Digestion and Absorption of Carbohydrate
DIGESTION OF DIETARY CARBOHYDRATES

- In the digestive tract, dietary polysaccharides and disaccharides are converted to monosaccharides by glycosidases, enzymes that hydrolyze the glycosidic bonds between the sugars.

- All of these enzymes exhibit some specificity for the sugar, the glycosidic bond (or), and the number of saccharide units in the chain.

- The monosaccharides formed by glycosidases are transported across the intestinal mucosal cells into the interstitial fluid and subsequently enter the bloodstream.

- Undigested carbohydrates enter the colon, where they may be fermented by bacteria.
Overview of carbohydrate digestion
Action of Salivary and Pancreatic $\alpha$-amylase

- Starch
- Maltose
- Isomaltose
- Trisaccharides (and larger oligosaccharides)
- $\alpha$-Dextrins (oligosaccharides with $\alpha$-$1,6$ branches)
Maltose

α-1,4 bond

HO-\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{H}\)

1. maltase activity
2. reducing end

Maltotriose

Lactose

β-1,4 bond

Galactose

Glucose

Trehalose

HO-\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{H}\)

1,6 bond

HO-\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{H}\)

isomaltase activity

HO-\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{D-}\)\(\text{H}\)

1. trehalase activity
2. Glucose
Carbohydrate Digestion

- In the small intestine, pancreatic amylase among other enzymes (maltase, sucrase, and lactase) hydrolyzes starches to disaccharides and monosaccharides.
- In the large intestine, fibers remain and attract water, soften stools and ferment.
Mouth and salivary glands
The salivary glands secrete saliva into the mouth to moisten the food. The salivary enzyme amylase begins digestion:
- Starch → Amylase → Small polysaccharides, malsose

Stomach
Stomach acid inactivates salivary enzymes, halting starch digestion.

Small intestine and pancreas
The pancreas produces an amylase that is released through the pancreatic duct into the small intestine:
- Pancreatic amylase → Small polysaccharides, maltose

Then disaccharidase enzymes on the surface of the small intestinal cells hydrolyze the disaccharides into monosaccharides:
- Maltose → Malase → Glucose + Glucose
- Sucrose → Sucrase → Fructose + Glucose
- Lactose → Lactase → Galactose + Glucose

Intestinal cells absorb these monosaccharides.

Mouth
The mechanical action of the mouth crushes and tears fiber in food and mixes it with saliva to moisten it for swallowing.

Stomach
Fiber is not digested, and it delays gastric emptying.

Small intestine
Fiber is not digested, and it delays absorption of other nutrients.

Large intestine
Most fiber passes intact through the digestive tract to the large intestine. Here, bacterial enzymes digest fiber:
- Bacterial enzymes
- Short-chain fatty acids, gas
Fiber holds water; regulates bowel activity; and binds substances such as bile, cholesterol, and some minerals, carrying them out of the body.
Carbohydrate Absorption

- Primarily takes place in the small intestine.
- Glucose and galactose are absorbed by active transport.
- Fructose is absorbed by facilitated diffusion.

Monosaccharides, the end products of carbohydrate digestion, enter the capillaries of the intestinal villi.

In the liver, galactose and fructose are converted to glucose.

Key:
- Glucose
- Fructose
- Galactose

Small intestine

Monosaccharides travel to the liver via the portal vein.
Carbohydrate Metabolism
Metabolism

- **Metabolite** = Biological compound

- **Catabolism**: All the reactions concerned with breaking down compounds and generating and storing energy for the needs of the cell and organism. Energy = ATP

- **Anabolism**: All the reactions concerned with the biosynthesis of complex compounds from simpler compounds. Usually use ATP.
Larger molecules → Metabolism → Smaller molecules + Energy

Catabolism

Anabolism
General Pathways of Metabolism

Catabolism

Breakdown of macromolecules to building blocks

- **Protein**: Amino acids
- **Polysaccharide**: Glucose, other sugars
- **Lipid**: Glycerol, fatty acids
- **Nucleic Acids**: Ribose, bases, phosphate
ATP Is Generated Through 3 Energy Systems

1. ATP-PCr system
2. Glycolytic system
3. Oxidative system
INTERACTION OF ENERGY SYSTEMS

Immediate

ATP/PCr system

Short-term

Anaerobic glycolysis

Long-term

Oxidative system

Duration of all-out exercise (s)
## Energy Systems for Exercise

<table>
<thead>
<tr>
<th>Energy Systems</th>
<th>Mole of ATP/min</th>
<th>Time to Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate: ATP - PCr (ATP &amp; Phosphocreatine)</td>
<td>4</td>
<td>5 to 10 sec</td>
</tr>
<tr>
<td>Short Term: Glycolytic (Glycogen-Lactic Acid)</td>
<td>2.5</td>
<td>1 to 2 min</td>
</tr>
<tr>
<td>Long Term: Oxidative</td>
<td>1</td>
<td>Unlimited time</td>
</tr>
</tbody>
</table>
Glucose Metabolism

MEDICAL AND BIOLOGICAL IMPORTANCE

• Glucose is the preferred source of energy for most of the body tissues.
• Glucose is central to all of the metabolism.
• In mammals, glucose is the only fuel that the brain uses under non-starvation conditions and the only fuel that red blood cells can use at all.
• Glucose is the precursor for the synthesis of an array of other sugars that are required for the production of specialized compounds, such as lactose, cell surface antigens, nucleotides, or glycosaminoglycans.
• Glucose is also the fundamental precursor of noncarbohydrate compounds; it can be converted to lipids, amino acids, and nucleic acids.
Carbohydrate → Simple sugars (mainly glucose) → Digestion and absorption → Acetyl-CoA → Citric acid cycle → 2CO₂

Protein → Amino acids → Digestion and absorption → Acetyl-CoA → Citric acid cycle → 2CO₂

Fat → Fatty acids + glycerol → Digestion and absorption → Acetyl-CoA → Citric acid cycle → 2CO₂

Acetyl-CoA → Citric acid cycle → 2H → ATP
Transport and fate of major carbohydrate and amino acid substrates and metabolites.
Glycolysis or Embden-Meyerhof–Parnas pathway
Glucose entry into cells

• Facilitated diffusion

• Sodium-glucose cotransporter

<table>
<thead>
<tr>
<th>Tissue Location</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitative bidirectional transporters</td>
<td></td>
</tr>
<tr>
<td>GLUT 1</td>
<td>Brain, kidney, colon, placenta, erythrocyte</td>
</tr>
<tr>
<td>GLUT 2</td>
<td>Liver, pancreatic B cell, small intestine, kidney</td>
</tr>
<tr>
<td>GLUT 3</td>
<td>Brain, kidney, placenta</td>
</tr>
<tr>
<td>GLUT 4</td>
<td>Heart and skeletal muscle, adipose tissue</td>
</tr>
<tr>
<td>GLUT 5</td>
<td>Small intestine</td>
</tr>
</tbody>
</table>
**Definition:** It is the sequence of 10 reactions that breakdown one molecule of glucose (six carbon) to three carbon molecules of pyruvate, with the production of ATP.

**Location:** All the cells of the body

**Site:** Cell cytosol
Cytoplasm of all tissue cells, but it is of physiological importance in:

1. Tissues with no mitochondria: mature RBCs, cornea and lens.

2. Tissues with few mitochondria: Testis, leucocytes, medulla of the kidney, retina, skin and gastrointestinal tract.

3. Tissues undergo frequent oxygen lack: skeletal muscles especially during exercise.
Functions and importance of glycolysis

- It is the only pathway that is taking place in all the cells of the body.
- In RBCs glycolysis is the only pathway which produce energy, because they lack mitochondria.
- In strenuous exercise, when muscle tissue lacks enough oxygen, anaerobic glycolysis
  Forms the major source of energy for muscles.
- Glycolysis also contributes to the synthesis of certain specialized intermediates e.g. 2,3-bisphosphoglycerate, an allosteric effector of haemoglobin.
- It provides carbon skeletons for synthesis of non-essential amino acids as well as glycerol part of fat.
Provides important intermediates:

a) Dihydroxyacetone phosphate: can give glycerol-3-phosphate, which is used for synthesis of triacylglycerols and phospholipids (lipogenesis).

b) 3 Phosphoglycerate: which can be used for synthesis of amino acid serine.

c) Pyruvate: which can be used in synthesis of amino acid alanine.

Aerobic glycolysis provides the mitochondria with pyruvate, which gives acetyl CoA for Krebs' cycle.
Stages of glycolysis

1. Stage one (the energy requiring stage/energy investment phase/priming stage):
   a) One molecule of glucose is converted into two molecules of glyceroldehyde-3-phosphate.
   b) These steps requires 2 molecules of ATP (energy loss)

2. Stage two (Splitting phase) (6C= 3C+3C):

3. Stage three (the energy producing stage):
   a) The 2 molecules of glyceroaldehyde-3-phosphate are converted into pyruvate (aerobic glycolysis) or lactate (anaerobic glycolysis).
   b) These steps produce ATP molecules (energy production).

Energy (ATP) production of glycolysis:

ATP production = ATP produced - ATP utilized
Stages of glycolysis

• Energy investment phase (reactions 1-3)

• Splitting phase (reaction 4-5)

• Energy generating phase (reactions 6-10)
Overview Reactions of glycolysis

The sequence of events occurs following as shown below:

A. Energy investment phase:

1. Glucose is phosphorylated to glucose 6-phosphate by enzyme hexokinase or glucokinase (both are isoenzymes). This is an irreversible reaction and dependent on ATP and Mg2+.
   Note: Glucose 6-phosphate is impermeable to the cell membrane. And it is a central a molecule with a variety of metabolic fates are occurred such as glycolysis, glycogenesis, gluconeogenesis and pentose phosphate pathway.

2. Glucose 6-phosphate undergoes isomerization to gives fructose 6-phosphate in the presence of the enzyme phosphohexose isomerase and Mg2+.

3. Fructose 6-phosphate is phosphorylated to fructose 1,6-bisphosphate by enzyme phosphofructokinase (PFK). It is an irreversible stage and a regulatory step in the glycolysis cycle.
B. Splitting phase

4. Fructose 1, 6-bisphosphate (6-carbon) is split into two three-carbon compounds such as glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by the enzyme aldolase (fructose 1,6-bisphosphate aldolase).

5. The reversible interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by the enzyme phosphotriose isomerase act as catalyzes. Thus, two molecules of glyceraldehyde 3-phosphate are obtained from a single molecule of glucose.
C. Energy generation phase:

6. Glyceraldehyde 3-phosphate converted into 1,3-bisphosphoglycerate by enzyme Glyceraldehyde 3-phosphate dehydrogenase. This is an important step because it is involved in the formation of NADH + H+ and high energy compound 1,3-bisphosphoglycerate. During the aerobic conditions, NADH passes through the electron transport chain and 6 ATP are synthesized by oxidative phosphorylation. Iodoacetate and arsenate inhibit the enzyme glyceraldehyde 3-phosphate dehydrogenase.

7. 1,3-bisphosphoglycerate converted into 3-phosphoglycerate and produces ATP by enzyme phosphoglycerate kinase. This step is a good example of substrate Level phosphorylation. Hence ATP is synthesized from the substrate without the involvement of the electron transport chain. It is a reversible reaction and a rare example among the kinase reactions.
C. Energy generation phase

8. 3-Phosphoglycerate is converted into 2-phosphoglycerate by enzyme phosphoglycerate mutase. It is an isomerization reaction.

9. 2-phosphoglycerate converted into high energy compound phosphoenolpyruvate by the enzyme enolase. This enzyme requires Mg$^{2+}$ or Mn$^{2+}$ and is inhibited by fluoride.

10. The enzyme pyruvate kinase catalyzes the transfer of high energy phosphate (pyruvate) from phosphoenolpyruvate to ADP, leading to the formation of ATP. This enzyme Pyruvate kinase requires K$^+$ and either Mg$^{2+}$ or Mn$^{2+}$. This reaction is irreversible.
• In the energy investment phase, ATP provides activation energy by phosphorylating glucose.
  – This requires 2 ATP per glucose.
• In the energy payoff phase, ATP is produced by substrate-level phosphorylation and NAD\(^+\) is reduced to NADH.
• 2 ATP (net) and 2 NADH are produced per glucose.
Energy Investment Phase (steps 1-5)
Glucose

1. Hexokinase
2. Phosphohexose isomerase
3. Phosphofructokinase-1
4. Aldolase
5. Triose phosphate isomerase

First priming reaction:
Glucose → Glucose 6-phosphate

ATP → ADP

Second priming reaction:
Fructose 6-phosphate → Fructose 1,6-bisphosphate

ATP → ADP

Cleavage of 6-carbon sugar phosphate to two 3-carbon sugar phosphates:
Glyceraldehyde 3-phosphate + Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate (2)

oxidation and phosphorylation

1,3-Bisphosphoglycerate (2)

first ATP-forming reaction (substrate-level phosphorylation)

3-Phosphoglycerate (2)

2-Phosphoglycerate (2)

Phosphoenolpyruvate (2)

Glyceraldehyde 3-phosphate dehydrogenase

Phosphoglycerate kinase

Phosphoglycerate mutase

Enolase

Pyruvate kinase
Each of these reactions occurs twice because two glyceroldehyde-3-phosphates are produced from one glucose.
<table>
<thead>
<tr>
<th>Reaction Number</th>
<th>Reaction</th>
<th>Enzyme(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glucose + ATP $\rightarrow$ glucose-6-phosphate + ADP</td>
<td>Hexokinase</td>
</tr>
<tr>
<td>2</td>
<td>Glucose-6-phosphate $\leftrightarrow$ fructose-6-phosphate</td>
<td>Phosphoglucoisomerase</td>
</tr>
<tr>
<td>3</td>
<td>Fructose-6-phosphate + ATP $\rightarrow$ fructose-1,6-bisphosphate + ADP</td>
<td>Phosphofructokinase</td>
</tr>
<tr>
<td>4</td>
<td>Fructose-1,6-bisphosphate $\leftrightarrow$ dihydroxyacetone phosphate + glyceraldehyde-3-phosphate</td>
<td>Aldolase</td>
</tr>
<tr>
<td>5</td>
<td>Dihydroxyacetone phosphate $\leftrightarrow$ glyceraldehyde-3-phosphate</td>
<td>Triose phosphate isomerase</td>
</tr>
<tr>
<td>6</td>
<td>Glyceraldehyde-3-phosphate + P(_i) + NAD(^+) $\leftrightarrow$ 1,3-bisphosphoglycerate + NADH(^+)</td>
<td>Glyceraldehyde-3-phosphate dehydrogenase</td>
</tr>
<tr>
<td>7</td>
<td>1,3-Bisphosphoglycerate + ADP $\leftrightarrow$ 3-phosphoglycerate + ATP</td>
<td>Phosphoglycerate kinase</td>
</tr>
<tr>
<td>8</td>
<td>3-Phosphoglycerate $\leftrightarrow$ 2-phosphoglycerate</td>
<td>Phosphoglycerate mutase</td>
</tr>
<tr>
<td>9</td>
<td>2-Phosphoglycerate $\leftrightarrow$ phosphoenolpyruvate + H(_2)O</td>
<td>Enolase</td>
</tr>
<tr>
<td>10</td>
<td>Phosphoenolpyruvate + ADP $\rightarrow$ pyruvate + ATP</td>
<td>Pyruvate kinase</td>
</tr>
</tbody>
</table>
Energy yield of glycolysis

Generation and consumption of ATP in anaerobic and aerobic glycolysis is given below.

In aerobic glycolysis:

1. Number of ATPs generated by phosphoglycerate kinase 2
2. Number of ATPs generated by Pyruvate kinase 2
3. Number of ATPs generated by respiratory chain
   oxidation of 2 NADH produced in reaction 6 6
4. Number of ATPs consumed in reaction 1 and 3 -2

Net = \( 8 \)

In anaerobic glycolysis, 2 NADH produced in reaction 6 are used to convert pyruvate to lactate. Hence, ATP is not generated. Therefore, the net ATP production in anaerobic glycolysis is only 2 \((8 - 6 = 2)\). Thus, oxidation of glucose to pyruvate (aerobic glycolysis) generates 8 ATP molecules whereas oxidation of glucose to lactate (anaerobic glycolysis) generates 2 ATP molecules.
Glycolysis

Glucose (6 C)

ATP
NADH

2 pyruvate (3 C)

CO₂

Acetyl CoA

FADH₂
NADH

Krebs

CO₂

ATP

Electrons

Electron transport

O₂ is final electron acceptor.
Regulation of glycolysis

- **Hexokinase**: Hexokinase is controlled by product inhibition: high level of glucose-6-phosphate allosterically inhibit it.

- **Glucokinase** is activated by high concentration of glucose in blood and insulin.

- **Phosphofructokinase**: ATP and Citrate are the most important inhibitor. Whereas AMP, ADP, and F-2,6-bisphosphate acts as a Allosteric activator.

- **Pyruvate kinase**: Inhibited by ATP and activated by F1,6-BP.

Insulin favors glycolysis by activating the above glycolytic enzymes. Glucagon and glucocorticoids inhibit glycolysis and favor gluconeogenesis.
Inhibitors of Glycolysis

1. Iodoacetate, arsenate and heavy metals like Hg$^{2+}$, Ag$^+$ inhibits activity of glyceraldehyde-3-phosphate dehydrogenase. They combine with -SH of active site and makes enzyme inactive.

2. Enolase is inhibited by fluoride.
Reduction of pyruvate to lactate

- Lactate, formed by the action of lactate dehydrogenase, is the final product of anaerobic glycolysis in eukaryotic cells.
- The formation of lactate is the major fate for pyruvate in red blood cells, lens and cornea of the eye.
Summary of anaerobic glycolysis

ATP consumption

Glucose → Glucose 6-P → Fructose 6-P → Fructose 1,6-bis-P → Glyceraldehyde 3-P → DHAP

NADH production

2 NAD^+ + Pi → 2 NADH + 2H^+

ATP production

2 ADP + 2 ATP → 2 (3-Phosphoglycerate) → 2 (2-Phosphoglycerate) → 2 (Phosphoenolpyruvate) → 2 (Lactate) → 2 (Pyruvate)

NADH consumption

2 NADH + 2H^+ → 2 NAD^+
Importance of lactate production in anaerobic glycolysis:

1. In absence of oxygen, lactate is the end product of glycolysis:

   \[
   \text{Glucose} \rightarrow \text{Pyruvate} \rightarrow \text{Lactate}
   \]

2. In absence of oxygen, NADH\(^+\) is not oxidized by the respiratory chain.

3. The conversion of pyruvate to lactate is the mechanism for regeneration of NAD\(^+\).

4. This helps continuity of glycolysis, as the generated NAD\(^+\) will be used once more for oxidation of another glucose molecule.
### Differences between aerobic and anaerobic glycolysis:

<table>
<thead>
<tr>
<th></th>
<th><strong>Aerobic</strong></th>
<th><strong>Anaerobic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. End product</td>
<td>Pyruvate</td>
<td>Lactate</td>
</tr>
<tr>
<td>2. Energy</td>
<td>8 ATP</td>
<td>2 ATP</td>
</tr>
<tr>
<td>3. Regeneration of NAD&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Through respiration chain in mitochondria</td>
<td>Through Lactate formation</td>
</tr>
<tr>
<td>4. Availability to TCA in mitochondria</td>
<td>Available and 2 Pyruvate can oxidize</td>
<td>Not available as lactate is cytoplasmic substrate</td>
</tr>
</tbody>
</table>
Shuttle Systems

Functions of the shuttles:
• Transport electrons from NADH into mitochondria for ATP generation by the electron transport chain.
• Regenerate NAD⁺ to allow glycolysis to continue.

Glycerol-3-phosphate shuttles

It is active in skeletal muscle and brain.

Figure: Glycerophosphate shuttle for transfer of reducing equivalents from the cytosol into the mitochondrion.
Malate-aspartate shuttle

It is active in liver, kidney and heart.

**Figure:** Malate shuttle for transfer of reducing equivalents from the cytosol into the mitochondrion. 1 Ketoglutarate transporter; 2, glutamate/aspartate transporter (note the proton symport with glutamate).
Glucose is metabolized differently in various cells

Red blood cells (RBCs)

- Glucose is metabolized mainly by glycolysis in red blood cells.
- Since red blood cells lacks mitochondria, the end product of the glycolysis is lactic acid.
- Pentose phosphate pathway in RBCs is active.
Brain cells

- Brain like RBCs take up glucose by mediated transport in an insulin independent manner.
- Glycolysis in the brain yields pyruvate, which is then oxidized completely to CO2 and H2O.
- The pentose phosphate pathway is also quite active in these cells.
Muscle and Heart tissue cells

- These cells readily utilized glucose and transport of glucose is dependent on the presence of insulin.
- Glucose can be utilized by glycolysis to give pyruvate and lactate.
- Pyruvate further utilized by pyruvate dehydrogenase complex and oxidized completely to CO2 and H2O via TCA cycle.
- Synthesis and Degradation of glycogen are important process in these cells.
Adipose tissue cells

- In these cells glucose accumulates by an insulin-dependent manner.
- Pyruvate as in other cells, is generated by glycolysis and is further oxidized to Acetyl COA.
- Instead of being completely oxidized to CO2 and H2O, Acetyl COA is used primarily for de novo fatty acid synthesis.
- Pentose phosphate pathway is active in these cells.
- Glycogenesis and glycogenolysis are limited in this tissue than in muscle and heart.
Liver Parenchymal cells

- Glucose uptake is insulin independent.
- Pentose phosphate is highly active.
- Glycogen storage is an important feature of the liver.
- Glucose can also be used in glucoronic acid pathway, important in drug and bilirubin detoxification.
- Liver also has significant capacity for glycolysis. Pyruvate produced being used as a source of
  - Acetyl CoA for complete oxidation by the TCA cycle and for the synthesis of fat.
- Liver also has capacity to convert three carbon precursors, such as lactate, pyruvate and
- Alanine in glucose by gluconeogenesis.
Rapoport-Luberin cycle

1,3 bisphosphoglycerate $\xleftrightarrow{\text{mutase}}$ 2,3 BPG

ADP $\xrightarrow{\text{phosphatase}}$ ATP $\xrightarrow{\text{Rapoport-Luberin shunt}}$ 3-phosphoglycerate

$\text{HbO}_2$ $\rightarrow$ Hb + O$_2$

1. Hydrogen ions
2. 2,3-Bisphosphoglycerate
3. Covalent binding of CO$_2$

RBCs
2,3-Bisphosphoglycerate (2,3-BPG) is formed in red blood cells from the glycolytic intermediate 1,3-bisphosphoglycerate.

2,3-BPG lowers the affinity of hemoglobin for oxygen. Therefore, oxygen is less readily bound (i.e., more readily released in tissues) when hemoglobin contains 2,3-BPG.

\[ \text{HbBPG} + \text{O}_2 \rightleftharpoons \text{HbO}_2 + \text{BPG} \]