Chapter 8

Overview

Metabolism - catabolic pathways that degrade organic molecules and release energy

Carbohydrate metabolism – central role as energy source for life processes

- Glycolysis – first step in glucose metabolism
- Citric acid cycle – cycle of reactions catalyzed by enzymes converting pyruvate to CO₂ & water to produce energy (ATP)
- Electron transport chain – electrons pass from one compound to another via redox reactions coupled with proton gradient creation
- Oxidative phosphorylation – formation of ATP
Chapter 8: Overview

- Energy transforming pathways - glycolysis, glycogenesis, glycogenolysis, gluconeogenesis, pentose phosphate pathway

Figure 8.2 Major Pathways in Carbohydrate Metabolism
Section 8.1: Glycolysis

- Anaerobic process occurs in almost every living cell
  - Glucose converted to fructose-1,6-bisphosphate producing two pyruvates

- Ten reactions in 2 stages:
  - Energy investment – 2 ATPs consumed creating substrates for oxidation
  - Energy producing – 4 ATP & 2 NADH produced
  - Catabolic process producing net 2 ATP and 2 NADH

- Summary equation:
  \[ \text{Glucose} + \ ADP + 2P_i + 2NAD^+ \rightarrow 2\text{pyruvate} + 2\text{ATP} + 2\text{NADH} + 2H^+ + 2H_2O \]
1. Synthesis of glucose-6-phosphate
   - Phosphorylation of glucose
     - Prevents export out of cell
     - Facilities binding to active site

2. Conversion of glucose-6-phosphate to fructose-6-phosphate
   - Conversion of aldose to ketose

3. Phosphorylation of fructose-6-phosphate
   - Irreversible, first committed step

4. Cleavage of fructose-1,6-bisphosphate
   - Aldol cleavage

5. Interconversion DHAP–G-3-P

Section 8.1: Reactions of the Glycolytic Pathway

6. Oxidation of glyceraldehyde-3-phosphate
   - Creates high-energy bond; NADH

7. Phosphoryl group transfer
   - Production of ATP - substrate-level phosphorylation

8. 3-phosphoglycerate ↔ 2-phosphoglycerate

9. Dehydration glycerate-2-phosphate
   - Formation of PEP

10. Synthesis of Pyruvate

Net production: 2 ATP, 2 NADH, and 2 pyruvate
**Section 8.1: Fates of Pyruvate**

**Aerobic conditions** – converted to acetyl-CoA
- Enters citric acid cycle forming CO$_2$, NADH, FADH$_2$
- Amphibolic pathway – functions in both anabolic/catabolic processes
- Electron Transport System – transfers electrons from NADH/FADH$_2$ to O$_2$

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Section 8.1: Fates of Pyruvate

- **Anaerobic conditions** – impedes oxidation
  - **Homolactic fermentation** – reduces to organic compound
  - Regenerates NAD$^+$ for glycolysis
Section 8.1: Fates of Pyruvate

Anaerobic conditions – impedes oxidation

- Alcoholic fermentation – produces ethanol, regenerates NAD$^+$
- Used to make alcoholic beverages
Three reactions – negative free energy

- Hexokinase
- Phosphofructokinase
- Pyruvate kinase

Essentially irreversible

Sites of allosteric control
### Section 8.1: Regulation of Glycolysis

#### HEXOKINASES I, II, AND III
- High affinity for glucose
- Inhibited by glucose-6-phosphate

#### HEXOKINASE IV (GLUCOKINASE) FOUND IN LIVER
- Requires higher glucose concentrations
- Not inhibited by glucose-6-phosphate
- Diverts glucose to storage as glycogen

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**TABLE 8.1** Allosteric Regulation of Glycolysis

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<td>Glucose-6-phosphate, ATP</td>
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<tr>
<td>PFK-1 (Fructose-1,6-bisphosphate, AMP)</td>
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<td></td>
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<td>Pyruvate kinase</td>
<td>Fructose-1,6-bisphosphate, AMP</td>
<td>Acetyl-CoA, ATP</td>
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### Phosphofructokinase-1
- Inhibited by citrate, ATP
- Fructose-2,6-bisphosphate, produced via hormone-induced covalent modification of PFK-2, activates PFK-1
- Accumulation of fructose-1,6-bisphosphate provides a feed-forward mechanism

### Pyruvate kinase
- Accumulated fructose-1,6-bisphosphate activates
- High AMP concentrations activate
- Inhibited by Acetyl-CoA, ATP

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Section 8.2: Gluconeogenesis

- **Gluconeogenesis** - formation of new glucose from precursors in the liver
  - Precursor molecules - lactate, pyruvate, α-keto acids

- **Gluconeogenesis Reactions**
  - Reverse of glycolysis
  - Except three irreversible reactions
    - Hexokinase, PFK-1, Pyruvate kinase
  - Stimulated by high concentrations – lactate, glycerol, amino acids

Section 8.2: Gluconeogenesis

Figure 8.11 Carbohydrate Metabolism: Gluconeogenesis and Glycolysis

Section 8.2: Gluconeogenesis

Figure 8.11 Carbohydrate Metabolism: Gluconeogenesis and Glycolysis

Section 8.2: Gluconeogenesis

Gluconeogenesis Substrates

1. **Lactate**—released by skeletal muscle from the Cori cycle
   - Transported to liver lactate, converted to pyruvate by **lactate dehydrogenase**, then to glucose

2. **Glycerol**—a product of fat metabolism
   - Transported to liver in blood, converted to G-3-P by **glycerol kinase**
### Section 8.2: Gluconeogenesis

**Glucose Alanine Cycle**

3. **Alanine**—generated from pyruvate in exercising muscle

- **Alanine transaminase** converts to pyruvate then glucose in the liver

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Section 8.2: Gluconeogenesis

Gluconeogenesis Regulation
- Stimulated - high lactate, glycerol, amino acid conc
- Allosteric modulators:
  - pyruvate carboxylase
  - pyruvate carboxykinase

Figure 8.14 Allosteric Regulation of Glycolysis and Gluconeogenesis

Activator (+); inhibitor (-)

Section 8.2: Gluconeogenesis

Gluconeogenesis Regulation

- Allosteric modulators:
  - glucose-6-phosphatase
  - fructose-1,6-bisphosphatase

- Hormonal regulation
  - Alter concentrations of allosteric effectors & key enzymes

Figure 8.14 Allosteric Regulation of Glycolysis and Gluconeogenesis

Activator (+); inhibitor (-)
Section 8.3: Pentose Phosphate Pathway

Alternate glucose metabolic pathway
- Produces NADPH and ribose-5-phosphate
- Two phases in cytoplasm
  - Oxidative & non-oxidative
  - Oxidative
    1. Glucose-6-phosphate to 6-phospho-D-glucono-δ-lactone
      - NADPH
    2. 6-phospho-D-glucono-δ-lactone to 6-phospho-D-gluconate

Figure 8.15a The Pentose Phosphate Pathway (oxidative)
Section 8.3: Pentose Phosphate Pathway

- Oxidative – cont.

3. 6-phospho-D-gluconate to 3-keto-6-phospho-D-gluconate
  - NADPH
3-keto-6-phospho-D-gluconate to D-ribulose-5-phosphate
  - CO₂
- Net yield - ribulose-5-phosphate; two NADPH
  - NADPH is a reducing agent used in anabolic processes

Figure 8.15a The Pentose Phosphate Pathway (oxidative)

Section 8.3: Pentose Phosphate Pathway

- **Nonoxidative**
  - Produces intermediates for nucleotide biosynthesis and glycolysis
    - Ribose-5-phosphate
    - Glyceraldehyde-3-phosphate
    - Fructose-6-phosphate

Figure 8.15b The Pentose Phosphate Pathway (nonoxidative)

Section 8.4: Metabolism of Other Important Sugars

Additional important sugars - fructose, mannose, galactose

- Galactose to UDP-glucose
  - Stored as glycogen
  - Converted to G-1-P directly to glycolysis

Fructose Metabolism

- Second to glucose in the human diet
- Can enter the glycolytic pathway in two ways:
  - Through the liver (multi-enzymatic process)
  - Muscle and adipose tissue (hexokinase)
Section 8.4: Metabolism of Other Important Sugars

Figure 8.17 Carbohydrate Metabolism: Other Important Sugars

Glycogenesis

- Synthesis of glycogen, the storage form of glucose, occurs after a meal
  - Both synthesis & degradation controlled primarily by interplay between insulin and glucagon
- Requires a set of three reactions (1 and 2 are preparatory and 3 is for chain elongation):
  1. Synthesis of glucose-1-phosphate (G1P) from glucose-6-phosphate by phosphoglucomutase
  2. Synthesis of UDP-glucose from G1P by UDP-glucose phosphorylase
3. Synthesis of Glycogen from UDP-glucose requires two enzymes:

- **Glycogen synthase** to grow the chain

![Diagram of glycogen synthesis](image_url)
Glycogen Synthesis Continued

- Branching enzyme amylo-\(\alpha(1,4\rightarrow1,6)\)-glucosyl transferase creates \(\alpha(1,6)\) linkages for branches

Figure 8.18 Glycogen Synthesis

1. Removal of glucose from nonreducing ends (glycogen phosphorylase) within four glucose of a branch point.
2. Hydrolysis of the $\alpha(1,6)$ glycosidic bonds at branch points by \textit{amylo-$\alpha(1,6)$-glucosidase} (debranching enzyme)
Section 8.5: Glycogen Metabolism

**Regulation** - Carefully regulated to maintain consistent energy levels

- Controlled via **insulin**, **glucagon**, **epinephrine**, **allosteric, effectors**

**Glucagon** – released from pancreas when blood glucose levels drop

- Binds to receptor site on hepatocytes cell membrane
- Initiates signal transduction process
- Elevates cAMP, leads to **glycogen phosphorylase** activation
- Glucose released into bloodstream

**Cori’s disease** - inherited defect, deficient in debranching enzyme
- Can store glycogen, cannot breakdown

Figure 8.22 Major Factors Affecting Glycogen Metabolism
Figure 8.22 Major Factors Affecting Glycogen Metabolism

- Glucagon activates glycogenolysis
- Epinephrine release activates glycogenolysis; inhibits glycogenesis
- Insulin inhibits glycogenolysis; activates glycogenesis
**Saccharomyces cerevisiae and the Crabtree effect**

- *S. cerevisiae* is the only yeast that can produce ethanol and CO$_2$ in such large quantities
- *S. cerevisiae* ferments carbohydrates efficiently and dominates its environment due to the Crabtree effect
- Unlike most fermenting organisms *S. cerevisiae* can also ferment sugar in the presence of O$_2$
- As glucose and/or fructose levels rise pyruvate is diverted away from the citric acid cycle into ethanol synthesis

**The Crabtree Effect**

- The phenomenon, in which glucose represses aerobic metabolism
- Rapid production of ethanol has the effect of eliminating microbial competitors
- Once glucose levels are depleted and O$_2$ is available the yeast reabsorbs the ethanol and converts it to acetaldehyde for use as an energy source
Figure 8A Ethanol Metabolism in S. cerevisiae