Chapter 15

**Cori and Alanine Cycles:**

Cori Cycle: Occurs between liver cells and cells without mitochondria or when O₂ is not available.

Alanine Cycle: Occurs between liver cells and cells with mitochondria and when O₂ is available.

**Gluconeogenesis:**

Maintaining levels of glucose in the blood is very important because the brain depends on glucose as its primary fuel and RBC rely on glucose as their only fuel. Gluconeogenesis is the synthesis of glucose from noncarbohydrate precursors. The major carbon sources for glucose synthesis are:

- Lactate, pyruvate, amino acids, glycerol, and other sugars (fructose, galactose, etc.)

****Note- Acetyl-CoA is not a carbon source for gluconeogenesis.

The major site of gluconeogenesis is the liver (so that the liver can maintain blood glucose levels). Little takes place in the brain, skeletal, or heart muscle.

Gluconeogenesis from Lactate:

Overall reaction: \[2\text{lactate} + 6\text{ATP} \rightarrow \text{glucose} + 6\text{ADP} + 6\text{Pi} + 4\text{H}^+\]

Step 1: lactate ↔ pyruvate (E=lactate dehydrogenase)

Now we can use the 7 reversible enzymes from glycolysis, but we cannot use the three irreversible enzymes:
Hexokinase, phosphofructokinase, and pyruvate kinase

In gluconeogenesis, the following new steps bypass these irreversible enzymes of glycolysis:

**Pyruvate → PEP**

\[
\text{Pyruvate} + \text{ATP} + \text{HCO}_3^- \rightarrow \text{Oxaloacetate} + \text{ADP} + \text{P}_i + \text{H}^+ \quad (E= \text{pyruvate carboxylase in mito})
\]

\[
\text{Oxaloacetate} + \text{GTP} \rightarrow \text{PEP} + \text{GDP} + \text{CO}_2 \quad (E= \text{phosphoenolpyruvate carboxykinase})
\]

The first step occurs in the mitochondria. The oxaloacetate formed must then be transported to the cytosol where the rest of the enzymes for gluconeogenesis are located. Oxaloacetate is converted to malate (by malate dehydrogenase); malate is transported across the inner mitochondrial membrane to the cytosol; malate is then reoxidized to oxaloacetate in the cytosol.

→ Decarboxylations often drive reactions that are otherwise highly endergonic. Remember we are making an unstable enol isomer of pyruvate and phosphorylating this molecule.

→ The conversion to oxaloacetate also links this process to the TCA cycle since oxaloacetate is a TCA intermediate.

**Fructose 1,6-bisphosphate → Fructose 6-phosphate**

\[
\text{Fructose 1,6-bisphosphate} + \text{H}_2\text{O} \rightarrow \text{fructose 6-phosphate} + \text{P}_i \quad (E= \text{fructose 1,6-bisphosphatse})
\]

This is not a “high energy” molecule, so the removal of the phosphate does not result in the generation of an ATP molecule, but results in the production of an inorganic phosphate molecule.

→ In most tissues, gluconeogenesis ends here.

**Glucose 6-Phosphate → Glucose**

\[
\text{Glucose 6-phosphate} + \text{H}_2\text{O} \rightarrow \text{Glucose} + \text{P}_i \quad (E= \text{glucose 6-phosphatase})
\]

This enzyme is only located in tissues involved in maintaining blood glucose levels (main-liver, minor-kidneys). This enzyme is located in the membrane of the ER and has a transport activity for glucose built into the enzyme complex. The glucose is routed through the ER and Golgi and out to the bloodstream.

Clinical: → Inhibitors of glucose 6-phosphatase may be used to decrease diabetic effects.

→ Chlocogenic acid (skin of peaches) inhibits glucose transport associated with this enzyme.
Therefore, 4 molecules of ATP and 2 molecules of GTP = equivalent to 6 ATP is required for gluconeogenesis from pyruvate or lactate. The liver gets the energy (ATP) from fatty acid oxidation.

**Gluconeogenesis from Amino Acids:**

→ All except Lysine and Leucine

catabolism

→ Amino Acid →→→ Pyruvate or oxaloacetate

Note: the amino acid may supply an intermediate in the TCA cycle which then leads to oxaloacetate formation.

Glu → α-ketoglutarate → (TCA cycle) → oxaloacetate

Note: If the amino acid is only broken down into acetyl-CoA (Lys, leu), then cannot be converted to glucose.

**Glucose from Fatty Acids:**

→ Usually, fatty acids have an even number of carbon atoms

FAeven →→ Acetyl-CoA X which is not converted to glucose

FAodd →→ Acetyl-CoA + a single propionyl-CoA → propionate → oxaloacetate

TAG → glycerol backbone → DHAP → glucose

**Glucose from Other Sugars:**

Other sugars such as fructose and galactose can be converted into glucose through a series of enzymatic steps.

Clinical: Galactosemia is a hereditary disorder in one enzyme in the conversion of galactose (milk sugar) to glucose. Since galactose cannot be converted into glucose, it gets converted to galactose 1-phosphate which builds up and becomes toxic. The results are cataract formation, growth failure, mental retardation, and even death. It can be controlled through the diet.

**Regulation of Gluconeogenesis:**

→ Regulate at the four new irreversible enzymes

→ The amounts and activities of the irreversible enzymes of both glycolysis and gluconeogenesis are controlled so that both pathways are not active at the same time.
fructose 1,6-bisphosphatase is activated by citrate (citrate reports on the status of the TCA cycle and high levels indicate an energy rich situation), and inhibited by AMP and F-2,6-BP.

Pyruvate carboxylase is activated by acetyl-CoA (indicates that TCA cycle is producing energy and biosynthetic intermediates) and inhibited by ADP.

PEP carboxykinase is inhibited by ADP.

Hormonal Control: a) Insulin activates glycolysis and also activates the uptake of glucose by cells and inhibits gluconeogenesis

b) Glucagon activates gluconeogenesis and inhibits glycolysis

c) Ethanol metabolism produces \( \uparrow \) NADH, this excess NADH promotes the conversion of pyruvate → lactate, thus promoting glycolysis and inhibiting gluconeogenesis. Lactate accumulates and blood glucose levels drop.

Glycogen Metabolism:

Glycogenesis- breakdown of glycogen to glucose

Glycogenesis- synthesis of glycogen

- Occurs somewhat in all cells of the body, but mainly in muscle cells (use glycogen for ATP production) and liver cells (use glycogen for glucose synthesis to maintain blood glucose levels).

Glycogenolysis:

- NO ATP INVOLVED
Step 1: Glycogen phosphorylase cleaves its substrate by the addition of inorganic phosphate to yield glucose 1-phosphate. Glycogen phosphorylase catalyzes the sequential removal of glucosyl residues from the nonreducing ends of the glycogen polymer.

\[(\text{Glucose})_n + P_i \leftrightarrow \text{glucose 1-phosphate} + (\text{Glucose})_{n-1}\]

- Phosphorylase only breaks the 1-4 linkage in glycogen; need a debranching enzyme to break a 1-6 cross-linkage.

Step 2: Phosphoglucomutase converts G1P to G6P

\[\text{Glucose 1-phosphate} \leftrightarrow \text{Glucose 6-phosphate}\]

Step 3: Only occurs in the liver. Glucose 6-phosphatase (same enzyme as in gluconeogenesis) removes the phosphate group producing glucose which can be transported into the blood stream.

\[\text{Glucose 6-phosphate} \rightarrow \text{Glucose} + P_i\]

- Lack of this enzyme leads to type I glycogen storage disease (can lead to heart failure, muscle cramps, decrease muscle function, hypoglycemia, and lactic acidosis).

**Glycogenesis:**

- Requires 2ATP/glucose molecule attached to a glycogen chain.

- Pathway utilizes UDP-glucose as the activated glucose donor. UDP-glucose is activated because its hydroxyl group is esterified to the diphosphate moiety of UDP.

- UDP-glucose is added to the nonreducing ends of the glycogen molecule.

Step 1:

\[\text{Glucose} + \text{ATP} \rightarrow \text{G6P} + \text{ADP} \quad (E=\text{hexokinase or glucokinase in liver})\]

Step 2:

\[\text{G6P} \leftrightarrow \text{G1P} \quad (E=\text{phosphoglucomutase; same as above})\]

Step 3:

\[\text{G1P} + \text{UTP} + \text{H}_2\text{O} \rightarrow \text{UDP-glucose} + 2\text{P}_i \quad (E=\text{UDP-glucose pyrophosphorylase})\]

Step 4:

\[\text{UDP-glucose} + (\text{Glucose})_n \rightarrow \text{UDP} + (\text{Glucose})_{n+1} \quad (E=\text{glycogen synthase})\]

The hydrolysis of the pyrophosphate supplies the energy necessary to perform the ligation reaction. This reaction produces 1-4 linkages; and additional enzymes are necessary to create the 1-6 cross-links. Glycogen
synthase is the key regulatory enzyme in glycogen synthesis. An ATP molecule is necessary to regenerate UTP from UDP; therefore, the UTP used in step 3 is eq. to an ATP.

**Glycogen Metabolism Regulation:**

The regulation of glycogen synthesis and degradation is complex. Several enzymes allosterically respond to metabolites that signal the energy needs of the cell. In addition, hormone signaling can alter the catalytic rates of these enzymes through reversible phosphorylation, thus signaling the needs of the entire organism.

Epinephrine- released in response to stress, stimulates glycogenesis and glycolysis to give a burst of energy to the cell

**Why Store Glycogen?**

1) Glycogen can be used rapidly to produce ATP
2) Cannot use fatty acids or amino acids as an energy source in absence of O$_2$
3) Fatty Acids cannot be converted to Glucose to maintain blood glucose levels