter  
  • Blocking a neurotransmitter from binding with a receptor  
  • Alter the flow of ions (minerals) into and out of neurons  
  • Inhibiting synthetic enzymes
Medications & Neurotransmitters

• Most medications are intended to affect a certain neurotransmitter pathway or receptor, however, other pathways and receptors may be inadvertently affected.

• In addition, no neurotransmitter signaling system exists in isolation; a specific neurotransmitter or receptor may send and receive signals that affect other neurotransmitter pathways.

• Additional side effects may occur if neuro-active medications are taken inappropriately or in conjunction with other neuro-active compounds such as herbs or vitamins.
Medications & Neurotransmitters

• Medications designed for other uses may sometimes have neurological side effects:

• Antihistamine medications alter the levels of histamine, an important neurotransmitter in the brain, causing drowsiness.

• Antibiotics may have neurotoxic side effects, and present with a wide variety of neurological symptoms. Individuals of advanced age and those with kidney insufficiency, liver disease or prior central nervous system disease may be most vulnerable to such side effects.

• Steroids, produced by the body or taken as medication, may affect neurotransmitter receptors and influence the release of glutamate, gamma-aminobutyric acid (GABA), acetylcholine, norepinephrine, dopamine and serotonin.
Environment & Neurotransmitters

• Environmental exposure may occur when neuro-active compounds are found in discharge from water treatment plants. A recent study found evidence of antivirals, antibiotics, muscle relaxants, antidepressants, tranquilisers, medications for treating cancer, diabetes, and hypertension in ground water below a waste treatment plant.

• Another study found neuro-active compounds, such as antidepressants, anti-seizure compounds, and mood stabilisers in 24 rivers across Minnesota (Iowa, USA).
Drugs disrupt neurotransmitters

• Drugs of abuse disrupt neurotransmission. While many drugs disrupt particular neurotransmitters or pathways, most drugs of abuse directly or indirectly enhance dopamine signaling in reward pathways. An excellent overview of the effect of drugs of abuse on neurotransmission may be found on the National Institute on Drug Abuse website: [http://www.drugabuse.gov/news-events/nida-notes/2007/10/impacts-drugs-neurotransmission](http://www.drugabuse.gov/news-events/nida-notes/2007/10/impacts-drugs-neurotransmission)
Medications that may alter catecholamine (Dopamine, Epinephrine, Norepinephrine) testing include:

- acetaminophen (Tylenol®)
- aminophylline
- amphetamines
- appetite suppressants
- caffeine
- chloral hydrate
- clonidine
- dexamethasone
- diuretics
- epinephrine
- insulin
- imipramine
- lithium
- methyldopa
- monoamine oxidase (MAO) inhibitors
- nicotine
- nitroglycerine
- decongestant nose drops
- propafenone
- reserpine
- salicylates (aspirin)
- theophylline
- tetracycline
- tricyclic antidepressants
- vasodilators
Medications may alter Serotonin

- morphine
- monoamine oxidase (MAO) inhibitors
- reserpine
- methyldopa
- lithium
- serotonin re-uptake inhibitors
- tryptophan or 5-hydroxy tryptophan (5-HTP) supplements
Methylation can also affect neurotransmitters
Methylation Pathways
# NeuroBiogenic Amines
(urine test)

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<tr>
<th>compound</th>
<th>RESULT/UNIT per g creatinine</th>
<th>REFERENCE INTERVAL</th>
<th>2.5&lt;sup&gt;th&lt;/sup&gt;</th>
<th>16&lt;sup&gt;th&lt;/sup&gt;</th>
<th>50&lt;sup&gt;th&lt;/sup&gt;</th>
<th>84&lt;sup&gt;th&lt;/sup&gt;</th>
<th>97.5&lt;sup&gt;th&lt;/sup&gt;</th>
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<tr>
<td>Dopamine, free</td>
<td>132 µg</td>
<td>52– 320</td>
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<tr>
<td>3,4-Dihydroxyphenylacetic acid (DOPAC)</td>
<td>949 µg</td>
<td>360–1950</td>
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<tr>
<td>3-Methoxytyramine (3-MT)</td>
<td>98.6 nmol</td>
<td>25– 200</td>
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<td>Norepinephrine, free</td>
<td>11.7 µg</td>
<td>12– 64</td>
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<td>Normetanephrine</td>
<td>76 µg</td>
<td>64– 400</td>
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<td>Epinephrine, free</td>
<td>1.9 µg</td>
<td>1.2– 16</td>
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<td>Metanephrine</td>
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<td>35– 200</td>
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<tr>
<td>Serotonin</td>
<td>34 µg</td>
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<td>5-Hydroxyindolacetic acid (5-HIAA)</td>
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<td>800– 7200</td>
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<td>Tryptamine</td>
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<td>Glutamate</td>
<td>8.1 µmol</td>
<td>5– 45</td>
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<tr>
<td>Gamma-aminobutyrate (GABA)</td>
<td>1.5 µmol</td>
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<tr>
<td>Tyrosine</td>
<td>31 µmol</td>
<td>23– 113</td>
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<tr>
<td>Tyramine</td>
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<tr>
<td>Phenethylamine (PEA)</td>
<td>864 nmol</td>
<td>13– 130</td>
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<tr>
<td>Taurine</td>
<td>36 µmol</td>
<td>170– 1200</td>
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<tr>
<td>Glycine</td>
<td>1279 µmol</td>
<td>280– 2800</td>
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<td>Histamine</td>
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<td>5– 48</td>
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<tr>
<td>Creatinine</td>
<td>295 mg/dL</td>
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</table>
Endogenous Effects

• Lifestyle and environment may contribute to neurotransmitter function or imbalance. Altered patterns of urinary neurotransmitters may highlight the need for precursor amino acids or nutritional cofactors essential for synthesis and metabolism.

• The assimilation and absorption of nutrients requires a healthy digestive tract and a healthy microbiome (the presence of expected and beneficial microbes in the gastrointestinal tract).
Endogenous Effects

• The metabolism of neurotransmitters requires functional detoxification pathways and metabolic enzymes. Neurotransmitter levels may be influenced by diet, medications, nutrition status, lifestyle and other factors such as high sodium intake, age, gender, body mass index, kidney function, detoxification capacity, environmental exposures, infection, tobacco use, stress and inheritance.
Correcting Neurotransmitter Imbalances

Diet, Lifestyle & Therapeutic Intervention
Diet & Neurotransmitters

• Foods and beverages may contain neuro-active molecules that may bind to neurotransmitter receptors and alter neurotransmitter levels or have other effects.

• Monosodium glutamate (MSG), a common food flavouring agent, is known to bind to glutamate receptors. Disorders of digestion and absorption may result in malnutrition; low levels of amino acid precursors and enzyme nutrient cofactors may affect neurotransmitter synthesis or metabolism.
Diet & Neurotransmitters

• The gastrointestinal bacteria (microbiome) may also synthesise and metabolise neuro-active compounds. A healthy microbiome may contribute to neurotransmitter balance through gut-brain-microbiome communications. A diet full of nuts, seeds, legumes, fresh fruits and vegetables provides the fibres required by beneficial and expected flora.
The Diet for Balanced Neurotransmitters?
Modern Foods

• Due to the industrialisation and over-processing of food, the diet is now a potential avenue of exposure to monosodium glutamate (MSG), preservatives, artificial colours and flavours. Calorie-dense, nutritionally depleted foods are common fare, and diets rich in such processed foods have been associated with depression and behaviour issues in some studies. Research continues in this area.

• Diets that eliminate allergens and intolerances (oligoantigenic or “elimination” diet) or sensitivities have been shown to decrease attention deficit hyperactivity disorder (ADHD) symptoms in multiple studies. This may be due to more than immunological reasons alone.
Artificial Additives

• Studies indicate that a subpopulation of children may be sensitive to artificial food dyes; symptoms of exposure may include irritability, sleep problems, inattention, impulsivity, and hyperactivity. The reactions may not be restricted to children with ADHD, but may occur in the general population.

• Three genes, histamine degradation gene polymorphisms HNMT T939C, HNMT Thr105Ile and dopamine transporter gene DAT1 polymorphism (short versus long) have been associated with susceptibility to food dyes. Blue #1 food dye is known to cross the blood brain barrier.
Healthy Way to Eat?

• Ketogenic diets are high in fat and low in carbohydrates; this diet is used to minimise symptoms and seizures in epileptic patients.

• Studies indicate that some ADHD children have epileptiform brainwave discharges. Animal studies indicate that ketogenic diets may decrease activity levels.

• Diets rich in fruits, vegetables, and healthy fats that avoid highly processed foods, food allergies or intolerances, and that employ more traditional cooking methods (such as steaming) have been consistently associated with improved health and decreased risk of chronic, degenerative diseases.
Nutrients that support Neurotransmitter Balance
Amino Acids in Supplement Form

• L-Tryptophan or 5-HTP
• DL-Phenylalanalanine
• L-Tyrosine
• Taurine

• Plus co-factors for enzyme functions: B6.
## Promoting GABA & Glutamate Balance

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
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<tbody>
<tr>
<td><strong>Taurine</strong></td>
<td>Acts as an endogenous GABA agonist</td>
</tr>
<tr>
<td></td>
<td>Rescues neurons from excitotoxnic effects induced by elevated glutamate</td>
</tr>
<tr>
<td><strong>Magnesium (malate)</strong></td>
<td>Blocks NMDA voltage gated receptors reducing excitatory post synaptic receptors</td>
</tr>
<tr>
<td></td>
<td>Reduces neuromuscular irritability, seizures, etc.</td>
</tr>
<tr>
<td><strong>B₆</strong></td>
<td>Cofactor in synthesis of GABA from the enzyme glutamic acid decarboxylase (GAD)</td>
</tr>
<tr>
<td><strong>Green tea extract</strong></td>
<td>Attenuates glutamate cytotoxicity</td>
</tr>
<tr>
<td>(Camilla sinensis) – 60% catechins, 40% EGCG</td>
<td>Activates PI3/AKT and inhibits GSK3, an effect similar to lithium</td>
</tr>
<tr>
<td><strong>N-acetylcysteine (NAC)</strong></td>
<td>Natural NMDA receptor antagonist</td>
</tr>
<tr>
<td></td>
<td>Protects nerve cells from harmful excitotoxic effects</td>
</tr>
<tr>
<td></td>
<td>Precursor to glutathione, a primary antioxidant in the body as well as in the central nervous system</td>
</tr>
</tbody>
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Recommendations

- Taurine: 1,000 to 2,000 mg/d
- NAC: 600 mg to 1,200 mg/d
- Green tea extract (60% catechins; 45% EGCG): 300 to 600 mg/d
- Magnesium malate: 200 to 400 mg/d (>200 mg/d can exceed bowel tolerance)
- B₆: 25 to 50 mg/d

Directions: Take with food
Progression/Incidence

- CDPcholine
- Melatonin
- Lithium
- Lipoic Acid
- Fatty Acids
- Nrf2 Activators
- Magnesium
- Acetyl-L-Carnitine (ALCAR)
- Antioxidants
- Iron chelators
- Natural Anti-inflammatory Agents
Nrf2 Activators

• Please read this free paper all about Nrf2!

• Pall ML, Levine S. Nrf2, a master regulator of detoxification and also antioxidant, anti-inflammatory and other cytoprotective mechanisms, is raised by health promoting factors. Sheng Li Xue Bao. 2015 Feb 25;67(1):1-18. [http://tinyurl.com/pgsmlkl](http://tinyurl.com/pgsmlkl)
## Nrf2 Activators

<table>
<thead>
<tr>
<th>Nrf2 Renew Ingredients per 2 caps</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredient</strong></td>
<td><strong>Dose</strong></td>
</tr>
<tr>
<td>Green Tea (standardised to 95% Polyphenols/75% Catechins/&lt;0.5% Caffeine/40% EGCG)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Milk Thistle (standardised to 30% Silybines/80% Silymarin)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Pomegranate Extract (standardised to 40% Ellagic Acid)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Green Coffee PE (standardised to 45% Chlorogenic Acids/1-5% Caffeine)</td>
<td>200 mg</td>
</tr>
<tr>
<td>Gingko (standardised to 24% Flavone Glycosides/6% Total Ginkgolides)</td>
<td>120 mg</td>
</tr>
<tr>
<td>Olive Leaf (standardized to 20% Oleuropein)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Sulforaphane</td>
<td>50 mg</td>
</tr>
</tbody>
</table>
Magnesium & NMDAR

- Blockers voltage gated calcium channels and NMDA receptors
- Intravenous magnesium efficacy in stroke (IMAGES) began after safety study revealed no incidence of adverse effects
- Recruiting 2700 patients, within 12 hours
- Multicentred, RCT
Nrf2 Turns on Detoxification Genes

Free Nrf2 enters nucleus and binds to ARE sequence (Antioxidant Response Element)

Promotes expression of phase 2 detoxification enzymes such as NQO1 and GSH that promote cell survival.
Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid

Jung H. Suh, Swapna V. Shenvi, Brian M. Dixon, Honglei Liu, Anil K. Jaiswal, Rui-Ming Liu, and Tory M. Hagen
The Diet for Balanced Health?
Non-Nutritional Support in the Pursuit of Happiness
The Blue Zones
The Blue Zones
The Blue Zones

1. Move Naturally

- Right Outlook
  - 2. Know your purpose
  - 3. Down shift

- Eat Wisely
  - 4. 80% rule
  - 5. Plant slant
  - 6. Wine@5

- Belong
  - 7. Family first
  - 8. Belong
  - 9. Right tribe

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The Blue Zones – Power Nine

1. Plant Slant - Lots of veggies, more beans & nuts, less meat & no processed foods.

2. Hara Hachi Bu - painlessly reduce 20% of calories.

3. Grapes of Life - drink red wine (in moderation)

4. Move Naturally - be active without having to think about it
The Blue Zones – Power Nine

5. **Purpose Now** - take time to see the big picture; craft a personal mission statement, find a partner to share this with, learn something new.

6. **Downshift time** to relieve stress, reduce the noise, meditate, be early not late.

7. **Belong** - participate in a spiritual community, be involved, explore a new tradition.

8. **Loved Ones First** - make family a priority.

9. **Right Tribe** - be surrounded by those who share the Blue Zones values; identify your inner circle, be likable, create time together.
Do’s and Don’ts
Action Steps to Take towards Happiness

- Exercise regularly, not too much
- Smile more, laugh a lot
- Spend more time in nature
- Sleep well, get enough rest
- Sunshine (light & heat)
- Hydrate optimally
- Balance your blood glucose
- Live a purposeful life
- Believe in something
- Meditate

- Eat whole, fresh, recognisable food
- Find happy friends to spend time with
- Be in the NOW
- Be grateful every day
- Listen to the right music!
- Go easy on yourself
- Correct specific imbalances in your neurotransmitters
The test could be a useful lever to motivate change
Things NOT to do to maintain Happiness

• Don’t worry
• Don’t drink too much (alcohol)
• Don’t do drugs too much (caffeine etc)
• Don’t stay up too late
• Don’t eat refined sugar
• Don’t eat the foods to which your body reacts negatively
• Don’t live in the dark
• Don’t believe in nothing
• Don’t DO nothing
Summary Seminar Review

• We all have NeuroBiogenic Amines within our bodies and brains all of the time.

• NeuroBiogenic Amines are complex, & are related to other aspects of overall metabolism.

• The urine test and questionnaires can give insight into the balance of NeuroBiogenic Amines & certain Neurotransmitters.

• NeuroBiogenic Amines are involved in our overall happiness.

• But then so are other things too.

• NeuroBiogenic Amines are a function of our nutrition as well as our environment and thought patterns.

• Neurobiogenic Amines can be altered, influenced & manipulated with targeted nutritional intervention.
Summary Seminar Review

• It is possible to improve well-being and happiness by optimising our NeuroBiogenic Amines.

• Eat well
• Think well
• Go well
• Be well

• 21st Century Living – no better time to be alive!