BIOCHEMISTRY
Carbohydrate Metabolism

BIOB111
CHEMISTRY & BIOCHEMISTRY

Session 20
Session Plan

- Digestion & Absorption of Carbohydrates
- Glycolysis
- Fates of Pyruvate
Carbohydrate Digestion & Absorption

- **Digestion** – hydrolysis of food molecules into simpler chemical units that can be used by cells for their metabolic needs.
- Begins **in the mouth** – *salivary α-amylase* catalyzes hydrolysis of α-glycosidic bonds of starch – producing smaller polysaccharides & disaccharide (maltose).
- No digestion in **stomach**.
- **Small intestine** – most carbs digestion – *pancreatic α-amylase* catalyzes hydrolysis of α-glycosidic bonds in polysaccharides & produce maltose.
- **Disaccharidase** enzymes (*maltase, sucrase & lactase*) break down disacharides maltose, sucrose & lactose into monosaccharides glucose, fructose & galactose – enter blood via active transport – transported to the liver – fructose & galactose are converted into compounds that enter the same pathway as glucose – **Glycolysis**.
Summary of carbohydrate digestion in the human body

1. Mouth
   - Salivary α-amylase—hydrolysis of some α-glycosidic linkages

2. Stomach
   - Gastric juice—no effect on digestion

3. Small Intestine
   - Pancreatic digestive enzymes—hydrolysis of polysaccharides to disaccharides

4. Intestinal Mucosal Cells
   - Maltase
   - Sucrase
   - Lactase
   - Hydrolysis of disaccharides

5. Intestinal Lining (Villi)
   - Active transport

Dietary carbohydrates
Polysaccharides, maltose, sucrose, lactose
Monosaccharides in bloodstream
Glucose, fructose, galactose
Maltose, sucrose, lactose

Stoker 2014, Figure 24-2 p885
Glycolysis

- The catabolic pathway in which Glucose (C$_6$) is broken down into 2 molecules of pyruvate (C$_3$), 2ATP & 2NADH are produced.

\[
\text{Glucose} + 2\text{NAD}^+ + 2\text{ADP} + 2\text{P}_i \rightarrow 2\text{pyruvate} + 2\text{NADH} + 2\text{ATP} + 2\text{H}^+ + 2\text{H}_2\text{O}
\]

- Series of 10 steps – each is catalyzed by a different enzyme.
- Takes place in the cytosol.
- An oxidation process where no O$_2$ is used – anaerobic process.
- The agent that accepts e$^-$ here is the coenzyme NAD$^+$.
- There are 2 stages: C$_6$ & C$_3$ stage of glycolysis.
Overview Of Glycolysis

Stoker 2014, Figure 24-3 p887
**C₆ Stage – Steps 1-3**

- The **energy-consuming stage**, as 2 ATPs are consumed.
- The intermediates of the C₆ stage are glucose or fructose derivatives.
1. Formation of Glucose 6-Phosphate

- **Phosphorylation** of glucose – phosphate group ($P_i$) from ATP is transferred to the hydroxyl group on $C_6$ of glucose.
- Catalyzed by *Hexokinase* – requires $Mg^{2+}$.

The symbol $\textcircled{P}$ is a shorthand notation for a $PO_3^{2-}$ unit.
2. Formation of Fructose 6-Phosphate

- **Isomerization** of Glucose 6-phosphate to Fructose 6-phosphate.
- Catalyzed by *Phosphoglucoisomerase*. 

![Chemical structures](image)
3. Formation of Fructose 1,6-Bisphosphate

- **Phosphorylation** of Fructose 6-Phosphate.
- 2\textsuperscript{nd} molecule of ATP is used up.
- Catalyzed by *Phosphofructokinase* – requires Mg\textsuperscript{2+}. 

![Chemical diagram showing the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate](image)
Summary of C₆ Stage

Stage 2014, Figure 24-3 p887
C3 Stage – Steps 4-10

• The energy-generating stage, as 2 ATPs are consumed.
• The intermediates are \( \text{C}_3 \)-compounds.

• Steps 7 & 10 produce 4 ATPs.
• Note that each molecule of glucose (\( \text{C}_6 \)) forms 2 \( \text{C}_3 \)-compounds & each of these produces 2 ATPs (\( 2 \times 2 = 4 \text{ATP} \)).

• In the energy-consuming phase 2 ATPs were used up, so the overall energy production for glycolysis = 2 ATPs.
4. Formation of 2 Triose-Phosphates

- **Cleavage** of Fructose 1,6-Bisphosphate (C₆) into 2 triose-phosphates (C₃), which are not identical.
- Catalyzed by **Aldolase**.

Fructose 1,6-bisphosphate (open-chain form) $\xleftrightarrow{\text{Aldolase}}$ Dihydroxyacetone phosphate + Glyceraldehyde 3-phosphate
5. Formation of Glyceraldehyde 3-Phosphate

- Only Glyceraldehyde 3-phosphate is oxidized in glycolysis.
- **Isomerization** of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate.
- Catalyzed by *Triosephosphate isomerase*. 

![Diagram showing the transformation from dihydroxyacetone phosphate to glyceraldehyde 3-phosphate](image-url)
6. Formation of 1,3-Bisphosphoglycerate

- **Oxidation & phosphorylation using** $P_i$.
- Requires $\text{NAD}^+$ & $P_i$ to convert Glyceraldehyde 3-phosphate into 1,3-bisphosphoglycerate.
- Catalyzed by **Glyceraldehyde 3-phosphate dehydrogenase**.

\[
\text{Glyceraldehyde 3-phosphate} + \text{NAD}^+ + P_i \rightleftharpoons \text{1,3-Bisphosphoglycerate} + \text{NADH} + H^+
\]
7. Formation of 3-Phosphoglycerate

- **Substrate-level phosphorylation** of ADP.
- The C₁ high energy phosphate group of 1,3-bisphosphoglycerate is transferred to an ADP molecule to form an ATP.
- Catalyzed by *Phosphoglycerokinase*.
8. Formation of 2-Phosphoglycerate

- **Isomerization** of 3-Phosphoglycerate to 2-Phosphoglycerate – the P_i is moved from C_3 to C_2.
- Catalyzed by *Phosphoglyceromutase*. 
9. Formation of Phosphoenolpyruvate

- **Dehydration** of an alcohol, producing an alkene.
- Catalyzed by *Enolase* – requires Mg\(^{2+}\).
10. Formation of Pyruvate

- **Substrate-level phosphorylation** of ADP.
- Phosphoenolpyruvate transfers its $P_i$ onto an ADP molecule forming ATP & Pyruvate.
- Catalyzed by **Pyruvate kinase** – requires $Mg^{2+}$ & $K^+$. 

![Diagram of the reaction](image-url)
Pyruvic acid vs. Pyruvate

- Pyruvic acid is a ketoacid.
- In an aqueous solution Pyruvic acid releases a H⁺ & forms Pyruvate ion.

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} = \text{O} \\
\text{COOH} & \quad \text{Pyruvic acid}
\end{align*}
\quad \rightarrow \quad
\begin{align*}
\text{CH}_3 & \quad \text{C} = \text{O} \\
\text{COO}^- & \quad \text{Pyruvate ion}
\end{align*}
+ \text{H}^+
\]
Summary of C$_3$ Stage

Stoker 2014, Figure 24-3 p887
Entry points for Fructose & Galactose into Glycolysis

Stoker 2014, Figure 24-5 p894
Regulation of Glycolysis

- **Control points of Glycolysis:**

- **Step 1** – *Hexokinase* is inhibited by high levels of Glucose 6-phosphate, which prevents further phosphorylation of Glucose (feedback inhibition).

- **Step 3** – *Phosphofructokinase* (an allosteric enzyme) is inhibited by high levels of ATP & Citrate & is activated by high levels of ADP.

- **Step 10** – *Pyruvate kinase* (an allosteric enzyme) is inhibited by high levels of ATP & Acetyl CoA.
Fates of Pyruvate

- Pyruvate is produced via glycolysis in most cells – the fate of pyruvate varies with cellular conditions & the type of organisms.
- There are 3 important ways in which pyruvate is converted into other substances & NADH is oxidized into NAD$^+$ & recycled for glycolysis so it can continue.

![Diagram showing the fates of pyruvate: Aerobic conditions lead to Acetyl CoA, Anaerobic conditions in humans, animals, and some microorganisms lead to Lactate, and Anaerobic conditions in some microorganisms lead to Ethanol.]

Stoker 2014, Figure 24-6 p896
Oxidation to Acetyl CoA

- In the presence of O$_2$ – **aerobic conditions**.
- Pyruvate is transported from cytosol through both mitochondrial membranes into the matrix, where it is oxidized & decarboxylated to Acetyl CoA.
- Catalyzed by **Pyruvate dehydrogenase complex**.
- Most pyruvate formed during glycolysis is converted to Acetyl CoA & enters the CAC & ETC, in which NADH is recycled into NAD$^+$. 

![Chemical Reaction](image)
Lactate Fermentation

- When $O_2$ is deficient in tissues (hypoxia) – **anaerobic conditions**.
- An enzymatic anaerobic reduction of Pyruvate to Lactate occurs mainly in muscles – leads to tiredness & pain.
- Purpose – conversion of NADH to NAD$^+$ for increased rate of glycolysis.
- Lactate is converted back to Pyruvate when aerobic conditions are re-established in the cell.
- Muscle fatigue associated with strenuous physical activity is attributed to increased build-up of Lactate.

\[
\text{CH}_3\text{C}≡\text{COO}^- + \text{NADH} + \text{H}^+ \xrightarrow{\text{Lactate dehydrogenase}} \text{CH}_3\text{CH}≡\text{COO}^- + \text{NAD}^+
\]
Ethanol Fermentation

• Enzymatic **anaerobic** conversion of Pyruvate to Ethanol & $\text{CO}_2$ – in simple organisms (yeast & bacteria).
• NADH is regenerated to NAD$^+$ for glycolysis.
• **Involves 2 reactions:**
  • Pyruvate decarboxylation – *Pyruvate decarboxylase*
  • Acetaldehyde reduction – *Alcohol dehydrogenase*
All 3 fates of Pyruvate result in regeneration of NAD\(^+\) from NADH.
Glycogen Synthesis & Degradation

- **Glycogen**
- A branched polymer of glucose that stores glucose in humans & animals.

- **Glycogen is stored:**
- **In muscles** – the source of glucose for Glycolysis
- **In the liver** – the source of glucose to maintain normal blood glucose levels.
Glycogen genesis

- Metabolic pathway by which glycogen is synthesized from glucose.
- Liver can store about 100-120g, muscle about 200-300g glycogen.

- **Involves 3 steps:**
  - Formation of Glucose 1-phosphate
  - Formation of UDP Glucose
  - Glucose transfer to a Glycogen Chain

- Operates when high levels of glucose-6-phosphate are formed in the 1st step of glycolysis.
- **Occurs in fed state**, insulin activates Glycogenesis – when glycogen stores are full any additional glucose is converted to body fat & stored.
1. Formation of Glucose 1-phosphate

- **Isomerization** of Glucose 6-phosphate from Glycolysis.
- Catalyzed by *Phosphoglucomutase*.
2. Formation of UDP-glucose

- Glucose 1-phosphate must be **activated by UTP** before it is added to the growing glycogen chain.
- Catalyzed by **UTP-glucose phosphorylase**.
3. Glucose transfer to a Glycogen Chain

- The glucose unit of UDP-glucose is attached to the end of a glycogen chain & UDP is produced, which reacts with ATP to reform UTP.
- Adding 1 glucose to a growing glycogen chain requires the investment of 2 ATP – 1ATP to form Glucose 6-phosphate & 1ATP to regenerate UTP.
- Catalyzed by *Glycogen synthase*.

\[
\text{UDP-glucose} + (\text{glucose})_n \xrightarrow{\text{Glycogen synthase}} (\text{glucose})_{n+1} + \text{UDP}
\]

\[
\text{UDP} + \text{ATP} \longrightarrow \text{UTP} + \text{ADP}
\]
Glycogenolysis

- Breakdown of glycogen to Glucose-6-phosphate:
- It is not just the reverse of Glycogenesis because it does not require UTP or UDP.

- **Involve 2 steps:**
  - Phosphorylation of a glucose residue
  - Glucose 1-phosphate isomerization

- Activated by glucagon (low blood glucose levels - hypoglycaemia) in the liver & by Adrenalin in muscles.
- Inhibited by Insulin.
1. Formation of Glucose 1-phosphate

- Enzyme *Glycogen phosphorylase* catalyzes the removal of an end glucose unit from a glycogen molecule in the form of Glucose 1-phosphate.

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

Glycogen

Glycogen with one fewer glucose unit
2. Formation of Glucose 6-phosphate

- **Isomerization** of Glucose 1-phosphate to Glucose 6-phosphate.
- Catalyzed by **Phosphoglucomutase**.
- Reverse of the 1\textsuperscript{st} step of Glycogenesis.

Glucose 1-phosphate $\iff$ glucose 6-phosphate
Glycogenolysis

- **Glycogenolysis in muscles**
  - The Glucose 6-phosphate directly enters glycolysis pathway.

- **Glycogenolysis in liver cells**
  - Stimulated by low blood glucose levels.
  - Glucose 6-phosphate is converted to free Glucose – catalyzed by *Glucose 6-phosphatase* – an enzyme found in liver, kidneys & intestines but not in muscles.
  - The free glucose is released into the bloodstream & transported to muscles & brain tissue.

\[
\text{Glucose 6-phosphate} + \text{H}_2\text{O} \xrightarrow{\text{6-phosphatase}} \text{glucose} + \text{P}_i
\]
Many B vitamins function as coenzymes in carbohydrate metabolism – without these the body would be unable to utilize carbohydrates as an energy source.

6 B vitamins in carbohydrate metabolism:
- Thiamin – as TPP
- Riboflavin – as FAD, FADH₂ & FMN
- Niacin – as NAD⁺ & NADH
- Pantothenic acid – as CoA
- Pyridoxine – as PLP (pyridoxal 5-phosphate)
- Biotin

Stoker 2014, Figure 24-19 p916
Readings & Resources

• Stoker, HS 2004, *General, Organic and Biological Chemistry*, 3rd edn, Houghton Mifflin, Boston, MA.
• Timberlake, KC 2014, *General, organic, and biological chemistry: structures of life*, 4th edn, Pearson, Boston, MA.