Autism Society of The Bluegrass

Thank you for this opportunity to share with you my work for children with Autism.
Autism is a complex neurobiological disorder of development that lasts throughout a person’s life. It is sometimes called a developmental disability because it usually starts before age three, in the developmental period, and because it causes delays in different skills that arise from infancy through adulthood.
Figure 1 - Distribution of Birth Dates of Regional Center Eligible Persons with Autism

PREVALENCE

From: Dr. E. F. Vogelaar
Dr. M. Nicholas Martin
Autism Society of the Bluegrass
A Report to the Legislature
March 1, 1999
Polymorphism
Functional Definition by Dr. M. Nicholas Martin

Polymorphism describes a variability of body forms and enzymatic functions resulting from an altered protein(s) for which the amino acid sequence variance exists in a population of organisms, but the variations do not destroy, but alters protein(s) function, in a way to produce the variability in body form and/or function, and or group interactions.
Polymorphism and Autism

• Autistic children have polymorphisms which result in altered enzymes. Dr. Jill James has demonstrated that autistic children have a “BIOCHEMICAL FINGERPRINT”.

• Enzyme function is not totally destroyed, and can be enhanced with supplementation.
Polymorphisms

**Definition**
Difference in DNA sequence among individuals, groups, or populations (e.g. a genetic polymorphism might give rise to blue eyes versus brown eyes, or straight hair versus curly hair). Genetic polymorphisms may be the result of chance processes, or may be caused by the effects of stressors (such as nutritional deficiencies, chronic viral infections, toxins, or radiation). (ref: Web definitions)
Polymorphisms

• A difference in DNA sequence can be one or a group of single nucleotide (genetic building blocks) substitutions (mutations) that is responsible for development of altered or nonfunctional enzymes leading to polymorphisms. More extensive mutations are called genetic syndromes. Examples of this are: Down’s Syndrome, often affecting multiple gene deletions or replications.
ENZYME

– An enzyme is a made up of amino acids linked together. (Amino acids are the building blocks of proteins)

– Our ability to make an enzyme is an inherited component of our genetic makeup. One gene codes for one enzyme.

– An enzyme functions to speed up the rate of a reaction. Without an enzyme the reaction will proceed too slowly to be of biological significance.
Polymorphisms in Methionine (an amino acid) Pathway

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Odds Ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>MTHFR 677 TT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control Individuals (183): 10.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autistic Children (231): 13.4%</td>
<td>1.26</td>
<td>0.28</td>
</tr>
<tr>
<td>2.</td>
<td><strong>MTHFR 677 CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control Individuals (183): 44.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autistic Children (231): 52.8%</td>
<td>1.4</td>
<td>0.05</td>
</tr>
<tr>
<td>3.</td>
<td><strong>MTHFR 677 CT/1298AC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control Individuals (183): 18.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autistic Children (231): 26.4%</td>
<td>1.6</td>
<td>0.03</td>
</tr>
<tr>
<td>4.</td>
<td><strong>MTHFR T Allele Frequency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control Individuals (183): 33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autistic Children (231): 40%</td>
<td>1.33</td>
<td>0.03</td>
</tr>
</tbody>
</table>

These numbers suggest that the problems are a result of environmental effects, i.e. mercury, CNS inflammation, etc.

From: Jill James
Amino Acid profiles in Autistic Children

- Deficiency of essential amino acids: 40-50%
- Increased essential amino acids: 20-30%
- Dysfunction of intestinal flora: 40-50%
- Decreased protein degradation: 35-45%
- Dysfunction of Vitamin B6: 85-95%
- Dysfunction of Folic acid/B12: 70-80%
- Dysfunction of Magnesium: 75-85%
- Deficiency of Taurine: 60-80%
Measuring Enzyme Function

Km
or
Michaelis-Menton Constant
Definition: a measurement of concentration. Km is the amount of enzyme needed to cover half the binding sites.

Mutations often result in increased Km. This is why increasing the amount of cofactors is therapeutic because it causes increased activation of the enzyme which may eliminate some of the unwanted signs and symptoms by correcting compromised metabolic pathways.
### Km of B vitamins of Autistic Children

#### Increase in Km:

- **Vitamin B1**: 3-250 X
- **Vitamin B3**: 4-150 X
- **Vitamin B6**: 2.5-4 X
- **Vitamin B7 (biotin)**: 3->100 X
- **Vitamin B12**: 50-5000 X
- **Other discussed nutrients**: Vitamin B2, B5, B11 (folic acid), D, E, K, Biopterin, Lipoic acid, Carnitine, Amino acids, Metals en Hormones
- **Next to Km also instability**

---

**Why is this Important?**

From: Dr. E. F. Vogelaar
# Kinetic Characteristics of PLP – Dependent Enzyme

<table>
<thead>
<tr>
<th>ENZYMES</th>
<th>NORMAL KM (µMOL/L)</th>
<th>AUTISTIC KM (µMOL/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PYRIDOXAL KINASE (2 X 40 KD)</td>
<td>2.84 ±</td>
<td>79.34 ±</td>
</tr>
<tr>
<td>PYRIDOXAL</td>
<td>1.34</td>
<td>22.12</td>
</tr>
<tr>
<td>GLUTAMATE TRANSAMINASE (2 X 47 KD)</td>
<td>5.73 ±</td>
<td>34.31 ±</td>
</tr>
<tr>
<td>GABA</td>
<td>2.16</td>
<td>15.43</td>
</tr>
<tr>
<td>GLUTAMATE DECARBOXYLASE (6 X 50 KD)</td>
<td>0.19 ±</td>
<td>11.34 ±</td>
</tr>
<tr>
<td>GLUTAMATE</td>
<td>0.10</td>
<td>5.26</td>
</tr>
<tr>
<td>DOPA DECARBOXYLASE (2 X 30 KD)</td>
<td>79.56 ±</td>
<td>926.34 ±</td>
</tr>
<tr>
<td>DOPA</td>
<td>19.24 ±</td>
<td>520.16 ±</td>
</tr>
<tr>
<td>HISTIDINE DECARBOXYLASE (2 X 55 KD)</td>
<td>56.71 ±</td>
<td>322.65 ±</td>
</tr>
<tr>
<td>HISTIDINE</td>
<td>20.32 ±</td>
<td>59.26</td>
</tr>
<tr>
<td>5-HTP – DECARBOXYLASE (2 X 34 KD)</td>
<td>26.44 ±</td>
<td>232.65 ±</td>
</tr>
<tr>
<td>5-OH-TRYPTOPHANE → SEROTONIN</td>
<td>9.18 ±</td>
<td>120.39 ±</td>
</tr>
</tbody>
</table>

**Normal**: (n = 20)  **Autistic**: (n = 32)
The decrease in methionine and homocysteine levels in autistic children indicates that they have reduced methionine synthase activity and reduced turnover of the methionine cycle.

The decrease in SAM and increase in SAH provides metabolic evidence that methylation capacity is reduced in some autistic children.

From: Jill James
Pathways that show polymorphisms

Protein synthesis

Creatine synthesis
Methylation of DNA, RNA, histones, membrane phospholipids

Supplementation:
800 µg folic acid, b.i.d.
1000 mg betaine, b.i.d.
75 µg/Kg methyl-B12

From S. Jill James
(Cystathione B-Synthetase Vit B6 dependent)

Transsulfuration Pathway

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Cofactor

• Definition:

Also known as a coenzyme because its presence is necessary for the enzyme to be functional. A coenzyme may alter the shape of an enzyme slightly so that the enzyme can then bind to the receptor site

Organic \(\rightarrow\) Vitamins, hormones (inc Vit A, Vit D, and Vit E)

Inorganic \(\rightarrow\) See next page
Inorganic Elements that serve as Cofactors for Enzymes

<table>
<thead>
<tr>
<th>Element</th>
<th>Enzyme(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu 2+</td>
<td>Cytochrome Oxidase</td>
</tr>
<tr>
<td>Fe 2+ o Fe 3+</td>
<td>Cytochrome Oxidase</td>
</tr>
<tr>
<td>K+</td>
<td>Pyruvate Kinase</td>
</tr>
<tr>
<td>Mag 2+</td>
<td>Hexokinase, glucose 6 Phosphate Pyruvate Kinase</td>
</tr>
<tr>
<td>Mn 2+</td>
<td>Arginase, Ribonucleotide reductase</td>
</tr>
<tr>
<td>Mo</td>
<td>Dinitrogenase</td>
</tr>
<tr>
<td>Ni 2+</td>
<td>Urease</td>
</tr>
<tr>
<td>Se</td>
<td>Glutathione Peroxidase</td>
</tr>
<tr>
<td>Zn +</td>
<td>Carbonic Anhydrase, Alcohol dehydrogenase, Carboxy peptidase A &amp; B</td>
</tr>
</tbody>
</table>

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
The Cofactor Vitamin B6

As a cofactor of 118 metabolic reactions, Pyridoxal-5-Phosphate(PLP), has the potential to influence the status of our health via neurotransmitters, synthesis, as well as in maintaining normal metabolic functions.

It is a water soluble, essential vitamin, unable to be synthesized by man. Much of our body stores are in muscle. P5P is necessary for energy metabolism, nerve function, Hemoglobin oxygen content, niacin formation, hormone receptor functions and nucleic acid synthesis.
Vitamin B6

Riboflavin (Vitamin B2) necessary for phosphorylation of Pyridoxine to Pyridoxal-5-Phosphate

1. Three forms found in foods: Pyridoxine, Pyridoxal, and Pyridoxamine
2. Phosphorylation necessary for active form of coenzyme
3. Kinase enzyme that phosphorylates shows an increased affinity for Pyridoxal over Pyridoxine
4. Riboflavin, which is needed for FADH2 (Flavin Adenine Dinucleotide) and generation of ATP, is a cofactor in formation of P5P
5. Thiamine (B1) is a cofactor for the activation of riboflavin (B2)
Vitamin B6
Functions for Pyridoxal-5-Phosphate as enzymatic cofactor

1. **Synthesis**
   - Transamination
   - Decarboxylation
   - Synthesis of a product (Cytathione) with elimination of a product (Homocystiene)
     - Homocysteine + Serine $\rightarrow$ Cystathione
   - Cleavage
     - Cystathione $\rightarrow$ cysteine + alpha-ketobutyric acid

   GSH Formation

2. **Energy**
   - Niacin synthesis
   - Alpha-ketoglutarate formation

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Vitamin B6
Pyridoxal-5-Phosphate functional relationships

Cofactor Deficiency

- B2 Deficiency causes a decrease in activated B6 levels (P5P) which are needed for ATP dependent enzymes
- Magnesium cofactor with B6 (required for kinase enzymes that phosphorylate)
- Zinc Deficiency- Over 300 enzyme systems use Zn as cofactor
- Folate – source of Methyl group, which is needed for B12 methylation, which is cofactored by P5P
Vitamin B6 cont’d

Pyridoxal-5-Phosphate functional relationships

- B12 – Tends to be deficient in certain groups of people due to lack of methylation or absorption
  - Autistic
  - Elderly
  - B6 deficient people
  - Pernicious anemia
  - People with mild dementia
- B1 (Thiamine) the most difficult vitamin to be found in food
  - Needed for ATP formation/neurological function, and activation of B2
Vitamin B6 cont’d

Pyridoxal-5-Phosphate functional relationships

– Glutathione –
  • needs P5P for synthesis/GSH also needed for reduction reactions
  • GSH needed for reduction reactions and detoxification of metals
  • Anti-oxidation (neutralizing chemical that is reconstituted by Vit C, Vit E
Vitamin B6

Elevated amino acids can be a sign that there is an increased demand for Pyridoxal-5-Phosphate, which is needed for these amino acids to be utilized in protein synthesis.

- alanine, aspartate, glycine (only if very high), serine, tyrosine, valine, leucine, isoleucine, homocysteine, cystathione, alpha-aminoadipic acid, aminoisobutyric acid, methionine, threonine, GABA, glutamine, ornithine, alpha-amino-N-butyric acid, beta-alanine
Vitamin B6

- Metallothionein contains a high quantity of the amino acid, Cysteine.
- Vitamin B6 deficiency could compromise the ability to synthesize Metallothionein (Zn driven), thus compromising the body’s ability to excrete excess metals (Copper, Mercury), particularly in the brain where the tertiary structure of Mt is found in the greatest concentration.
Vitamin B6

• Interrelationships will influence the product synthesis.
  – Coenzyme Q10\(\Rightarrow\) Will be deficient secondary to P5P deficiency. Without CoQ10, there is less cellular energy produced and decreasing range of P5P activity
  – State of Stress – Increased Cortisol reduces effectiveness of P5P
  – Polymorphism
    • Affect activation\(\Rightarrow\) limits enzyme’s effectiveness
    • Change the effects of deficiencies (Folate) \text{ex:} Uracil misincorporation
    • Antioxidant Status (positive and negative)
    • Detoxification of Nutrients secondary to toxin induced detoxification enzymes
      » Phytonutrients
      » Vitamins
      » Glutathione S-transferase (needs P5P)
Vitamin B6

• Elevated B6 – due to inactivated form will result in low blood levels of enzymatic products.
• Elevated B6 can be caused by the following:
  – Magnesium deficiency
  – Increased B2 deficiency (activates B6)
  – Increased B1 deficiency
  – Increased Glucocorticoid effect
  – Polymorphism preventing activation and utilization
  – Abnormally low mitochondria ATP output
  – Phosphorous deficiency (Calcium induced)
Secondary deficiencies due to B6 deficiency

B6 deficiency = antioxidant deficiency

- **Taurine**
  - Low blood levels of Taurine are most dependable indicators of P5P deficiency
  - Very low levels of Taurine = very low levels of P5P
- **Histamine**
- **CoQ10/Vit E (Gamma E)**
- Decreased Glutathione Production
- Decreased GSH effectiveness 2nd to Decreased Vit
- Decreased Vit E (Tocopherol)
Secondary deficiencies due to B6 deficiency cont’d

- **Concomitant Folic Acid deficiency causes Histidine deficiency**
  - which creates increased requirement for Histidine. B6 def causes unusual utilization of Histidine to be converted to Histamine

- **Niacin**

- **Oxygen binding** (decreases affinity of O2 in heme molecule)

- **Decreased blood levels of Amino Acids**
  - Secondary to P5P
  - Contrasted with increased blood levels of Amino Acids secondary to P5P def.
Taurine

**Protector of Cell Integrity**

- Taurine is an amino-sulfonic acid. Unlike other amino acids it is abundant in its free form and is incorporated into proteins. Except for Glutamine, Taurine is present in greater intracellular concentrations than all other amino acids.
- Taurine functions as protector of CNS functions by opposing Glutamate release
- Taurine protects from cardiac arrhythmia by decreasing intracellular Calcium release
- Taurine protects the mitochondria during surgery
Functions of Taurine

1. Inhibits inflammation; antioxidant.
2. Inactivates HClO-hypochlorite.
3. Stimulates cellular immune systems.
4. Stimulates absorption of fat soluble vitamins such as vit A, D, E, and K.
5. Helps control cellular levels of minerals such as K+, Na+, and Ca.
6. Inhibitory neurotransmitters.
Taurine

Taurine Protective Functions

1. Modulates *cation flux*, especially for calcium by its ability to sequester membrane calcium during depletion of electrolytes.

2. It acts as an *oxidant scavenger* due to its amino group, which reacts with hypochlorous acids to form nontoxic monochlorotaurine. Taurine (due to its anti-glutamate activity) was administered as a preoperative rapid intravenous infusion prior to human myocardial revascularization and significantly decreased the percentage of damaged mitochondria in the cardiac muscle and the brain.

3. Taurine is a *neuromodulator* indirectly depressing neuroexcitation through its control over glutamate. It mediates contractility in the cardiac muscle, and decreases aggregation sensitivity (platelet clumping).
Intervention
Intervention

• Intervention can be focused in three areas:

  – Remove Toxins
  – Regenerate dysfunctional systems
  – Compensate for Genetically altered pathways

I will spend most of my time talking about the last one
Intervention

• Symptom Driven Intervention
  – Patients present to the office with a set of signs and symptoms which when put together with a history compatible with the classification of autism and suggests the abnormal pathways associated with the biochemical fingerprint of Autism.
Case Presentation

NF

- 5 year old CM- previously DX Asperger’s
- Slow development beginning at about 18 mo.
- Craves Pork
- Eats fairly healthy meals w/ supplemental Multi-vit
- Social-
  - would answer only when spoken to
  - Little interaction
  - Now he initiates interaction
  - Reads at the 3 rd grade level (still in kindergarten)
  - Still has sensory problems –Intolerant of skin creams
Case Presentation cont’d

Initial blood levels

- CoQ 10 .5 Low
- Cysteine 2.6 Low
- Sulfate 2.9 Low
- GlutConjugation 5.5 Low
- Sulfation 3 Extremely Low
- G Tocopherol .9 Low
- Selenium 120 Normal
Case Presentation Cont’d

• Homocysteine <2 Low
• Creatinine .5 Low
• CO2 22 Low
• Pantothenic Acid 10,180 Marked elevation
  » Normal Range 200-1,800 ng/ml
## Levels of Coenzymes & Amino Acids

<table>
<thead>
<tr>
<th>Pt.</th>
<th>B6 3.3-26 ng/ml</th>
<th>B2 6.2-39 nmol/l</th>
<th>Tauri 54-210 umol/l</th>
<th>Histi. 72-124 Umol/l</th>
<th>CoQ10 0.8-2.5 mg/l</th>
<th>Homocy 5.4-11.9 um/l</th>
<th>CO2 21-33 mmol/l</th>
<th>Folate &gt;5.4 Ng/ml</th>
<th>B-12 200-1100 Pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 2nd FU</td>
<td>225.0</td>
<td>23.9</td>
<td>32</td>
<td>66</td>
<td>.8</td>
<td>8.0</td>
<td>27</td>
<td>9.9</td>
<td>973</td>
</tr>
<tr>
<td>F</td>
<td>Pantthenic Acid 200 - 1,800 ng/ml 12,700</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>11.0</td>
<td>9.6</td>
<td>42</td>
<td>60</td>
<td>1.1</td>
<td>3.1</td>
<td>22.0</td>
<td>&gt;24</td>
<td>1398</td>
</tr>
</tbody>
</table>

S Niacin = 3.9 (4.3-7.4 range)  F Normal Niacin

*supplements*^39^  

P5P necessary coenzyme for 1st step of CoQ10 synthesis

---

Dr. M. Nicholas Martin  
Autism Society of the Bluegrass
## FR Family

<table>
<thead>
<tr>
<th></th>
<th>B6 3.3-26 ng/ml</th>
<th>B2 6.2-39 nmol/l</th>
<th>Tauri. 54-210 umol/l</th>
<th>Histi. 72-124 Umol/l</th>
<th>CoQ10 0.8-2.5 mg/l</th>
<th>Homoc 5.4-11.9 um/l</th>
<th>CO2 21-33 Mmol/L</th>
<th>Folate &gt;5.4 Ng/ml</th>
<th>B-12 200-1100 Pg/ml</th>
<th>Pantotenic acid Ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K</strong></td>
<td>118.5</td>
<td>45.4</td>
<td>34</td>
<td>56</td>
<td>1.2</td>
<td>2.9</td>
<td>22</td>
<td>&gt;24</td>
<td>908</td>
<td>11500</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>103.0</td>
<td>19.3</td>
<td>22.0</td>
<td>52.0</td>
<td>.5</td>
<td>&lt;2.0</td>
<td>22.0</td>
<td>16.4</td>
<td>1166</td>
<td>10180</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>12.1</td>
<td>18.6</td>
<td>22.0</td>
<td>54.0</td>
<td>.57</td>
<td>&lt;2.0</td>
<td>16.0</td>
<td>15.6</td>
<td>1374</td>
<td></td>
</tr>
</tbody>
</table>
Pathways that show polymorphisms

- Methionine
- Protein synthesis
- Creatine synthesis
- Methylation of DNA, RNA, histones, membrane phospholipids

DNA synthesis
- dNTPs
- THF
- 5,10 CH₂ THF
- Me-B12
- BHMT
- Folinic Acid
- B6

Supplementation:
- 800 µg folinic acid, b.i.d.
- 1000 mg betaine, b.i.d.
- 75 µg/Kg methyl-B12

From S. Jill James

(Cystathione B-Synthetase Vit B6 dependent)

Transsulfuration Pathway

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
## Vitamin B6

Levels of Coenzymes & Amino Acids in Autistic Children

<table>
<thead>
<tr>
<th>Pt</th>
<th>B6 3.3-26 ng/ml</th>
<th>B2 6.2-39 nmol/l</th>
<th>Tauri. 54-210 umol/l</th>
<th>Histi. 72-124 Umol/l</th>
<th>CoQ10 0.8-2.5 mg/l</th>
<th>Beta Alanine 0-7 Umol/L</th>
<th>B-12 200-1100 Pg/ml</th>
<th>Homocys 5.4-11.9 um/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89.8</td>
<td>11.7</td>
<td>36</td>
<td>32</td>
<td>0.8</td>
<td>8</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4.3</td>
<td>5.1</td>
<td>28</td>
<td>66</td>
<td>0.9</td>
<td>8</td>
<td>473</td>
<td>8.9</td>
</tr>
<tr>
<td>3</td>
<td>37.7</td>
<td>8.9</td>
<td>30</td>
<td>66</td>
<td>0.9</td>
<td>32</td>
<td>769</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>229.0</td>
<td>60.2</td>
<td>82*</td>
<td>70</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10.6</td>
<td>40</td>
<td>46</td>
<td>1.0</td>
<td>16</td>
<td></td>
<td>2000</td>
<td></td>
</tr>
</tbody>
</table>

* Taurine supplementation

P5P necessary coenzyme for 1st step of CoQ10 synthesis
Elevated B6/Inactive B6
Results from Dr. Vogelaar

Distribution of vitamin B6 in autistic children with (+S) or without (-S) supplementation

Number of children
Metabolic Pathways to Influence

• Many factors influence mitochondrial function prior to a mutation. Nutritional deficiency with associated decreased mitochondrial ATP production is the primary cause of mitochondrial dysfunction. Toxin exposure that depletes nutrients often results in mitochondrial damage after a period of decreased energy output.
Monitor your BMP by evaluating your CO2/lactic acid for signs of mitochondrial function decline and thus reduced ATP output.

Source: Mitochondrial Structure and Function: Morgan R. McKeller, Biol, 4410, Perez, John

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Metabolism

Coenzymes for Energy Formation
Thiamine, Riboflavin, and Niacin
Alpha Lipoate
Pantothenic Acid

Electron Transport & Oxidative Phosphorylation

Krebs Cycle – Mitochondria (Plasma)

Glycolytic Pathway (Glucose Metabolism)

Pyruvic Acid

Krebs cycle in mitochondrial plasma

Synthesis Vitamins
B1
B2
B6
B12
B9 (Folic Acid)
Biotin

Cofactors
Iron
Manganese
Magnesium

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Metabolism

Kreb’s Cycle
(Mitochondrial Cavity)
Mitochondrial Activity

(B-3)NADH
(B-2)FADH₂
Electron Transport Chain

The Cristae of the Mitochondrial Inner Membrane

ATP’s x 6

Electron Transport Chain for Extraction of Energy from H⁺

Electron Transport chain on Cristae membrane

NADH and FADH₂ form Kreb’s cycle

Electron transport chain pumps H⁺ out of matrix

Large electrochemical proton gradient drives ATP synthase to synthesize ATP

University of Texas Medical Branch,
Cell Biology Graduate Program: Mitochondrial Substructure

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Urea Cycle

- **Guanidinoacetate**
- **SAM**
- **Creatinine**
- **Creatine-P**
- **ORNITHINE**
- **ARGININE**
- **CITRULLINE**
- **ARGINOSUCCINATE**
- **ATP**
- **ADP**

Methionine:
- Over 70% of Methylation goes to Creatinine synthesis
- OTC (Ornithine Transcarbamylase)

Arginine & Uracil exert negative feedback

- Carbamoyl phosphate
- Pi
- Urea
- NH4 or Glutamine

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Vitamin B6

Clinical manifestations which show demand for Vitamin B6

Neurological Diseases

- Peripheral neuritis can result from both B6 def and elevated inactive B6
- Seizure → severe B6 def (Infants most severe)
  - Severe Taurine deficiency will result in status epilepticus in infants
Vitamin B6

Clinical Manifestations…cont’d

Stress Reaction

– Physiological response leads to increased insulin which increases Cortisol which decreases the level of activated B6(P5P). Cortisone receptor sensitivity is decreased which lessens the effects of stress. A dose of 300-400mg of P5P is suggested to desensitize the receptors.

– Increased sugar intake results in increased insulin-hypoglycemia increases Cortisol

– Increased intake of activated B6 (P5P) can desensitize receptors
### Vitamin B6

**Stabilizing Cellular Function for Metal Toxic Cells**

Immediate stabilization fast IV push Glutathione accompanied by daily supplementation with fortified Liposomal Glutathione Complex (includes above ingredients) *SJ James et al, 2005. RC Shoemaker, 2001*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Deficiency</th>
<th>Replacement</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylation</td>
<td>Tetrahydrofolate</td>
<td>Tetrahydrofolate/Folinic acid P5P</td>
<td>Stimulates enzymes by increasing concentration of substrates, cofactors</td>
</tr>
<tr>
<td>Deficiency</td>
<td>Folinic acid</td>
<td>Folinic acid</td>
<td>Supplements activate P5P for Glutathione</td>
</tr>
<tr>
<td></td>
<td>Cobalamin/Methylcobalamin</td>
<td>Cobalamin</td>
<td></td>
</tr>
<tr>
<td>Sulfuration</td>
<td>Homocysteine</td>
<td>Methionine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methionine</td>
<td>N-Acetyl Cysteine</td>
<td></td>
</tr>
</tbody>
</table>

**Deficiency**
- Tetrahydrofolate
- Folinic acid
- Cobalamin/Methylcobalamin
- Homocysteine
- Methionine
- N-Acetyl Cysteine

**Replacement**
- Tetrahydrofolate/Folinic acid P5P
- (Betaine) TMG Methylcobalamin
- Methionine P5P
- Replace or add Betaine, MeB12, Folinic acid and P5P
- Replace, add P5P

**Treatment**
- Cofactors
- Coenzymes

**Outcome of Treatment:** Activated enzymes, increased cofactors ➔ decreased toxins, increased substrates for biochemical needs.
Pathways that show polymorphisms

**DNA synthesis**
- THF
- 5,10 CH₂ THF
- Me-B12
- B6

**Protein synthesis**
- SAM
- MTase

**Creatine synthesis**
- Methylation of DNA, RNA, histones, membrane phospholipids

**Methylation of DNA, RNA, histones, membrane phospholipids**
- SAHH
- Homocysteine
- Homoserine
- B6
- Cystathionine
- Cysteine
- Glutathione

**Supplementation:**
- 800 µg folinic acid, b.i.d.
- 1000 mg betaine, b.i.d.
- 75 µg/Kg methyl-B12

From S. Jill James

Dr. M. Nicholas Martin
Autism Society of the Bluegrass

800 µg folinic acid, b.i.d.
1000 mg betaine, b.i.d.
75 µg/Kg methyl-B12

**Pathways that show polymorphisms**

**DNA synthesis**
- THF
- 5,10 CH₂ THF
- Me-B12
- B6

**Protein synthesis**
- SAM
- MTase

**Creatine synthesis**
- Methylation of DNA, RNA, histones, membrane phospholipids

**Methylation of DNA, RNA, histones, membrane phospholipids**
- SAHH
- Homocysteine
- Homoserine
- B6
- Cystathionine
- Cysteine
- Glutathione

**Supplementation:**
- 800 µg folinic acid, b.i.d.
- 1000 mg betaine, b.i.d.
- 75 µg/Kg methyl-B12

From S. Jill James

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Interventions

N-Acetyl Cysteine

Precursor to Glutathione

Component of Pantothenic Acid (Provides the sulfur group)
**Intervention for Autism**

**RX**

- Enzyme activation through treatment with coenzymes
  - Increase Methylation
  - Increase Sulfuration
  - Increase MSM

- Understand genetic defects by understanding enzyme deficiencies due to inactivation secondary to increased Km

- Correct major biochemical deficiencies found in autistic spectrum disorder

- Eliminate mercury if possible with zinc/selenium.
  - Chelation can be as simple as taking Selenium with a fatty meal or transdermal DMSA
  - Increase MT function by:
    - Decreasing Cu, toxic metals
    - Increase immune system function
    - Maintain healthy Gl tract
    - Decrease food sensitivities
    - Increase zinc, GSH
    - Increase selenium (works as natural chelator)
    - Increase P-5-P, Vit C, Vit E, B1, B2, NAC
    - Consume high quality protein, low casein whey

- Eliminate activation of neurodegeneration by balancing Omega III: Omega VI, IX and increasing antioxidants

- Urocholine Stimulates verbal expression and interest in reading
  - Selegiline, Natural Protector
  - (Stimulates brain after good physiological balance has been achieved)

- Eat high quality Protein and preload with zinc to increase MT to remove Mercury
  - Chelation (Natural with GSH, Selenium, or use DMSA)*
    - Methyl B-12, folic acid, Vit A
    - GSH, DMSA/DMPS (powerful Antioxidants and Chelators)

*Do not chelate with increased levels blood cystine → causes renal failure
Intervention

NEURO-PROTECTORS
1. Selegeline
2. Testosterone
3. Gamma E/Delta E
   • ↓ By alpha tocopherol
   • ↓ By B6 def
4. Melatonin*
   • Glutathione – Vits C & E*
   • ↓ By B6 Def
5. Phytochemicals
6. Omega III, IV, VI
7. Enzymes
8. NADH, Pyruvate
   • ↓ By B6 Def
9. Xanthones from plants of the Garcinia Genus Mangostana, Calophyllum inophyllum, or Mesua Ferrera
10. Pyridoxal-5-Phosphate

TOXIN REMOVAL
1. Cholestyrine (binds w/ Toxins)
2. D- Glutarate
3. Milk Thistle
4. Chelation
5. Glutathione* (also protector)
   • ↓ By B6 Def
6. DMPS

NEURO-REGENERATION
1. Tianeptine (SSRI)
2. Lithium
3. Depakote
4. Pregnenolone
5. SSRI
   • ↓ By B6 Def
6. Melatonin*
7. Glutathione* (3rd Function)
   • ↓ By B6 Def
8. HGH
9. Progesterone
10. Folate
ANTIOXIDANT FUNCTION OF GLUTATHIONE

Major intracellular antioxidant: $\text{H}_2\text{O}_2$, superoxide, hydroxyl radical, peroxynitrite, membrane lipid peroxidation

From: Jill James
Chemical Imbalances in Autism Leading to Low Glutathione

Related Metabolic Disorders/causes of Glutathione Inadaquacy

1. Methylation Disorder
2. Sulfuration Disorder
3. Metal-Metabolism Disorder
4. Pyrrole Disorder (occurs in 10% of certain populations)
5. Malabsorption
6. Toxic Overloads
7. Essential Fatty Acid Imbalances
8. Abnormal Levels of Neurotransmitter Precursors

Walsh, Usman, Tarpey, Kelly. 2002
Kryptopyrrol, Vitamin B6 and Zinc:

Dr. E. F. Vogelaar
Anti-Oxidant/Anti-Toxic Metals
Mercury Toxicity and Autism
Shared Characteristics

1. Psychiatric
2. Speech
3. Language
4. Sensory
5. Motor Disorders
6. Cognitive Impairment
7. OCD
8. Abnormal Biochemistry
   ➢ Lack of Methylation
   ➢ Low Sulfate
   ➢ Low Glutathione

Glutathione

REGENERATION OF GLUTATHIONE: IMPORTANT FOR TOTAL ANTIOXIDANT CAPACITY

From S. Jill James

* Supplement with the Gamma, Delta, Beta, Alpha to prevent depletion of Gamma, Delta which will occur if supplementation is only alpha tocopherol in doses greater than 400 IUs.
Intervention

Antioxidant Function of Glutathione (GSH)

• Low GSH has been demonstrated in neurodegenerative Diseases
  *The Lancet 344: 796-798, 1994*

• GSH Levels were dramatically reduced in Parkinson’s Disease
  *Jenner et al*

• Alzheimer’s-type dementia in Down’s Syndrome is related to GSH depletion and elevated levels of SOD
  *Jenner et al*

• In Alzheimer’s patients GSH was found to be lower in the hippocampus (the primary site of short-term memory)
  *Glutathione: Systemic Protectant Against Oxidative and Free Radical Damage Parris M. Kidd PH.D.*
OVERVIEW

Adequate
- Nutrition
- Coenzymes/Vitamins
- Cofactors/Minerals
- DNA/Membranes/Mit
- Energy
- GSH
- Detoxification
- Hormones
- Oxygen
- Antioxidant
- Immunity
- Biochemical

Low Presence of:
- Toxins/Metals
- No Metabolic Syndrome
- Stress
- Replicating Organisms
- Sedentary lifestyle
- T.V. watching
- Poor Diet

Long Life Genetics
- Apo E2/E3 (No polymorphisms)
- Good Reparative Genes
- Better Detoxification
- Less Inflammation
- Less Obesity
- Health Positive Polymorphisms

Inadequate
- Coenzymes/Vitamins
- Cofactors/Minerals
- Energy
- GSH
- Detoxification
- Metals
- Chemicals
- Hormones
- Oxygen
- Antioxidants
- Immunity
- Biochemical

Increased Environmental
- Increased Toxins
- Chemical Metas
- Increased Stress
- Increased Replication
- Induced sedentary activity
- Toxic Diet
- Toxic Workplace

Compromised Genetics
- Apo E4/E3
- Poor reparative Genes
- Mutations – Neg. Polymorphisms
- Genetics of Syndrome X
- Increased Metabolic toxins
- Reduced Detoxification Capacity
- Increased Inflammation
- More Obesity

Dr. M. Nicholas Martin
Autism Society of the Bluegrass
Thank You!

Dr. Nicholas Martin