Glycogen Synthesis

Chapter 25, Stryer Short Course

Glucose Metabolism Overview

- Gluconeogenesis
- Glycogen metabolism
- Pentose Phosphate Pathway

Glycogen

- Storage molecule
- Multiple ends allow for quick synthesis and degradation
- Glucose must be activated
Chemistry of Synthesis

• Step 1
  - Near equilibrium
  - The link to glucose-6-phosphate, our central molecule

Chemistry of Synthesis

• Step 2
  - Count high energy bonds
  - Pyrophosphatase – Common motif
  - UDP-glucose: activated for incorporation

Chemistry of Synthesis

• Step 3
  - Glycogen synthase
  - Growing end is non-reducing
  - Must be added to core
  - UDP released
Energetics of Synthesis

- Total cost: one ATP equivalent from G-6-p

Step 4: Branching

Overall Energetics

Glucose \rightarrow\text{glycogen costs 2 ATP per stored glucose}
Key Regulation Enzymes

Glucose-6-P → UTP → Glucose-6-P

Glycogen Synthase

Glycogen Phosphorylase

Compare/Contrast

- α = “usually active”
  - Favors R-state
- But in the synthase, α is dephosphorylated

Liver: Phosphorylated State

- Liver phosphorylase α “usually active”
- Turned off by [glucose]
- Liver glycogen synthase β “usually inactive”
- Turned on by [glucose-6-P]
Reciprocal Regulation

- Epinephrine turns on phosphorylase
  - PKA phosphorylation
- Epinephrine turns off glycogen synthase
  - PKA phosphorylation

Protein Phosphatase 1

- Opposite of PKA
  - Deactivates phosphorylase
  - Activates glycogen synthase
- Active in cell unless epinephrine signals PKA
  - PKA activates its inhibitors

Insulin stimulates glycogen synthesis

- Insulin blocks the “turn off” switch for glycogen synthase
- Allows PP1 to “turn on” glycogen synthase
Glucose stimulates glycogen synthesis

- Insulin is main stimulating signal
- Blood glucose level also controls glycogen
  - First, phosphorylase turned off
  - Then synthase turned on
  - No wasted overlap
  - Mechanism?

Phosphorylase a is Glucose Sensor

- Phosphorylase a (R state) binds and inactivates PP1
- When [glucose] up, PP1 is released and deactivates phosphorylase
- Only when all phosphorylase a has been inactivated is PP1 available to activate glycogen synthase

Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Defect's enzyme</th>
<th>Organ affected</th>
<th>Enzyme activity</th>
<th>Global effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>4A-phosphomannose isomerase</td>
<td>Liver, kidney</td>
<td>Decreased</td>
<td>Pulmonary stenosis, liver and kidney dysfunction</td>
</tr>
<tr>
<td>Type B</td>
<td>GAA deficiency</td>
<td>Muscle</td>
<td>Decreased</td>
<td>Muscle weakness, hypoketotic hypoglycemia</td>
</tr>
<tr>
<td>Type C</td>
<td>UGA deficiency</td>
<td>Muscle, liver</td>
<td>Decreased</td>
<td>Muscle weakness, hypoketotic hypoglycemia</td>
</tr>
<tr>
<td>Type D</td>
<td>6-glycerol-3-phosphate dehydrogenase</td>
<td>Muscle</td>
<td>Decreased</td>
<td>Muscle weakness, hypoketotic hypoglycemia</td>
</tr>
<tr>
<td>Type E</td>
<td>Phosphoglycerate mutase</td>
<td>Muscle</td>
<td>Decreased</td>
<td>Muscle weakness, hypoketotic hypoglycemia</td>
</tr>
</tbody>
</table>

Many disrupt glycogen breakdown in muscle and/or liver (hypoglycemia, enlarged liver, muscle cramps...)