23.2 Glucose Metabolism: An Overview

• When glucose enters a cell from the bloodstream, it is immediately converted to glucose 6-phosphate.
• Once this phosphate is formed, glucose is trapped within the cell because phosphorylated molecules cannot cross the cell membrane.
• Like the first step in many metabolic pathways, the formation of glucose-6-phosphate is highly exergonic and not reversible in the glycolytic pathway, thereby committing the initial substrate to subsequent reactions.
• When cells are already well supplied with glucose, the excess glucose is converted to other forms for storage: to glycogen, the glucose storage polymer, by the **glycogen synthesis pathway**, or to fatty acids by entrance of acetyl-S-CoA into the pathways of lipid metabolism rather than the citric acid cycle.

• When energy is needed, glucose 6-phosphate undergoes **glycolysis** to pyruvate and then to acetyl-S-coenzyme A, which enters the citric acid cycle.
Glucose 6-phosphate can be converted to pentose products, stored as glycogen, or broken down to acetyl-SCoA for production of energy, proteins, or fats.
23.3 Glycolysis

- **Glycolysis** is a series of 10 enzyme-catalyzed reactions that break down glucose molecules.
- The net result of glycolysis is the production of two pyruvate molecules, two ATPs, and two NADH/H⁺s.

*Net result of glycolysis*

\[
\text{C}_6\text{H}_{12}\text{O}_6 + 2 \text{NAD}^+ + 2 \text{HOPO}_3^{2-} + 2 \text{ADP} \rightarrow 2 \text{CH}_3\text{C}==\text{C}==\text{O}^- + 2 \text{NADH} + 2 \text{ATP} + 2 \text{H}_2\text{O} + 2 \text{H}^+
\]

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• Steps 1-5 of glycolysis break one glucose molecule down into two D-glyceraldehyde 3-phosphate fragments.

• An investment of 2 ATP molecules is required.
• Steps 6-10 occur twice for each glucose that enters in at step 1.

• Steps 6-10 produce:
  2 pyruvates,
  4 ATP’s
  2 NADH/H⁺ per glucose.
Mannose is a product of the hydrolysis of plant polysaccharides other than starch.
23.5 The Fate of Pyruvate

• The conversion of glucose to pyruvate is a central metabolic pathway in most living systems.

• The further reactions of pyruvate depend on metabolic conditions and on the nature of the organism.
• **Aerobic:** In the presence of oxygen.
• Under normal oxygen-rich (aerobic) conditions, pyruvate is converted to acetyl-SCoA.
• Pyruvate diffuses across the outer mitochondrial membrane, then is carried by a transporter protein across the inner mitochondrial membrane.
• Once inside, Pyruvate dehydrogenase complex catalyzes the conversion of pyruvate to acetyl-SCoA.

\[
\text{CH}_3\text{C} - \text{C} - \text{C} - \text{O}^- \quad + \quad \text{HS} - \text{CoA} \quad \xrightarrow{\text{Pyruvate dehydrogenase complex}} \quad \text{CH}_3\text{C} - \text{SCoA} \quad + \quad \text{CO}_2
\]

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• **Anaerobic:** In the absence of oxygen.

  - If electron transport slows because of insufficient oxygen, NADH concentration increases, NAD$^+$ is in short supply, and glycolysis cannot continue.

  - An alternative way to reoxidize NADH is essential because glycolysis, the only available source of fresh ATP, must continue. The reduction of pyruvate to lactate solves the problem.

![Chemical Reaction Diagram](image-url)

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23.6 Energy Output in Complete Catabolism of Glucose

• The total energy output from oxidation of glucose is the combined result of
  – (a) glycolysis
  – (b) conversion of pyruvate to acetyl-SCoA
  – (c) conversion of two acetyl groups to four molecules of CO₂ in the citric acid cycle
  – (d) the passage of reduced coenzymes from each of these pathways through electron transport and the production of ATP by oxidative phosphorylation.
• The sum of the net equations for each pathway that precedes oxidative phosphorylation is shown below.

• Since each glucose yields 2 pyruvates and 2 acetyl-SCoAs, the net equations for pyruvate oxidation and the citric acid cycle are multiplied by 2.

*Net result of catabolism of one glucose molecule*

**Glycolysis** (Section 23.3)

Glucose + 2 NAD\(^+\) + 2 HOPO\(_3\)^{2-} + 2 ADP \rightarrow 2 Pyruvate + 2 NADH + 2 ATP + 2 H\(_2\)O + 2 H\(^+\)

**Pyruvate oxidation** (Section 23.5)

2 Pyruvate + 2 NAD\(^+\) + 2 HSCoA \rightarrow 2 Acetyl-SCoA + 2 CO\(_2\) + 2 NADH + 2 H\(^+\)

**Citric acid cycle** (Section 21.8)

2 Acetyl-SCoA + 6 NAD\(^+\) + 2 FAD + 2 ADP + 2 HOPO\(_3\)^{2-} + 4 H\(_2\)O \rightarrow

\[
\text{2 HSCoA + 6 NADH + 6 H}^+ + 2 \text{FADH}_2 + 2 \text{ATP} + 4 \text{CO}_2
\]

Glucose + 10 NAD\(^+\) + 2 FAD + 2 H\(_2\)O + 4 ADP + 4 HOPO\(_3\)^{2-} \rightarrow

\[
10 \text{NADH} + 10 H^+ + 2 \text{FADH}_2 + 4 \text{ATP} + 6 \text{CO}_2
\]

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23.7 Regulation of Glucose Metabolism and Energy Production

- Normal blood glucose concentration a few hours after a meal ranges roughly from 65 to 110 mg/dL.
- **Hypoglycemia**: Lower-than normal blood glucose concentration.
- **Hyperglycemia**: Higher-than normal blood glucose concentration.
• Two hormones from the pancreas have the major responsibility for blood glucose regulation.
• The first, insulin, is released when blood glucose concentration rises.
• The second hormone, glucagon, is released when blood glucose concentration drops.
23.8 Metabolism in Fasting and Starvation

• The metabolic changes in the absence of food begin with a gradual decline in blood glucose concentration accompanied by an increased release of glucose from glycogen.

• All cells contain glycogen, but most is stored in liver cells (about 90 g in a 70 kg man) and muscle cells (about 350 g in a 70 kg man). Free glucose and glycogen represent less than 1% of our energy reserves and are used up in 15–20 hours of normal activity (3 hours in a marathon race).
• During the first few days of starvation, protein is used up at a rate as high as 75 g/day.
• Lipid catabolism is mobilized, and acetyl-SCoA molecules derived from breakdown of lipids accumulate.
• Acetyl-SCoA begins to be removed by a new series of metabolic reactions that transform it into ketone bodies.
23.10 Glycogen Metabolism: Glycogenesis and Glycogenolysis

• Glycogen synthesis, known as **glycogenesis**, occurs when glucose concentrations are high.
• Glucose 6-phosphate is first isomerized to glucose 1-phosphate.
• The glucose residue is then attached to uridine diphosphate (UDP):
**Glycogenolysis:** The biochemical pathway for breakdown of glycogen to free glucose.

- Glycogenolysis occurs in muscle cells when there is an immediate need for energy.
- Glycogenolysis occurs in the liver when blood glucose is low.
23.11 Gluconeogenesis: Glucose from Noncarbohydrates

- **Gluconeogenesis**, which occurs mainly in the liver, is the pathway for making glucose from noncarbohydrate molecules—lactate, amino acids, and glycerol.

- This pathway becomes critical during fasting and the early stages of starvation. Failure of gluconeogenesis is usually fatal.

- During exercise lactate produced in muscles under anaerobic conditions during exercise is sent to the liver, where it is converted back to glucose.
Gluconeogenesis requires energy, so shifting this pathway to the liver frees the muscles from the burden of having to produce even more energy.
• Steps 1, 3, and 10 in glycolysis are too exergonic to be directly reversed. Gluconeogenesis uses reactions catalyzed by different enzymes that reverse these steps. The 7 other steps of glycolysis are reversible because they operate at near-equilibrium conditions.

• Gluconeogenesis begins with conversion of pyruvate to phosphoenolpyruvate, the reverse of the highly exergonic step 10 of glycolysis. Two steps are required, utilizing two enzymes and the energy provided by two triphosphates, ATP and GTP.