Preventing brain injury in GA-1: Lessons from mice

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Professor of Pediatrics
Director, CDRC Metabolic Clinic
Goals

• Biochemistry and Pathophysiology 101
• Clinical Symptoms
• Treatment and Rationale
• Lessons from Mice:
  – Mechanisms of injury
  – Diet therapy
  – Gene and Cell Therapy
Goals
GA-1: Glutaric Acidemia Type I

- Autosomal recessive disorder of metabolism
- Loss of Glutaryl-CoA dehydrogenase
- Elevated glutaric and 3-OH glutaric acid
  - Blood, Urine, and Cerebrospinal fluid / Brain
- Identified by newborn screening
Clinical Symptoms

- Delayed Motor Development
Development of Motor Milestones

- walking alone
- standing alone
- walking with assistance
- hands-and-knees crawling
- standing with assistance
- sitting without support

Age (months)
Clinical Symptoms

- Delayed Motor Development
- Hypotonia / Dystonia
Dystonia: Opisthotonos
Clinical Symptoms

• Delayed Motor Development
• Hypotonia / Dystonia
• Striatal (basal ganglia) injury
Brain MRI following an acute striatal injury

*axial*  

*coronal*
Clinical Symptoms

• Delayed Motor Development
• Hypotonia / Dystonia
• Striatal (basal ganglia) injury
• Learning Impairments ?
Treatment

• Reduce Lysine intake
  – Decrease production of GA and 3OHLGA

• Lysine restriction vs. protein restriction?
## Lysine Content of Foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Lysine content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>9</td>
</tr>
<tr>
<td>Meat and meat products</td>
<td>8</td>
</tr>
<tr>
<td>Breast milk</td>
<td>8</td>
</tr>
<tr>
<td>Cow’s milk, milk products</td>
<td>7</td>
</tr>
<tr>
<td>Eggs (whole)</td>
<td>6</td>
</tr>
<tr>
<td>Potatoes</td>
<td>6</td>
</tr>
<tr>
<td>Soy and soy products</td>
<td>6</td>
</tr>
<tr>
<td>Nuts</td>
<td>2–8.5</td>
</tr>
<tr>
<td>Vegetables</td>
<td>4–6.5</td>
</tr>
<tr>
<td>Fruit</td>
<td>2–6.5</td>
</tr>
<tr>
<td>Cereals and cereal products</td>
<td>2–4</td>
</tr>
</tbody>
</table>
Treatment

- **Reduce Lysine intake**
  - Decrease production of GA and 3OHGA

- **Lysine restriction vs. protein restriction**
  - Protein restriction can cause nutritional deficiencies

- **Tryptophan deficiency lowers brain serotonin**
  - Depression
  - Sleep disturbances
Treatment

• Carnitine
  – Avoid carnitine deficiency
  – Increase GA and 3OHGA excretion
  – Avoid depletion of Acetyl-CoA
Treatment During Illness

• Goal: Prevent acute brain injury

• Stop protein intake
  – Reduce availability of lysine for GA and 3OHGA

• IV glucose infusion
  – Suppress catabolism = breakdown of protein

• IV Carnitine
Long Term Therapy?

• Is there a benefit of dietary treatment after age 6

• There is evidence of chronic neurologic deterioration in patients with no documented metabolic crisis

• Case reports suggest a potential benefit, therefore it may be advisable to continue dietary treatment, using a relaxed protocol
Lessons from GA-1 Mice

• Biochemically similar to human patients
• Mild motor impairment
• No dystonia or striatal necrosis on normal diet
• Brain injury can be induced by high lysine intake
Research Question

• Is the neurologic damage in GA-1 due to circulating glutaric and 3-hydroxyglutaric acids or a lack of brain GCDH activity?

• Do GA and 3-OHGA enter the brain from the blood?
Experiment

- Use gene therapy to correct the liver of GA-1 mice
- Compare the levels of GA and 3-OHGA
Conclusion

- Gene therapy and other studies in GA-1 mice indicate that the elevated GA and 3-OHGA in the brain are not imported from the blood.
Research Question

• Can brain production of GA and 3-OHGA be reduced?

• Can brain lysine be reduced?
Low Lysine Diet

Glutaric Acid Levels
Transport into the Brain: The Blood Brain Barrier
Uptake of Lysine by the Brain

Blood

Amino Acid Transporter

Brain
Uptake of Lysine by the Brain
Low Lysine Diet + Arginine

Glutaric Acid Levels
Summary of Studies in GA-1mice

- Brain GA and 3-OHGA result from brain lysine metabolism
- A low lysine diet reduces brain GA and 3OHGA
- Low Lysine diet + arginine work synergistically
- Reduction of cerebral lysine uptake with either arginine or homoarginine protects mice from the brain injury associated with a high lysine diet
- The use of IV glucose further improves the effects of arginine or homoarginine on lysine toxicity
So Now What?
Safety, efficacy and physiological actions of a lysine-free, arginine-rich formula to treat glutaryl-CoA dehydrogenase deficiency: Focus on cerebral amino acid influx

Kevin A. Strauss a,b,c,*, Joan Brumbaugh b,1, Alana Duffy d, Bridget Wardley d,e,1, Donna Robinson a, Christine Hendrickson a, Silvia Tortorelli f, Ann B. Moser g, Erik G. Puffenberger a,b,c, Nicholas L. Rider a,c, D. Holmes Morton a,b,c

Complementary dietary treatment using lysine-free, arginine-fortified amino acid supplements in glutaric aciduria type I – A decade of experience

Stefan Kölker a,*, S.P. Nikolas Boy a, Jana Herlinger a, Edith Müller a, Esther M. Maier b, Regina Ensenauer b, Chris Mühlhausen c, Andrea Schlune d, Cheryl R. Greenberg e, David M. Koeller f,g, Georg F. Hoffmann a, Gisela Haege a,1, Peter Burgard a,1
Lysine and Arginine Content of Formulas

<table>
<thead>
<tr>
<th>Company</th>
<th>Applied Nutrition Corporation</th>
<th>Nutricia GmbH</th>
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<th>Nutricia GmbH</th>
<th>Milupa Metabolics GmbH</th>
<th>Milupa Metabolics GmbH</th>
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</thead>
<tbody>
<tr>
<td>Product name</td>
<td>GlutarAde Junior GA-1 drink mix</td>
<td>LT-AM infant</td>
<td>LT-AM 1</td>
<td>LT-AM 2</td>
<td>GA 1</td>
<td>GA 2 prima</td>
</tr>
<tr>
<td>Lysine</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>Tryptophan</td>
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<td>Arginine</td>
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<td>49</td>
<td>59</td>
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<td>Threonine</td>
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<tr>
<td>Tyrosine</td>
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<tr>
<td>Valine</td>
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<td>Alanine</td>
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<td>63</td>
<td>50</td>
<td>58</td>
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<tr>
<td>Aspartate</td>
<td>n. d.</td>
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<td>121</td>
<td>155</td>
<td>118</td>
<td>144</td>
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<tr>
<td>Glutamate + glutamine</td>
<td>150</td>
<td>102</td>
<td>213</td>
<td>225</td>
<td>252</td>
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<tr>
<td>Glycine</td>
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<td>81</td>
<td>31</td>
<td>56</td>
<td>30</td>
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<tr>
<td>Proline</td>
<td>n. d.</td>
<td>98</td>
<td>117</td>
<td>104</td>
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<tr>
<td>Serine</td>
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<td>61</td>
<td>60</td>
<td>65</td>
<td>62</td>
<td>76</td>
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### Table 1
Amino acid content (in mg per g protein) in lysine-free amino acid supplements fortified with amino acids, minerals, trace elements, and vitamins.

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<td>52</td>
</tr>
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### AAS group
- **MILUPA GA series**
- **SHS LT series**
Future Therapies:

• Need to confirm that studies in the $Gcdh^{-/-}$ mice are a true characterization of what happens in patients with GA-1

• New formulas with increased arginine / ornithine?

• Arginine or homoarginine during acute illness?

• Brain specific gene and cell therapies?
5th International Workshop on Glutaric Acidemia Type I

San Diego, September 3rd, 2009
Thank You