The Path From Hormone Abnormality to Hypoglycemia

Linda J. Steinkrauss, MSN, CPNP
Pediatric Endocrinology

Conflicts of Interest

• None

Objectives

• Discuss the human body systems required for normal fasting adaptation.
• Describe how hormone abnormalities can lead to hypoglycemia.
• Discuss case studies of infants and children with hypoglycemia and determine which hormone excess or deficiency could be implicated as a cause of hypoglycemia.
Body and Brain need a constant source of fuel

Glucose

Glucose and the Adult Brain
- Glucose = main fuel for the body and brain
- At rest, 60% of glucose is used by the brain
- Glucose Utilization Rate = ~2mg/kg/min
- Glucose from food = 3 hours
- Then, fasting adaptation is required
- Fasting time to hypoglycemia = ~48 hours
Glucose and the Infant Brain

- Infant brain
  - Brain:body mass
  - Glucose utilization
  - Fuel stores
- Comparison with Adults (10kg infant)
  - Fuel stores = 15% of adult
  - Caloric needs = 60% of adult
  - Glucose utilization = 2-3X faster
  - Glucose Utilization Rate = 4-6mg/kg/min
- Fasting time to hypoglycemia = 24+ hours


Older/Bigger = Fast Longer

Fasting Metabolites by Age – 20 hour fast

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>0-1</th>
<th>2-6</th>
<th>7-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>59</td>
<td>72</td>
<td>76</td>
</tr>
<tr>
<td>Beta-hydroxybutyrate (mmol/L)</td>
<td>2.23</td>
<td>1.19</td>
<td>0.62</td>
</tr>
</tbody>
</table>


Guideline for Fasting Time to Hypoglycemia

<table>
<thead>
<tr>
<th>Age</th>
<th>Hours Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>12</td>
</tr>
<tr>
<td>Infant</td>
<td>24</td>
</tr>
<tr>
<td>Child</td>
<td>36</td>
</tr>
<tr>
<td>Adult</td>
<td>48</td>
</tr>
</tbody>
</table>
Normal Fasting Adaptation

Fasting Fuel Production
- Gluconeogenesis
- Glycogenolysis
- Lipolysis/Fatty Acid Oxidation/Ketogenesis

Fasting Systems in Normal Child
Gluconeogenesis

- The creation of glucose in the body from non-carbohydrate substrates
- Not a significant source of glucose production

Fasting Systems in Normal Child

Slide borrowed with permission from Charles A. Stanley, MD.
Gluconeogenesis

Muscle ➔ Lactate ➔ Glucose

Fat ➔ Glycerol ➔ Glucose

Protein ➔ Amino acids ➔ Glucose

Substrates


Glycogenolysis

• Breakdown of glycogen to glucose in the liver
• Main source of fuel in the early hours of fasting

Glycogen ➔ Glucose-6-phosphate ➔ Glucose


Lipolysis, Fatty Acid Oxidation, and Ketogenesis

• Fat breakdown and ketone production
• Ketones = alternate fuel
• Main source of fuel later in fasting
• Ketogenic diet
• Atkins diet
Summary

- Three main mechanisms the body has for producing fuel in the fasting state:
  - Gluconeogenesis
  - Glycogenolysis
  - Lipolysis/Fatty Acid Oxidation/Ketogenesis

Hormones and Hypoglycemia

What hormones (in excess or deficient amounts) cause hypoglycemia?

- Insulin
- Glucagon
- Epinephrine
- Cortisol
- Growth Hormone
Hormonal Control of Fasting Systems

<table>
<thead>
<tr>
<th></th>
<th>Glycogenolysis</th>
<th>Gluconeogenesis</th>
<th>Lipolysis</th>
<th>Fatty Acid Oxidation/Ketogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glucagon</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cortisol</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Growth Hormone</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>


Insulin
- Insulin ↑ BG levels by transporting glucose molecules into the cells and out of the blood stream
- Insulin inhibits all parts of fasting adaptation
- Eat food = ↑ Glucose = ↑ Insulin = inhibition of fasting systems


Hyperinsulinized State
- Excess exogenous insulin – diabetes
- Excess endogenous insulin – congenital hyperinsulinism (HI)
- Fasting systems are inhibited by insulin when they are really needed

- Treatment
  - Diabetes – administer carbohydrate, glucagon
  - Congenital HI – medication, surgery, continuous dextrose, glucagon
Glucagon
- Hormone released by alpha cells in the pancreas
- Stimulates glycogenolysis and gluconeogenesis
- Glucose = Glucagon

Glucagon Deficiency
- Leads to hypoglycemia
- Isolated glucagon deficiency is very rare
- Other causes:
  - Pancreatectomy
  - T1DM
  - Advanced T2DM
- Treatment?

Epinephrine
- Hormone secreted from adrenal medulla
- Released during stress
- Epinephrine actions:
  - HR
  - Vasodilation of vessels to muscle and liver
  - Vasoconstriction of most other blood vessels
  - Stimulates all fasting systems


**Epinephrine**
During stress or fasting:
Epinephrine = Stimulation of Fasting Systems
Result = \( \uparrow \) Fuel

**Epinephrine Deficiency**
- Leads to hypoglycemia
- Deficiency is rare
- More common = Epinephrine is blocked
- What medications block Epinephrine?
  - Beta-blockers
  - atenolol
  - propranolol
  - nadolol
  - metoprolol
  - labetalol
  - timolol

**Epinephrine Blocked**
- Child on beta blocker
- Develops fasting ketotic hypoglycemia
- Treatment = decrease fasting time
Cortisol

- Produced by adrenal cortex
- Maintains homeostasis
  - Immune response
  - Anti-inflammatory action
  - BP
  - HR
  - CNS activation
- Another stress hormone
- Stimulates gluconeogenesis

Cortisol

During stress or fasting:

\[ \uparrow\text{Cortisol} = \text{Stimulation of Gluconeogenesis} \]

Result = \( \uparrow\text{Fuel} \)
**Cortisol Deficiency**
- Many causes
- Results in:
  - Inability to stimulate gluconeogenesis during fasting and stress
  - Fasting and stress-induced hypoglycemia
- Presentation
  - Neonates = hypoketotic hypoglycemia
  - Children = ketotic hypoglycemia
- Treatment
  - Replace cortisol
  - Shortened fasting time


**Growth Hormone**
- Pituitary hormone
  - Growth factor release
  - Long bone growth
- Various additional functions
- Stimulates lipolysis
- Levels ↑ with fasting
  - Lipolysis
  - Ketogenesis


**Growth Hormone Deficiency**
- Leads to impaired lipolysis and ketogenesis and hypoglycemia
- Presentation
  - Neonates = hypoketotic hypoglycemia
  - Children = ketotic hypoglycemia
- Treatment – replace growth hormone
Case Studies

Case Study 1
- 6 year old male with 2 recent episodes of fasting hypoglycemia
  
  **Episode 1:**
  - Normal overnight fast – 12 hours
  - Difficult to arouse in the morning
  - Floppy, crying
  - No illness
  - Parents called 911
  - Glucose in ED was 42mg/dL (2.3mmol/L)
  - Large ketonuria
  - BG rose with juice and child discharged

**Case Study 1**
- **Episode 2**
  - Slightly longer overnight fast - ~15 hours
  - Very irritable, sleepy, lethargic in the morning
  - Parents tried to give juice and brought to ED
  - Glucose = 55mg/dL (3.05mmol/L)
  - Large Ketonuria
  - CO₂ = 15 mmol/L (18-28)
  - GH = 11 mg/mL (>10)
  - Cortisol = 25 mcg/dL (>18)
  - BG rose with IV dextrose and child discharged and referred to Endocrinology
Case Study 1

- Remembering he is 6, what do you think of his fasting duration? (12-15 hours)
  Short

- What do you think about his:
  - Ketonuria? (Large)
  - GH? (11 mg/mL)
  - Cortisol? (25 mcg/dL)
  Hypoglycemia not from excess insulin or GH/Cortisol deficiency

Case Study 1

- Endocrinology Clinic
  - No previous symptoms of hypoglycemia
  - Growth and development normal
  - FH: No hypoglycemia
    Father with prolonged QT syndrome
  - ROS: Child recently diagnosed with prolonged QT syndrome and started on atenolol
  - PE: Unremarkable

Case Study 1

- Why did he have low glucose levels?
  - Beta blocker = blocked epinephrine = impaired fasting adaptation = ketotic hypoglycemia
- How do we treat him?
  - Shorten fasting time
    - 10 hours when well
    - 5 hours when ill
- How long should he be able to fast at 6 years?
  - 36 hours

- Remembering he is 6, what do you think of his fasting duration? (12-15 hours)
  Short

- What do you think about his:
  - Ketonuria? (Large)
  - GH? (11 mg/mL)
  - Cortisol? (25 mcg/dL)
  Hypoglycemia not from excess insulin or GH/Cortisol deficiency
Case Study 2

- 3 week old male
  - Hyperbilirubinemia
  - Hypoglycemia
- Transferred to NICU from another hospital for evaluation and management of hypoglycemia
- Birth History: 38 weeks, 3047 grams - AGA, maternal PIH, Apgars 61 and 85, hypoglycemia measured shortly after birth

Case Study 2

- Hypoglycemia
  - Persistent since birth - 3 weeks
  - GIR = 10mg/kg/min
  - Lowest glucose = 38mg/dL on DOL 11

- What do you think about his GIR?
  - Too high – normal max is ~6mg/kg/min
  - Indicates organic hypoglycemia disorder

Case Study 2

<table>
<thead>
<tr>
<th>Critical sample</th>
<th>Result</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>37 mg/dL</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Insulin</td>
<td>&lt;1 uIU/mL</td>
<td>&lt;1</td>
</tr>
<tr>
<td>BOHB</td>
<td>0.32 mmol/L</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>FFA</td>
<td>0.39 mmol/L</td>
<td>&gt;2</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.3 mmol/L</td>
<td>0.5-1.6</td>
</tr>
<tr>
<td>Ammonia</td>
<td>24 umol/L</td>
<td>9-33</td>
</tr>
<tr>
<td>GH</td>
<td>5.96 ng/mL</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.3 mcg/dL</td>
<td>&gt;15</td>
</tr>
<tr>
<td>ACP</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine OA</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Glucagon Stim</td>
<td>&lt; 40</td>
<td>&lt; 25</td>
</tr>
</tbody>
</table>

Thoughts?
Case Study 2

Differential Diagnosis
- Congenital Hyperinsulinism
- Cortisol Deficiency
- GH Deficiency

• What should we do next?

Case Study 2

Pituitary Stimulation Testing

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>GH (ng/mL)</th>
<th>Cortisol (mcg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.01</td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>4.44</td>
<td>0.4</td>
</tr>
<tr>
<td>60</td>
<td>5.66</td>
<td>0.4</td>
</tr>
<tr>
<td>180</td>
<td>5.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Free T4 (0.8-11.6 mcg/dL)</th>
<th>0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total T4 (5-13 mcg/dL)</td>
<td>3.3</td>
</tr>
<tr>
<td>Total T3 (0.9-2.6 ng/mL)</td>
<td>1.1</td>
</tr>
<tr>
<td>TSH (0.57-19.5 mU/mL)</td>
<td>6.18</td>
</tr>
</tbody>
</table>

Case Study 2

Brain MRI:

Septo Optic Dysplasia:
- Absent septum pellucidum
- Optic nerve hypoplasia
- Ectopic posterior pituitary
- Hypoplastic pituitary stalk
Case Study 2

- **Diagnosis:**
  - Anterior Hypopituitarism
    - TSH
    - ACTH
    - GH

- **Treatment**
  - Thyroxine 44mcg daily
  - Hydrocortisone 12mg/m²/day – tid
  - Growth hormone 0.3mg/kg/week – daily

Case Study 2

- **Outcome**
  - Able to fast 8 hours with BGs all >80mg/dL
  - Discharged to home

Case Study 3

- 3 year old with SOD and Anterior Hypopituitarism
- Treated with thyroxine, hydrocortisone, and growth hormone
Case Study 3

- One night he started vomiting
- Parents gave oral stress hydrocortisone
- Continued with intermittent vomiting for several hours
- He became more lethargic
- Parents called Endocrinology doctor and were told to give him IM Solucortef and come to the ED
- Parents did not give Solucortef but came right to the ED

Case Study 3

- ED
  - Arrived with hypotension and tachycardia
  - Serum glucose 17mg/dL
  - Treated with IV glucose and hydrocortisone
  - Crisis resolved
  - Residual seizure disorder, learning disability, and food aversion that were not previously present

Questions?
That’s All, Folks

Thank you

THE GIRLS HAVE GONE WILD