GLUCONEOGENESIS

- Gluconeogenesis is the **re-synthesis** of glucose
- Provides the source of blood glucose other than glycogen to **prevent hypoglycemia**
- Major **users** of glucose: brain and muscles
  
  **Top Priority glucose supply for Brain, because the brain:**
  1. Need relative large amount of Energy:
  2. Does not have significant energy store
  3. Dependent on blood glucose as energy source
  4. Not sensitive to hormone regulation
  5. Can adapt to use ketone body (fatty acids) but only after prolonged fasting

- Major **producers** of glucose: Liver (90%) and kidney (10%)
  - Pyruvate and lactate produced returned to liver and kidney
- Under fasting conditions, gluconeogenesis supplies almost all of the body’s glucose
- Gluconeogenesis is the process by which glucose is **MADE** from small, non-carbohydrates
  - Major gluconeogenic precursors in mammals:
    1. **Lactate and pyruvate**
    2. Most **amino acids** (especially alanine)
       (Muscle proteins break down and aa transported to liver)
    3. **Glycerol** (from triacylglycerol hydrolysis)
- Any metabolite that can be converted to **pyruvate** or **oxaloacetate** can be a glucose precursor

\[
2 \text{Pyruvate} + 2 \text{NADH} + 4 \text{ATP} + 2 \text{GTP} + 6 \text{H}_2\text{O} + 2 \text{H}^+ \\
\rightarrow \text{Glucose} + 2 \text{NAD}^+ + 4 \text{ADP} + 2 \text{GDP} + 6 \text{P}_i
\]

- Not a simple reversal of glycolysis, but employs many of the same enzymes of glycolysis
- Employs 4 new steps to avoid “irreversible steps” of glycolysis
  - Irreversible and regulated steps of glycolysis
    - Hexokinase
    - Phosphofructokinase
    - Pyruvate kinase
- Gluconeogenesis occurs when pyruvate kinase, PFK and hexokinase are relatively inactive
- These steps must be bypassed to prevent futile cycles
- Making glucose is **expensive**
  - Synthesis of 1 mole of glucose from 2 moles of pyruvate needs 6 moles of ATP
Figure 15-12 Concepts in Biochemistry, 3/e
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Interaction of glycolysis and gluconeogenesis: The Cori Cycle

- The Cori Cycle operates during exercise, when aerobic metabolism in muscle cannot keep up with energy needs.
- Glucose synthesized in liver and transported to muscle and blood.
- A highly exercising muscle generates a lot of NADH from glycolysis but without oxygen there is no way to regenerate NAD$^+$ from the NADH (need NAD$^+$!).
- Lactic acidosis can and would result from insufficient oxygen (an increase in lactic acid and decrease in blood pH)
- So, the NADH is reoxidized by reduction of pyruvate to lactate by enzyme lactate dehydrogenase; Results in replenishment of NAD$^+$ for glycolysis

<table>
<thead>
<tr>
<th>GLYCOGEN</th>
<th>GLUCOSE</th>
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<tbody>
<tr>
<td>Glycogenolysis</td>
<td>Glycogenesis</td>
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<tr>
<td>Glycolysis</td>
<td>Gluconeogenesis</td>
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<tr>
<td>LACTATE</td>
<td>LACTATE</td>
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\[
\begin{align*}
\text{Pyruvate} & \xrightarrow{\text{Lactate dehydrogenase}} \text{Lactate} \\
\text{COO}^- & \quad \text{NADH, H}^+ & \quad \text{NAD}^+ \\
\text{CH}_3 & \framebox{\text{C} = \text{O}} \\
\end{align*}
\]

\[(11.11)\]

- Then the lactate formed in skeletal muscles during exercise is transported to liver where it is used for gluconeogenesis
  - Lactate is transported through the bloodstream to the liver
  - Lactate is oxidized to pyruvate in the liver
  - Liver lactate dehydrogenase reconverts lactate to pyruvate since has high NAD$^+$/NADH ratio
  - Pyruvate is used to remake glucose by gluconeogenesis
- Glucose is transported back to the muscles via the bloodstream
**FUELS USED DURING EXERCISE**

- **Glycogen Utilization**
  - Figure 15-6 Concepts in Biochemistry, 3/e
  - © 2006 John Wiley & Sons

- **Glycogen Recovery**
PANEL A:

The Immediate Energy System
- Provides energy rapidly but for only a short period of time
- It is used to fuel activities that last for about **10 or fewer seconds**
- For example weight lifting and picking up a bag of groceries
- Components includes existing cellular ATP stores and creatine phosphate (CP)

The Nonoxidative (Anaerobic) Energy System
- Used at the start of an exercise session and for high intensity activities lasting for about **10 seconds to 2 minutes**
- Examples, 400 meter run or to dash up several flights of stairs
- Creates ATP by breaking down glucose and glycogen.
- Does not require oxygen
- 2 key limiting factors
  1. body’s supply of glucose and glycogen is limited
  2. nonoxidative system results in the production of lactic acid

The Oxidative (Aerobic) Energy System
- Requires oxygen to generate ATP
- The aerobic production of energy does not produce any toxic waste products and so is the preferred system for prolonged exercise.
- Used during physical activity that lasts longer than ~2 minutes (e.g. distance running, hiking
- ATP production takes place in cellular structures called mitochondria – can use carbohydrates (glucose and glycogen) or fats to produces ATP
  - The actual fuel source depends on:
    - Intensity and duration of the activity
    - Fitness status of the individual

PANEL B:

In general, carbohydrate use increases with increasing intensity and falls with increasing duration of an activity. Fats are used for lower – intensity exercise.

Glycogen stores are finite, and inevitably become depleted during long continuous exercise lasting in excess of 70-92 minutes (the more intensive the exercise, the quicker the glycogen is depleted). This applies not only to endurance events, such as marathon running but also to intermittent exercise sports such as soccer and rugby. When glycogen stores have been used up, the muscles attempt to cover their energy needs from fat metabolism. Unfortunately, because fat cannot supply energy at as rapid a rate as carbohydrate, the competitor is forced to slow down or reduce his/her rate of work to the level at which energy expenditure and energy synthesis are matched.

This situation is made worse by the fact that when glycogen stores in the muscles are used up, blood glucose (hypoglycemia) reduces the supply of glucose to the brain, contributing to the feeling of exhaustion and causing a decrease in technique and the ability to make correct decisions.

PANEL C:

Choice of diet has a dramatic effect on glycogen recovery following exhaustive exercise. A diet consisting mainly of protein and fat results in very little recovery of muscle glycogen even after 5 days! On the other hand a high carbohydrate diet provides faster restoration of muscle glycogen. Even though, however, complete recovery of glycogen stores takes about 2 days.
During a prolonged exercise session, carbohydrates are the predominant fuel at the start of a workout, but fat utilizations (aerobic) increases over time.

Carbohydrate metabolism is an energy system that does not depend on oxygen, but is only available for a short period of time as it rapidly causes fatigue. One of the reasons for this fatigue is the accumulation of lactic acid which quickly reduces the ability of the muscles to contract effectively. Lactic acid in the muscles can cause discomfort both during and after exercise, and total recovery will not occur until the excess lactic acid produced during exercise has been fully degraded.

Remember, entry of glucose into muscles requires insulin! (Fed-state!)