Neurotransmitters in Mental Health – An Introduction

Neurotransmitter Workshop

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Why is it so important to understand Neurotransmitters?
Workshop Outline

• Neurotransmission Overview
• Neurotransmitters (NT)
  – Role in brain function
  – Imbalances
  – Nutritional Support
• Assessment of NT imbalances
• Putting it together – Using the protocol
• Case Studies
• Contributing factors to Imbalance
Neurotransmitters are:

Specialised chemical messengers that send messages from one neuron to another or from a neuron to another cell.
Neurotransmitters include:

• Amino acids e.g.
• Biogenic amines e.g.
• Monoamines e.g.
• Neuropeptides e.g.
Neurotransmitters include:

- Amino acids e.g. GABA, glutamate, glycine, taurine, aspartate
- Biogenic amines e.g. acetylcholine
- Monoamines e.g. Serotonin, melatonin, dopamine, histamine, epinephrine, norepinephrine
- Neuropeptides e.g. Neuropeptide Y, substance P, endog. opioids
Abnormalities

Any abnormalities of NT
• Synthesis
• Storage
• Release
• Degradation

And / or changes to
• Affinity or number of receptors

can affect neurotransmission and cause clinical disorders
How do anti-depressants work?

- SSRI’s – slow down the process of returning serotonin to the neuron it came from, therefore the NT remains in the vicinity of the receptor for longer, making it more likely that enough will build up to set off an impulse (making use of little serotonin)
  - Proxetine (Aropax)
  - Citalopram (Cipramil)
  - Fluoxetine (Luvox)
  - Sertraline (Zoloft)
• MAOIs – (= older class of anti-depressants) inhibit the breakdown (oxidation) of NTs (both serotonin & dopamine) by inhibiting the enzyme that breaks them down, therefore prolonging and increasing their concentration

• Tricyclics – work like SSRIs, but affect the uptake of three NTs (serotonin, NE, dopamine)
Neurotransmitters essentially produce an Excitatory or Inhibitory response.
<table>
<thead>
<tr>
<th>True Excitatory</th>
<th>Modulatory Primarily excitatory</th>
<th>True Inhibitory</th>
<th>Modulatory Primarily inhibitory</th>
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<tr>
<td>Glutamic acid</td>
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<td>GABA</td>
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<td></td>
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<td>Taurine</td>
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<td>Histamine</td>
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<tr>
<td>Phenylethylamine</td>
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<td>Glycine</td>
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<td>Acetylcholine</td>
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*Remember inhibitory and excitatory at a cellular level do not necessarily translate to the same behavioural responses.*
Post-synaptic Glutamate Receptor - Excitatory

- Glutamate binds to receptor
- Channel opens
- More Na+ moves in than K+ moves out
- Neuron is less negatively charged
- Glutamate unbinds, channel closes: Small, brief change (EPSP)
Post-synaptic GABA receptor - Inhibitory

- GABA binds to receptor
- channel opens
- Cl\(^{-}\) moves in
- neuron is more negatively charged
- GABA unbinds: small, brief change (IPSP)
The action of many NT’s depends on:

2. **Area of the Brain NT is located**  
   E.g. Histamine  
   - Wakefulness (brainstem, thalamus, basal forebrain)  
   - Anti-epileptic (basal ganglia - movement)

3. **The type of receptor it acts on**  
   E.g. Norepinephrine  
   - Generally excitatory – alpha 1 receptor, beta receptors  
   - Alpha 2 receptors (inhibitory)

4. **Modulation of another neurotransmitter**  
   May act by stimulating or releasing another neurotransmitter  
   E.g. Acetylcholine activates cerebral cortex and facilitates learning,  
   however the information that is learned and remembered is facilitated  
   by neurons secreting Gluamate and GABA.
1. Essential to understand the concept of
   1. Excitatory
   2. Inhibitory
   3. Modulatory (primarily excitatory or inhibitory)

If you understand this, clinically you are half way there
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*Remember inhibitory and excitatory at a cellular level do not necessarily translate to the same behavioural responses.*
Neurotransmitters:
- Role in Brain function and Mental Health
- Symptoms of Imbalance
- Nutritional Support
In the normal brain the prominent glutamatergic pathways are: the cortico-cortical pathways; the pathways between the thalamus and the cortex; and the extrapyramidal pathway (the projections between the cortex and striatum). Other glutamate projections exist between the cortex, substantia nigra, subthalamic nucleus and pallidum.
Glutamate

- Major excitatory NT in brain
- 70% of fast excitatory synapses use glutamate
- Memory formation
- Generation of new synaptic connections between neurons
  - Plays a key role in brain development
- Attention and concentration
- Receptors – NMDA, AMPA, Kainate and Glutamate receptors
Glutamate Excess

- Anxiety
- Compulsive disorders
- Amyotrophic lateral sclerosis
- Alzheimer’s disease
- Neurodegeneration
- Parkinson’s disease
- Epilepsy

- The large number of glutamatergic synapses combined with wide distribution throughout the brain makes CNS vulnerable towards uncontrolled release of glutamate.

“A growing body of evidence suggests that perturbations in systems using the excitatory amino acid L-glutamate may underlie the pathogenic mechanisms of (e.g.) hypoxia-ischemia, epilepsy, and chronic neurodegenerative disorders such as Huntington's disease and AD. Almost all neurons in the CNS carry the (NMDA) subtype of ionotropic L-glutamate receptors, which can mediate post-synaptic Ca2+ influx. Excitotoxicity resulting from excessive activation of NMDA receptors may enhance the localized vulnerability of neurons in a manner consistent with AD neuropathology, as a consequence of an altered regional distribution of NMDA receptor subtypes.”

Glutamate Deficiency

- Deficiency
  - Poor memory
  - Cognitive impairment
  - Poor attention span
GABAergic inhibition is seen at all levels of the CNS, including the hypothalamus, hippocampus, cerebral cortex and cerebellar cortex.
GABA (gamma amino butyric acid)

- Major inhibitory NT in brain
- 30-40% of all synapses
- Relaxing effect, plays a role in sleep
- Inhibits glutamate activity and NT firing
- $\text{GABA}_A$ and $\text{GABA}_B$ receptors
GABA Excess

- Impaired learning
- Decreased memory
GABA Deficiency

- Anxiety
- Alcohol craving
- Seizures
- Insomnia
- Panic attacks
- Premenstrual syndrome
Imbalance b/n Excitatory and Inhibitory NT activity

- E.g. epilepsy
  - Imbalance believed between glutamate and GABA activity
  - Carbamazepine (Tegretol), phenytoin (Dilantin) and lamotrigine (Lamictal) and sodium valproate (Epilim) inhibit Na+ channels
  - Enhancement of GABA(A) inhibitory neurotransmission is primary mechanism of benzodiazepines and phenobarbital

GABA synthesis

Glutamate synthase

Glutamate decarboxylase

PLP → CO₂

GABA
• **Glutamine**
  – Glutamine is the amino acid precursor to GABA
  – Glutamine supplementation has shown strong stimulation of GABA synthesis in nerve terminals.\(^1\)

• **Taurine**
  – May increase expression of glutamate decarboxylase\(^2\)
  – A recent study has shown that taurine reduced the occurrence of tonic seizures and the duration of tonic-clonic convulsions.\(^3\)

• Vitamin B6 (P5P)
  – Glutamate decarboxylase enzyme activity is dependent upon vitamin B6 availability\(^4\)

• Zinc
  – released into the synaptic cleft may serve as an inhibitory modulator of glutamate release in the hippocampus.\(^5\)


Each capsule contains:
Glutamine 600mg
Taurine 145mg
Pyridoxal 5-phosphate 10mg
Zinc 5mg

Excipients: glycine, silica, vege capsules.
L-Theanine

- Amino acid found in green tea
- May increase GABA levels in the brain
- Promotes alpha brain waves, involved in relaxation states


• Theanine possesses neuroprotective activity.

• Binding to AMPA, kainate and NMDA receptors may prevent excitotoxic glutamate induced neuronal death.

• Ischaemia induced neuronal death was significantly prevented in a dose-dependent manner in theanine pre-treated animals compared to controls.


Acetylcholine – Modulatory (primarily excitatory)

Dorsolateral pons
- REM sleep

Basal Forebrain
- activates cerebral cortex and facilitates learning

Medial Septum
- control hippocampus
- memory formation

Parasympathetic Nervous System
- muscle contraction
Acetylcholine

- Primarily excitatory
- Widely secreted in the central nervous system and peripheral nervous system
- Memory
- Facilitatory role in learning
- REM sleep
- Muscular movement
- Muscarinic and Nicotinic receptors
Acetylcholine Deficiency

- Alzheimer’s disease
- Dementia
- Huntington’s disease
- Short term memory problems
- Poor concentration
- Mania
- Sympathetic dominance
- Light sleeper
- Learning problems
Acetylcholine Synthesis

\[
\begin{align*}
CH_3C\text{SCoA} + HOCH_2CH_2N(CH_3)_3 &\xrightarrow{\text{Choline Acetyltransferase}} CH_3C-OCH_2CH_2N(CH_3)_3 + CoA-SH \\
&\text{Acetylcholine}
\end{align*}
\]
• Pantothenic acid is a component of coenzyme A, a key substance in the intermediary pathway of metabolism. Coenzyme A plays a role in the synthesis of acetylcholine from choline (a co-enzyme of cholinacetylase).

• Vitamin B1 may be involved in the presynaptic release of acetylcholine.


• Animal studies have shown Acetyl-l-carnitine to restore *choline acetyltransferase* activity in the hippocampus.

• Animal studies have also shown the transfer of the acetyl moiety from acetyl-l-carnitine to acetylcholine


Orthoplex Parachol Plus

Each tablet contains:
Choline bitartrate                500mg
Thiamine hydrochloride            100mg
Calcium pantothenate              200mg
Acetyl-L-carnitine                50mg
Dopamine – Modulatory (primarily excitatory)

**Mesocortical system**
(ventral tegmental area to the Prefrontal cortex)
- Memory
- Planning
- Strategy
- Problem Solving

**Mesolimbic system**
(ventral tegmental area to the limbic system)
- Reinforcing/reward

**Nigrostriatal system**
(substantia nigra to the caudate nucleus and putamen)
- Movement
Dopamine

- Excitatory and Inhibitory
- Control of movement
- Rewarding effects, pleasure
- Short term memory formation, planning, strategy preparation
- Can modulate neurons to favour glutamate activity
- Receptors – D1, D2, D3, D4, D5
Dopamine Excess

- Schizophrenia
- Aggression
- ADD
Dopamine Deficiency

- Alzheimer’s disease
- ADD
- Parkinson’s disease
- Tremors
- Stress and mental exhaustion
- Depression
- Low libido
- Addictive behaviour
- Sleep disorders
- General fatigue and exhaustion
- Can’t remember dreams
- Lack of motivation
A recent study examined 23 depressed patients and 31 healthy subjects. Plasma levels of ACTH, cortisol and monoamines were examined. Plasma levels of dopamine metabolite homovanillic acid (HVA) were significantly decreased in depressed patients.

Catecholamine Synthesis

Tyrosine hydroxylase

S-adenosylhomocysteine
Phenylethanolamine-N-methyltransferase

DOPA decarboxylase

Dopamine beta hydroxylase

Dopamine
DVPI PreDop

Each capsule contains:

- **L-Tyrosine** 500mg
- **Pyridoxal 5-phosphate** 5mg
- **Mucuna pruriens** 150mg

*Excipients*: glycine, silica, vege capsule.

Contraindications: pregnancy and breastfeeding

Interactions: Digoxin, MAO Inhibitors, Clonidine, Levadopa, tricyclic antidepressants, other antidepressants.
• Mucuna pruriens cotyledon powder treatment significantly restored the endogenous levodopa, dopamine, norepinephrine and serotonin content in the substantia nigra.

• Studies also show *mucuna pruriens* to control Parkinson’s disease.


• A single oral dose of tyrosine 110 – 150mg/kg has been shown to significantly increase urinary levels of norepinephrine, epinephrine, dopamine, 3-methoxy-4-hydroxyphenylglycol (MHPG), vanilmandelic acid (VMA) and homovanillic acid (HVA).

Norepinephrine – Modulatory (primarily excitatory)

**Neocortex**
- Perceptual learning
- Emotional Response

**Locus coeruleus**
- Vigilance and Attentiveness

**Sleep/Arousal**

**Autonomic NS**
SNS
Norepinephrine

- Arousal and wakefulness
- REM sleep
- Concentration, memory formation
- Stimulates release of hormones that stimulate thymus gland
- May modulate firing of serotonergic and dopaminergic neurons
Norepinephrine Excess

- Panic disorder
- Acute stress
- Schizophrenia
Norepinephrine deficiency/depletion

- Depression
- Chronic stress
- Poor memory and concentration
- Alzheimer’s disease
Catecholamine Synthesis

Tyrosine hydroxylase

DOPA decarboxylase

Dopamine beta hydroxylase

Phenylethanolamine - N-methyltransferase

S-adenosylhomocysteine

S-adenosylmethionine

Dr Vera’s Formulations
Energy Medicine for Today

Dr Vera’s Pure Innovation
DVPI PreDop

Each capsule contains:
L-Tyrosine 500mg
Pyridoxal 5-phosphate 5mg
Mucuna pruriens 150mg

Excipients: glycine, silica, vege capsule.
Serotonin – Modulatory

Neocortex
- Mood, emotions
- arousal

Raphe nuclei

Hypothalamus
- blocks dopamine
- Inhibition of prolactin
- Pain regulation, dreaming

Dr Vera’s FORMULATIONS
Energy Medicine for Today

Dr Vera’s PURE INNOVATION

ORTHOPLEX
Serotonin

- Control of eating/appetite
- Regulation of pain
- Mood
- Anxiety
- Involved in regulation of arousal state and sensory perception (exact mechanism not clear)
- Important modulator of catecholamine activity
- May inhibit glutamate activity
- At least 15 receptors have been identified
Serotonin Excess

- Confusion
- Extreme agitation
- Drunk and dizzy
- GI distress
- High blood pressure
- Muscle twitching
Serotonin Deficiency

- Depression
- Aggression
- Insomnia
- Eating disorders
- Carbohydrate craving
- Low self esteem
- Poor dream recall
- Obsessive compulsive behaviour
- Anxiety
- Impulsive behaviour
- Seasonal affective disorder
• Tryptophan depletion is a recognised method of reducing serotonin levels in investigative studies.

• Tryptophan depletion studies have found

Measuring plasma levels of homovanillic acid (dopamine metabolite), 5-hydroxyindoleacetic acid (serotonin metabolite), cortisol and serotonin turnover in depressed patients illustrates that these levels could be good markers for evaluating depression.

Mitani, H., et al., Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients. Prog Neuropsychopharmacol Biol Psychiatry. 2006 Jan 12
**Serootonin Synthesis**

- **Tryptophan Pyrrolase**
  - Kyneurenine
  - Vitamin B3

- **L-Tryptophan**
  - 5-Hydroxytryptophan
  - 5-Hydroxytryptamine (Serotonin)

- **Tryptophan Hydroxylase**
  - 5-HTP Decarboxylase
Each ½ level 5ml metric spoonful (1g) contains:

- Tryptophan: 100mg
- Vitamin B6: 3.2mg
- Vitamin B3: 6mg
- Zinc: 3mg
- Magnesium: 40mg
- Vitamin B1: 2.2mg
- Vitamin C: 40mg
- Folate: 100µg
- Calcium: 84mg
Dr Vera’s Formulations 5-HTP

Each capsule contains:
5-Hydroxytryptophan: 100mg
Pyridoxal-5-phosphate: 10mg
Tryptophan and Serotonin

Double blind, placebo controlled, cross over study.

Rapid depletion of tryptophan, the precursor to serotonin causes a transient return of depression in 67% of patients who have had a therapeutic antidepressant response.

TRYPTOPHAN VS ANTIDEPRESSANTS

• Double blind study compared L-tryptophan with Amitriptyline over 3 month period. L-tryptophan was more effective than placebo, as effective as amitriptyline and produced significantly fewer side effects.¹

DEPRESSION AND 5-HTP

• Studies in patients with either unipolar or bipolar depression have demonstrated significant clinical response in 2 – 4 weeks at doses of 50-300mg of 5-HTP, TDS.²


5-HTP Versus SSRI’s

• In a 1988 open study of 25 patients, the therapeutic efficacy of 5-HTP was found to be equal to traditional antidepressants.\(^1\)

• A 1991 Swiss study compared 100mg TDS 5-HTP with fluvoxamine 50mg TDS. Both treatment groups showed significant and nearly equal reductions in depression from wk 2 to wk 6.\(^2\)


Histamine – Modulatory

**Posterio Hypothalamus**
Histaminergic neurons located almost exclusively
Project fibres to almost all regions of the brain

**Cerebral Cortex**
Activation and arousal
Wakefulness
Learning & memory
Emotions

Appetite control
Histamine

- Released from mast cells
- Many don’t realise the role histamine plays in the brain as a neurotransmitter
  - Arousal and wakefulness
  - High activity during waking/low during sleep
  - Appetite, drinking and eating behaviour
  - May modulate other neurotransmitters e.g. stimulate release of serotonin and norepinephrine
Histaminergic arousal mechanisms

- Functional neuroimaging studies have demonstrated a role for Histamine 1 receptors in maintaining arousal and cognition in humans.

- Anti-histamine allergy medications, result in a side effect of drowsiness through blocking H1 receptors in the brain.

Histamine Excess

- Histadelia schizophrenia (positive symptoms, hallucinations)
- Depression
- Asthma
- Difficulty thinking/focusing
- Allergies – seasonal allergies
- Fatigue
- Lumbago
The dysfunction of the histamine neuron system may participate in the extradopaminergic brain dysfunction of schizophrenia, and **histamine agents may improve the refractory schizophrenia**.

Histamine Deficiency

- Histopenic schizophrenia
- Depression
- Chemical sensitivity
- Appetite dysfunction
- Low libido
- Anxiety
- Memory loss

Animal studies illustrate the role of histamine in anxiety and cognition.

Examination of histidine decarboxylase deficient mice showed these mice had increased measures of anxiety and hypoactivity.

<table>
<thead>
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<th>Histamine Deficiency</th>
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<tbody>
<tr>
<td>Sneeze in bright sunlight</td>
<td>Canker sores</td>
</tr>
<tr>
<td>Shy and sensitive as a teenager</td>
<td>Difficult orgasm</td>
</tr>
<tr>
<td>Cry, salivate and feel nauseous easily</td>
<td>No headaches or allergies</td>
</tr>
<tr>
<td>Hear pulse in head on pillow at night</td>
<td>Excess fat in lower extremities</td>
</tr>
<tr>
<td>Easy orgasm with sex</td>
<td>Heavy growth body hair</td>
</tr>
<tr>
<td>Regular headaches and seasonal allergies</td>
<td>Ideas of grandeur</td>
</tr>
<tr>
<td>Little body hair</td>
<td>Undue suspicion of people</td>
</tr>
<tr>
<td>Lean build</td>
<td>Seeing or hearing things abnormally</td>
</tr>
<tr>
<td>Abnormal fears, compulsions</td>
<td>Ability to stand pain well</td>
</tr>
<tr>
<td>Long tingers and toes</td>
<td>Ringing in ears</td>
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The results of a study on whether the histaminergic neuron system is involved in human depression demonstrate that depressed patients have decreased brain $H(1)R$ binding and that this decrease correlates with the severity of depression symptoms. It is therefore suggested that the histaminergic neuron system plays an important role in the pathophysiology of depression and that its modulation may prove to be useful in the treatment of depression.

Histamine Synthesis

Histidine decarboxylase

Histidine → Histamine
Each capsule contains:

- Histidine: 500mg
- Pyridoxal 5-phosphate: 5mg

Excipients: glycine, silica, vege capsules.
Melatonin
Melatonin

- Regulation of circadian rhythms
- Promotes sleep
- May regulate GABA receptor complex
Melatonin Deficiency

- Insomnia
- Fibromyalgia
- Epilepsy
- Migraines
There is now evidence that melatonin may have a role in the biological regulation of circadian rhythms, sleep, mood, and ageing. Altered melatonin levels in cluster headache and migraine have been documented. Melatonin mechanisms are related to headache pathophysiology in many ways, including its anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine up-regulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, GABA and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of chemical structure to that of indomethacin.

Melatonin Synthesis

Tryptophan Pyrrolase

- Kyneurenine
- L-Tryptophan

Vitamin B3

- 5-Hydroxytryptophan

Tryptophan Hydroxylase

5-HTP Decarboxylase

5-Hydroxytryptamine (Serotonin)

Serotonin Transferase (SNAT)

N-Acetylserotonin

Hydroxy Indole O-Methyl Transferase (HIOMT)

Melatonin
Opioids

Opiates Act on Many Places in the Brain and Nervous System

Opiates can change the brain stem, an area that controls automatic body functions, and depress breathing.

Opiates can change the limbic system, which controls emotions to increase feelings of pleasure.

Opiates can block pain messages transmitted by the spinal cord from the body.
Endogenous Opioids

- Endogenous analgesic system – inhibits pain sensation
- Reinforcement and reward
- Endorphins activate dopamine release in nucleus accumbens (Alcohol-induced release of certain endogenous opioids similarly results in dopamine release in those brain regions)
- May inhibit norepinephrine release
- May stimulate serotonin and acetylcholine release
- Receptors – mu, kappa and delta
Opioid deficiency

- Addictions
- Pain
- Stress
- Depression
- Headaches
- Learning disorders
- Antisocial behaviour
- Alcohol craving
- Inflammatory states
- Memory loss
There is increasing evidence to implicate the mesolimbic dopamine system in the rewarding effects of drugs of abuse such as opioids, psychostimulants and alcohol, and in addition endogenous opioids may play a key role in the underlying adaptive mechanisms.

Alcohol exerts numerous pharmacological effects through its interaction with various neurotransmitters and neuromodulators. Among the latter, the endogenous opioids play a key role in the rewarding (addictive) properties of ethanol.

Herz, A., Endogenous opioid systems and alcohol addiction. Psychopharmacology (Berl). 1997 Jan;129(2)
Endogenous Opioids

- Activates analgesic system
- Reward/ re-inforcement
- Inhibits species typical defence responses e.g. fleeing and hiding
Orthoplex Inkephalin

Each tablet contains:
- DL-phenylalanine: 400mg
- Glutamine: 25mg
- Tryptophan: 25mg
- Thiamine hydrochloride: 50mg
- Pyridoxine hydrochloride: 5mg
- Zinc gluconate: 25mg
  (equiv. zinc 3.6mg)
- Magnesium oxide: 100mg
  (equiv. Magnesium 60mg)
Up-regulation of the 'endogenous analgesia system' (EAS), a neural pathway that projects caudally from medullary nuclei to the dorsal horn of the spinal column; when stimulated by chronic pain or therapeutic measures such as opiates or acupuncture, the EAS suppresses activation of second-order pain-receptive neurons in the dorsal horn, and thereby alleviates pain. Since serotonin and enkephalins are key neurotransmitters in the EAS, it is reasonable to predict that measures which promote serotonin activity (such as 5-hydroxytryptophan and serotonin-reuptake inhibitors) as well as enkephalin activity (such as D-phenylalanine, an enkephalinase inhibitor) should potentiate EAS-mediated analgesia.

Russell, AL., McCarty, MF., DL-Phenylalanine markedly potentiates opiate analgesia – an example of nutrient/ pharmaceutical up-regulation of the endogenous analgesia system.
Phenylethylamine

- Modulatory neurotransmitter resulting in stimulatory activity
- Modulates potentials to favour glutamate and excitatory neurotransmission
- Mood enhancing effects associated with exercise and chocolate consumption
Phenylethylamine excess

- Insomnia
- High blood pressure
- Hyperglycaemia
- Migraine
Phenylethylamine Deficiency

- Depression
- ADD
Orthoplex Inkephalin

Each tablet contains:
DI-phenylalanine 400mg
Glutamine 25mg
Tryptophan 25mg
Thiamine hydrochloride 50mg
Pyridoxine hydrochloride 5mg
Zinc gluconate 25mg
(equiv. zinc 3.6mg)
Magnesium oxide 100mg
(equiv. Magnesium 60mg)
Neurotransmitters affect each other, therefore an imbalance of one neurotransmitter may affect balance of another.
Steps for Clinical Application

1. What are the patient’s symptoms?

2. Are there any specific symptoms that clearly indicate a particular neurotransmitter?

3. If unsure… test

4. Consider symptom picture and testing results to establish clinical priorities

5. Consult protocol and prescribe according to neurotransmitter priority

6. Investigate underlying causes and contributing factors to the NT deficiency
Why has the patient come to see you? What are their symptoms?

Depression
Are there any specific symptoms that indicate a particular neurotransmitter deficiency?

CHO cravings
Impulsive behaviour

Addictive behaviour
Poor learning
Low libido
Lack of motivation

Inattention
Drowsiness
Low libido
Anxiety

Consider Serotonin

Consider Dopamine

Consider Histamine
If uncertain… test

- MDA
  - may confirm
  - Establish baseline
  - Assist differentiation

- Neuroendocrine metabolites
  - Confirm
  - Establish baseline
  - Establish priorities

- Blood histamine
  - Confirm
  - Establish baseline
  - Establish priorities

- Amino Acid Profile
  - confirm
  - Precursor deficiencies
Consider symptom picture and testing results to establish initial therapy priorities

Prescribe according to protocol with regards specific NT deficiencies
Continue to investigate underlying causes/Contributing factors

- Diet/lifestyle
- EFA deficiency
- Methylation abnormalities
- GI issues e.g. Dysbiosis
- Chronic Inflammation
- Mitochondrial dysfunction
- Nutrient def: - precursor - co-factors
- Heavy metal toxicity
Case Study

• Patient
• Low dopamine
• Low norepinephrine

• Discuss
Peripheral functions of Neurotransmitters
Acetylcholine

- Main neurotransmitter in the peripheral nervous system
  - Parasympathetic, excitatory muscle motor, secretomotor, Intrinsic sensory, interneurons

- Involved in muscle movement – peripheral motor nerves

- Secreted in the intestines
  - Contraction of smooth muscle
  - Relaxation of sphincters
  - Increases salivary secretion
  - Increases gastric secretion
  - Increases pancreatic secretion
Seroert plays a role in GI pathophysiology

- Recent evidence suggests that up to 80% of the body’s serotonin is found in the gut.
  - Stimulates peristalsis
  - Increases intestinal secretion
  - Plays role in sensation in the gut
  - Stimulation of 5HT3 receptors by some drugs can cause nausea and vomiting

- Serotonin dysfunction suspected to play role in:
  - Functional dyspepsia
  - Impaired gastrointestinal motility
  - Impaired GI secretions
  - Irritable Bowel Syndrome
• Brain-gut DVD
• Jacques workshop
Assessment of Neurotransmitter Imbalances
Avenues of Assessment

1. Assess signs and symptoms (full patient history)
2. Mood Disorder Appraisal
3. Pathology testing
   - Neuroendocrine metabolite testing
   - Histamine testing
   - Amino acid profile
   - Kryptopyrroles
   - Fatty acids
   - Minerals – hair mineral analysis, 24hr zinc
Mood Disorder Appraisal

- Questions designed associated with specific symptomatology
- Randomised controlled trials
- Textbook evidence
- Review papers
MDA Results

Relative Neurotransmitter Deficiencies

- Serotonin
- Endogenous Opioids
- Phenylethylamine
- Norepinephrine
- Melatonin
- Epi-epinephrine
- Histamine
- GABA
- Dopamine
- Acetylcholine
Relative Neurotransmitter Deficiencies Over Time

- Serotonin
- Endogenous Opioids
- Phenylethylamine
- Norepinephrine
- Melatonin
- Epepinephrine
- Histamine
- GABA
- Dopamine
- Acetylcholine

Date: 02-May, 07-Jun, 10-Jul
Relative Neurotransmitter Deficiencies Over Time

- Serotonin
- Endogenous Opioids
- Dopamine

Date Range:
- 2-May
- 7-Jun
- 10-Jul
Pathology Testing

- Neuroendocrine metabolites
- Amino acid profile
- Kryptopyrroles
- Histamine
Neuroendocrine metabolites

- Urine test (spot morning void or 24 hr specimen)
- Measures the metabolites of dopamine, norepinephrine, adrenaline, serotonin and COMT enzyme action

- Not Released Yet – Neuroendocrine panel
  - Glutamate, epinephrine, norepinephrine, dopamine, phenylethylamine, GABA, serotonin, glutamine, histamine
### INTEGRATIVE MEDICINE

#### URINE SPOT NEUROENDOCRINE METABOLITES

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Range</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Homovanillic Acid</td>
<td>3.1 - 10</td>
<td>mmol/mol Cr</td>
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<tr>
<td>Dihydroxyphenylaceta</td>
<td>1.2 - 4</td>
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<tr>
<td>Noradrenaline Activity</td>
<td>0.6 - 3</td>
<td>mmol/mol Cr</td>
</tr>
<tr>
<td>3-Methyl-4-Oh-phenylglycerol</td>
<td>0.7 - 2</td>
<td>mmol/mol Cr</td>
</tr>
<tr>
<td>Dihydroxyphenylglycol</td>
<td>3.2 - 10</td>
<td>mmol/mol Cr</td>
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<tr>
<td>Adrenergic Activity</td>
<td>1.5 - 10</td>
<td>mmol/mol Cr</td>
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<td>Vanillylmandelic Acid</td>
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<td>mmol/mol Cr</td>
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<tr>
<td>Dihydroxymandelate</td>
<td>2.0 - 6</td>
<td>mmol/mol Cr</td>
</tr>
<tr>
<td>Serotoninergic Activity</td>
<td>2.0 - 6</td>
<td>mmol/mol Cr</td>
</tr>
<tr>
<td>5-OH-Indoleacetic Acid</td>
<td>2.0 - 6</td>
<td>mmol/mol Cr</td>
</tr>
<tr>
<td>COMT Enzyme Activity</td>
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<td>RATIO</td>
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<tr>
<td>HVA/DOPAC Ratio</td>
<td>2.0 - 6</td>
<td>RATIO</td>
</tr>
<tr>
<td>VMA/DOMA Ratio</td>
<td>2.0 - 6</td>
<td>RATIO</td>
</tr>
<tr>
<td>MHPG/DHPG Ratio</td>
<td>0.9 - 4</td>
<td>RATIO</td>
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#### Integrative Medicine Comments

Only Serotonergic pathway is low. Suggest supplementation as outlined if indicated. Prudent to check the catecholamines and neuroendocrine hormones GABA, PEA, Histamine. Also consider thyroid, progesterone to estrogen ratio, pregnenolone levels and consider the kryptopyroles urine test if indicated.

5-Hydroxyindoleacetaet (5-HIAA)
Breakdown of the neurotransmitter serotonin leads to excretion of 5-hydroxyindoleacetaet (5-HIAA). Inadequate production of serotonin has been associated with constipation, depression, fatigue, insomnia, suicide, attention deficit syndrome. Diet therapy should focus on improving protein digestion (digestive enzymes for hydrochlorhydria and pancreatic insufficiency) and increasing consumption of foods high in tryptophan (turkey, bananas, low fat milk, lentils and eggs). These actions maximises the need for oral tryptophan or 5HTP supplementation.

If supplementation is to be considered suggest 5HTP (5-Hydroxytryptophan) 50mg t.i.d. and Magnesium 300mg.
• Metabolites are considered to give a more accurate picture of NT activity in the brain.
  – The NTs themselves do not cross the BBB
  – Breakdown metabolites do cross the BBB

  – Carlson text reference serotonin metabolites
Example

- MDA/ Neuroendocrine metabolite test indicates:
  - High dopamine
  - High norepinephrine
  - Low adrenaline
  - Normal serotonin
Amino Acid Profile

- 24 hr urine test  OR
- Blood plasma test (fasting)

- Full profile or just specific Amino Acids includes all essential and non essential amino acids

- Neuroendocrine amino acids panel:
  - Aspartate, Glutamate, GABA, Glycine
• Following a Neuroendocrine metabolite test with an Amino acid profile may assist with determination of whether a deficiency of NT is due to deficiency of precursor amino acid.
Histamine

- Blood sample in heparin tube
- Determination of histamine levels may help pinpoint methylation abnormalities.
Kryptopyrroles

- Kryptopyrroles/ mauve factor is……
- Measures the amount of pyrroles in the urine, determining whether an individual suffers from abnormal pyrrole metabolism.
- Pyrroluria associated with deficiency of zinc, vitamin B6 and possibly B3
- Pyrroluria associated with depression, anxiety, autism, aggression, hyperactivity, epilepsy.
- Urine sample is corrected for hydration status
Other Relevant testing

• Nutritional status for co-factor deficiencies

• To investigate underlying causes and contributing factors
  – e.g. intestinal permeability, hair mineral analysis, functional liver detoxification profile
Putting it all together

Using the Protocols
Steps for Clinical Application

1. What are the patient’s symptoms?

2. Are there any specific symptoms that clearly indicate a particular neurotransmitter?

3. If unsure… test

4. Consider symptom picture and testing results to establish clinical priorities

5. Consult protocol and prescribe according to neurotransmitter priority

6. Investigate underlying causes and contributing factors to the NT deficiency
Depression

Neurotransmitter Deficiencies to Consider:
– Serotonin
– Histamine
– Dopamine/Norepinephrine
– Opioids/PEA
Depression

- Testing for confirmation
  - MDA
    - May help to confirm symptom picture and differentiate priorities
  - Neuroendocrine metabolites

- Blood histamine
  - For accuracy on histamine levels

- Amino acid profile
  - May help to determine if there is a specific precursor deficiency
Depression

Consider symptom picture and testing results

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<th>MDA</th>
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Establish neurotransmitter imbalance priorities
Depression

Prescribe according to priorities

– **Serotonin**
  - Dr Vera’s Formulations 5-HTP
– **Histamine**
  - DVPI PreHist
– **Dopamine/norepinephrine**
  - DVPI PreDop
  - DVPI Vitamin C (optional)
– **Opioids/PEA**
  - Orthoplex Inkephalin
Depression

• Investigate underlying causes/ contributing factors
  – Essential fatty acid deficiency: studies show strong correlation between EFA intake and depressive symptoms.
  – GI function, dysbiosis
  – Mitochondrial dysfunction
  – Nutritional deficiencies

• Co-factors, precursors (amino acid profile)
Anxiety

Neurotransmitter Deficiencies to Consider:

– Serotonin
– Histamine
– GABA
Anxiety

- Testing for confirmation
  - MDA
    - May help to confirm symptom picture and differentiate priorities
  - Neuroendocrine metabolites
- Blood histamine
  - For accuracy on histamine levels
- Amino acid profile
  - May help to determine if there is a specific precursor deficiency
Anxiety

Consider symptom picture and testing results

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Establish neurotransmitter imbalance priorities
Anxiety

• Investigate underlying causes/ contributing factors
  – Essential fatty acid deficiency: studies show strong correlation between EFA intake and depressive symptoms.
  – GI function, dysbiosis
  – Mitochondrial dysfunction
  – Nutritional deficiencies
  • Co-factors, precursors (amino acid profile)
Stress

- Neurotransmitter deficiencies to consider
  - Serotonin
  - GABA
  - Norepinephrine/ epinephrine
Stress

• Testing for confirmation
  – MDA
    • May help to confirm symptom picture and differentiate priorities
  – Neuroendocrine metabolites
  – Cortisol
  – Amino acid profile
    • May help to determine if there is a specific precursor deficiency
Stress

Consider symptom picture and testing results

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Establish neurotransmitter imbalance priorities
Stress

- Investigate underlying causes/ contributing factors
  - HPA dysfunction
  - High cortisol
  - Essential fatty acid deficiency: studies show strong correlation between EFA intake and depressive symptoms.
  - GI function, dysbiosis
  - Mitochondrial dysfunction
  - Nutritional deficiencies
    - Co-factors, precursors (amino acid profile)
Dementia

• Neurotransmitter deficiencies to consider:
  – Acetylcholine
  – Dopamine/norepinephrine
Dementia

• Testing for confirmation
  – MDA
    • May help to confirm symptom picture and differentiate priorities
  – Neuroendocrine metabolites
  – Cortisol
  – Amino acid profile
    • May help to determine if there is a specific precursor deficiency
Dementia

Consider symptom picture and testing results

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Establish neurotransmitter imbalance priorities
Dementia

- Investigate underlying causes/ contributing factors
  - Heavy metal toxicity
  - Essential fatty acid deficiency: studies show strong correlation between EFA intake and depressive symptoms.
  - GI function, dysbiosis
  - Mitochondrial dysfunction
  - Nutritional deficiencies
    - Co-factors, precursors (amino acid profile)
• One case study
  – New from ??
Neurotransmitters in Mental Health
– An Introduction

Neurotransmitter Imbalances

Causes/ contributing factors
Causes or contributing factors of Neurotransmitter Imbalances

- Genetic polymorphisms
- Emotional and/or physical stress
- Nutrient deficiencies (poor diet or disease)
- Side effects of medication
- Long term drug use
- Oxidative damage
- Disease
- Heavy metal toxicity
- Blood sugar irregularities
- Underlying inflammation – cytokine effect neurotransmitters
- Receptor deficiencies
- Imbalances of other neurotransmitters
• Genetic polymorphisms
  – E.g. dopamine DRD2 receptor polymorphism, results in reward deficiency syndrome (decreased activity and response of dopamine) promotes activities that may enhance dopamine activity.

Vitamin D

- The finding that 1,25-(OH)2D3 treatment results in an increase in choline acetyltransferase activity in specific rat brain nuclei has prompted the suggestion that this hormone might influence certain aspects of anterior pituitary lobe function.¹

- Another study has reported that vitamin D deficiency in the weanling rat increased the dopamine concentration in the cortex.²

Vitamin D

- 1,25-(OH)2D3 also increases expression of the gene encoding tyrosine hydroxylase in adrenal chromaffin cells.

- The extension of this regulation to neurons could be of interest, because tyrosine hydroxylase is the rate-limiting enzyme in the biosynthesis of catecholamines.

Puchacz, E. et al. (1996) Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. Mol. Brain Res. 36, 193–196
Dietary peptides can affect brain neurotransmission

- **Casomorphins and gliadomorphins**
  - Peptides from digestion of gluten and casein
  - Opioid activity – bind opioid receptors in gut
  - Can enter the CNS and mimic beta-endorphin
  - Implicated in post partum psychosis
  - Implicated in Schizophrenia and Autism

Exorphins
↓
competitively binding to the opioid receptor
↓
disturbance in neurotransmitter function
↓
stress, anxiety and aggression
# Heavy Metal Toxicity

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Essential fatty acids (EFAs) have been shown to benefit patients with depression, schizophrenia and dementia.

- PUFAs may determine the fluidity of synaptosomal membranes and thereby regulate neuronal transmission.

- EFAs can modify the function of neurotransmitter receptors (cholinergic, nicotinic, dopaminergic, adrenergic, NMDA)

- Free fatty acids, lipid metabolites and phospholipids modify function of membrane proteins including ion channels.

Yehuda, S., et al., Essential fatty acids are mediators of Brain biochemistry and cognitive functions. Journal of Neuroscience Research 56:565-570.
Essential Fatty Acids

- Research published in *Lancet* found a significant negative correlation between worldwide fish consumption and prevalence of depression. In research involving a random sample within a nation, frequent fish consumption in the general population is associated with a decreased risk of depression and suicidal ideation.¹

- A recent cross-sectional study conducted in New Zealand found fish consumption is significantly associated with higher self-reported mental health status.²

Other Considerations in detail

- Covers a number of factors that may play a role in neurotransmitter imbalance and mood disorders.