Carbohydrate Metabolism

Biochemistry-2 (PHL-285)

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FUEL METABOLISM

- **Fed State.**
- **Fasting State.**
- **Starvation**

CARBOHYDRATE METABOLISM

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- **Absorption.**
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FUEL METABOLISM

The average 70 kg man has fuel stores consisting of :

- 15 kg of triglyceride,
- 6 kg of protein and
- 0.2 kg of glycogen

FED STATE

Signals:	**Storage forms:**
Insulin: Up	Glycogen: Up
Glucagon: Down	Fat: Up
	Protein: Up

FASTING STATE

Signals:	**Storage forms:**
Insulin: Down	Glycogen: Down
Glucagon: Up	Fat: Down
	Protein: Down

STARVATION

Signals:	**Storage forms:**
Insulin: Down	Glycogen: Exhausted
Glucagon: Up	Fat: Down
	Protein: Down

INSULIN:

- It is a signal for high blood glucose levels.
- It stimulates synthesis of glycogen,fat,and protein.
- It inhibits breakdown of glycogen, fat ,and protein.
- It increases glucose transport into cells (muscle and adipose tissue).

GLUCAGON:

- It is a signal for low blood glucose levels.
- It stimulates breakdown of glycogen,fat,and protein.
- It inhibits synthesis of glycogen, fat ,and protein.
- It increases protein phosphorylation.

  It activates cAMP-dependent protein kinase.

DIGESTION OF CARBOHYDRATES

The major dietary carbohydrates are **starch**, **sucrose**, and **lactose**. They are digested mainly to: **glucose**, **fructose** and **galactose**.

MOUTH:

-Salivary α-amylase cleaves starch by breaking α-1,4 linkages between glucose residues within the chains. α -Dextrins are the major products.

STOMACH:

The stomach acid inhibits the action of salivary α -amylase.

INTESTINE:

A. Digestion by Pancreatic Enzymes:

-Pancreatic α-amylase cleaves α-1,4 linkages between glucose residues within glucose polymers.

The products are the disaccharide maltose, the trisaccharide maltotriose, and small oligosaccharides containing α-1,4 and α-1,6 linkages.

B. Digestion by Enzymes of Intestinal Cells:

- α-glucosidase cleaves glucose residues from the nonreducing ends of oligosaccharides.

- α-dextrinase cleaves α-1,6 linkages ,releasing glucose residues from branched oligosaccharides.

-Sucrase converts sucrose to glucose and fructose.

-Lactase converts lactose to glucose and galactose.

C. Carbohydrates that cannot be Digested:

Cellulose (which consists of glucose units linked β-1,4) are part of the dietary fiber that passes through the intestine into the feces.

D. Intestinal Lactase Deficiency:

Very common condition in which lactose cannot be digested and is oxidized by bacteria in the gut, producing gas, bloating, and watery diarrhea.

ABSORPTION OF CARBOHYDRATES

The final products of carbohydrate digestion, **glucose**, **fructose**, and **galactose**, are absorbed by intestinal epithelial cells and enter the blood.

GLYCOLYSIS

1. Definition:

Glycolysis is a process in which glucose is enzymatically split into two molecules of pyruvate. It is an oxidative pathway that does not require oxygen.

2. Site:

It occurs in the cytosol of all cells of the body.

3. Stages:

1. The conversion of hexose to triose phosphate: ATP-consuming phase,
2. The conversion of triose phosphate to pyruvate: ATP-producing phase.

4. The reactions of glycolysis:

1. Glucose is converted to glucose 6-phosphate in a reaction that utilizes ATP and produces ADP. Enzymes**: hexokinase** and, in liver, **glucokinase**.
2. Glucose 6-phosphate is isomerized to fructose 6-phosphate.
Enzyme: **phosphoglucose isomerase**.
3. Fructose 6-phosphate is phosphorylated by ATP. Fructose 1,6-bisphosphate and ADP are formed.
Enzyme: **phosphofructokinase** (PFK1).
4. Fructose 1,6-bisphosphate is cleaved to form the triose phosphates, glyceraldehyde 3-phosphate and dihydroxyacetone phosphate.
Enzyme: **aldolase**.
5. Dihydroxyacetone phosphate is isomerized to glyceraldehyde 3-phosphate. Enzyme: **triose phasphate isomerase**.
6. Glyceraldehyde 3-phosphate is oxidized by NAD^+ and reacts with inorganic phosphate (Pi). 1,3-Bisphosphoglycerate and NADH + H^+ are formed. Enzyme**: glyceraldehyde 3-phosphate dehydrogenas**e**.**
The aldehyde group of glyceraldehyde-3-phosphate is oxidized to a carboxylic acid which forms a high-energy anhydride with Pi.
7. The energy in the anhydride group of 1,3-bisphosphoglycerate is used to produce ATP from ADP in a reaction that also produces 3-phosphoglycerate. Enzyme: **phosphoglycerate kinase**.
8. The phosphate group of 3-phospholgycerate is transferred to carbon 2, and 2-phosphoglycerate is formed. Enzyme: **phosphoglyceromutase**.
9. 2-Phosphoglycerate is dehydrated, forming phosphoenolpyruvate (PEP)
Enzyme: **enolase**.
Phosphoenolpyruvate has a high-energy enol phosphate.

10. Pyruvate is formed from phosphoenolpyruvate, and ATP is produced from ADP. Enzyume: **pyruvate kinase**.

5. The Fate of Pyruvate:

A. Conversion to Lactate:

Pyruvate can be reduced in the cytosol by NADH, forming lactate.
by lactate dehydrogenase. Lactate is produced by tissues such as red blood cells or exercising muscle.

B .Conversion to Acetyl CoA:

Pyruvate can enter mitochondria and be converted to acetyl CoA by pyruvate dehydrogenase.

C. Convertion to oxaloacetate:

Pyruvate may be converted to oxaloacetate by pyruvate carboxylase, an enzyme found in tissues such as liver and brain but not in muscle. This reaction serves to replenish intermediates of the TCA cycle.

D. Conversion to Alanine:

Pyruvate may be transaminated to form the amino acid alanine.

6. The Fate of NADH:

A. Anaerobic glycolysis: NADH is utlilized to reduce pyruvate to lactate.

B. Aerobic glycolysis: NADH is reoxidized in mitochondria to produce ATP. NADH cannot directly cross the mitochondrial membrane. Therefore, the electrons are passed to the mitochondrial electron transport chain by **two** shuttle systems:

A. The Glycerol Phosphate Shuttle:

Each mole of $FADH_2$ that is produced generates 2 moles of ATP via oxidative phosphorylation.
Because glycolysis produces 2 moles of NADH per mole of glucose, 4 moles of ATP are produced by this shuttle.

B. The Malate Aspartate Shuttle:

Each mole of NADH generates 3 moles of ATP via oxidative phosphorylation.
Because glycolysis produces 2 moles of ATP per mole of glucose, 6 moles of ATP are produced by this shuttle.

7. The Generation of ATP by Glycolysis:

A. Glycolysis Produces ATP and NADH:

Overall, when one mole of glucose is converted to two moles of pyruvate, two moles of ATP are utilized in the process, and four moles of ATP are produced, for a net yield of 2 moles of ATP.

In addition, 2 moles of cytosolic NADH are generated.

B. Energy Generated by Conversion of Glucose to Lactate (Anaerobic glycolysis):

If the NADH generated by glycolysis is utilized to reduce pyruvate to lactate, the net yeield is 2 moles of ATP per mole of glucose converted to lactate.

C. Energy generated by conversion of glucose to pyruvate(Aerobic glycolysis):

6 moles of ATP are produced if glycerol phosphate shuttle is used or

8 moles of ATP if the malate aspartate shuttle is used.

D. Energy Generated by Conversion of Glucose to CO_2 and H_2 and H_2O:

Totally, when one mole of glucose is oxidized to CO_2 and H_2O, 36 moles of ATP are produced if the glycerol phosphate shuttle is used or 38 moles if the malate aspartate

8. Regulation of glycolysis:

A. Hexokinase: Hexokinase is found in most tissues

-Hexokinase has a low Km for glucoes (about 0.1 mM) and a low Vmax.

-It is very active even at fasting blood glucose levels (5 mM).

-Hexokinase is inhibited by its product, glucose- 6-phosphate.

B. Glucokinase: Glucokinase is found in the liver and functions at a significant rate only after a meal (fed state).

-Glucokinase has a high Km for glucose (10 mM) and a high Vmax.

It is very active after a meal when glucose levels are high, and relatively inactive during fasting when glucose levels are low.

-Glucokinase is induced when insulin levels are high.

-Glucokinase is not inhibited by glucose 6-phosphate.

C. Phosphofructokinase (PFK1):

-PFK1 is activated by **AMP**. and **fructose-2,6-bisphosphate**

-Fructose-2,6-biphosphate is formed from fructose-6-phosphate by phosphofructokinase 2 (PFK2)..

PFK1 is inhibited by **ATP** and **citrate**.

D. Pyruvate Kinase:

Pyruvate kinase is inhibited in the liver during fasting when glucagon levels are high.

-Glucagon via cAMP activates protein kinase.
-Protein kinase phosphorylates and inactivates pyruvate kinase.

9. Inhibitors of glycolysis:

Enzyme	**Inhibitor**
Hexokinase	2-Deoxyglucose
Glyceraldehyde-3-phosphate dehydrogenase	Iodoacetate
Enolase	Fluoride

10.Glycolysis in red blood cells:

- Lactic acid is the end product of glycolysis in red blood cells because there is no other means for regenerating NAD^+ except by reducing pyruvate to lactate (no respiratory chain).
- Energy is obtained from glycolysis (2 ATP).
- 1,3-bisphosphoglycerate are converted to 2,3-bisphosphoglycerate, a compound that decreases the affinity of hemoglobin for oxygen.

11. Diseases associated with impaired glycolysis:

1. Lactic Acidosis:

This condition can be caused by:

Hypoxia: Lack of oxygen results in increased NADH levels, and more pyruvate is converted to lactate than normal.

Alcohol ingestion: High NADH levels from alcohol metabolism cause pyruvate to be converted to lactate.

2. Pyruvate Kinase Deficiency:

Deficiency of pyruvate kinase causes:
-Decreased production of ATP from glycolysis. (Hemolytic anemia)
-Decreased hemoglobin oxygen affinity through the increase in 2,3-BPG.

3. Hexokinase deficiency:

Deficiency of hexokinase causes:
-Decreased production of ATP from glycolysis. (Hemolytic anemia)
-Increased hemoglobin oxygen affinity through the decrease in 2,3-BPG. In consequence, the oxygen is less available for the tissues.

12. Biological importance of glycolysis:

1. It is a source of ATP.
2. It connects between carbohydrates and fat metabolism through dihydroxyacetone phosphate.
3. It is essential part of gluconeogenesis

GLYCOGEN SYNTHESIS AND DEGRADATION

1. Glycogen Structure:

- Glycogen is a branched polymer consisting of D-glucose residues.
- The Linkage between glucose residues is α-1,4 except at branch points where the linkage is α-1,6.
- On the average, there is a branch every 10 residues.
- Each glycogen molecule has one reducing end and many nonreducing ends.
- Nonreducing ends are the points at which elongation of the polymer occurs during synthesis and where release of glucose residues occurs during degradation.

2. Site of Glycogen storage and metabolism:

Cytosol of muscle and liver cells .

3. Glycogen Synthesis:

A. Synthesis of UDP-Glucose:

Glucose enters the cell and is phosphorylated to glucose 6-phosphate by hexokinase (or by glucokinase in the liver).

Phosphoglucomutase converts glucose 6-phosphate to glucose 1-phosphate.Glucose 1-phosphate reacts with UTP, forming UDP-glucose in a reaction catalyzed by UDP-glucose pyrophosphorylase.

B. The Action of Glycogen Synthetase:

Glucose residues from UDP-glucose are transferred to the nonreducing ends of a glycogen primer by the enzyme glycogen synthetase.

C. The Formation of Branches:

When a chain contains 11 or more glucose residues, an oligomer, 6 to 8 residues in length, is removed from the nonreducing end of the chain. It is attached via an α-1,6 linkage to a glucose residue within an α-1,4-linked chain. Enzyme: 4,6-transeferase (branching enzyme)

D. Growth of Glycogen Chains:

Glycogen synthetase continues to add glucose residues to the nonreducing ends of newly formed branches as well as to the ends of the original chains. As the chains continue to grow, additional branches are produced by the branching enzyme.

4. Glycogen Degradation:

A. The Action of Phosphorylase:

Phosphorylase removes glucose residues, one at a time, from the nonreducing ends of glycogen molecules.

-Phosphorylase utilizes inorganic phosphate (Pi) to cleave α -1,4 bonds, producing glucose 1-phosphate.

Phosphorylase can act only until it is four glucose units from a branch

B. The Removal of Branches:

The four units remaining on the branch are removed by the debranching enzyme that has both glucosyl 4:4 transferase and α -1,6-glucosidase activity.

-Three of the four residues that remain at the branch point are removed as a trisaccharide and attached to the nonreducing end of another chain.

-The enzyme is a -4:4-transferase, which cleaves an α -1,4 bond and forms a new α -1,4 bond.

-One glucose unit remains linked α -1,6 at the branch point.

-This single glucose residue is hydrolyzed by α-1,6-glucosidase, which forms free glucose.

C. Degradation of Glycogen Chains:

The phosphorylase/debranching process is repeated, generating glucose 1-phosphate and free glucose in about a 10:1 ratio that reflects the length of the chains in the outer region of the glycogen molecule.

D. The Fate of Glucosyl Units Released from Glycogen:

In liver, glycogen is degraded to maintain blood glucose.

-Glucose 1-phosphate is converted by phosphoglucomutase to glucose 6-phosphate. Inorganic phosphate is released by glucose 6-phosphatase, and free glucose enters the blood.

In muscle, glycogen is degraded to provide energy for contraction.

-Phosphoglucomutase converts glucose 1-phosphate to glucose 6-phosphate, which enters the pathway of glycolysis and is converted either to lactate or to CO_2 and H_2O, generating ATP.

-Muscle does not contain glucose 6-phosphatase and, therefore, does not contribute to the maintenance of blood glucose.

5. Regulation of Glycogen Stores:

A. Glycogen Degradation:

Glucagon acts on liver cells

Epinephrine (adrenaline) acts on both liver and muscle cells

.These hormones activate adenyl cyclase in the cell membrane, which converts ATP to cAMP. cAMP activates protein kinase Protein kinase phosphorylates glycogen synthetase, causing it to be inactive, thereby decreasing glycogen synthesis.

Protein kinase causes phosphorylase to be activated, thereby increasing glycogen degradation.

-Protein kinase phosphorylates phosphorylase kinase, an enzyme that phosphorylates phosphorylase b, converting it to its active form, phosphorylase a.

-Phosphorylase a stimulates glycogen breakdown, producing glucose 1-phosphate.

Muscle utilizes mechanisms in addition to the one mediated by cAMP.

a) Muscle responds to changes in AMP levels. As AMP rises, phosphorylase is activated. AMP levels rise when muscle is contracting.

b) Phosphorylase kinase is activated by Ca^{2+}, which is released from the sarcoplasmic reticulum during muscle contraction.

B. Glycogen Synthesis:

Insulin timulates the synthesis of glycogen in both liver and muscle.

1. Factors that Promote Glycogen Synthesis in Liver:

In the fed state, glucagon is low, and the cAMP cascade in liver is not activated.

-cAMP is converted to AMP by a phosphodiesterase.-

-Dephosphorylation of phosphorylase kinase and phosphorylase a cause these enzymes to be inactivated.

-Insulin, via a factor produced in cells, activates the phosphatases that dephosphorylate these enzymes.

Glycogen synthesis is promoted by activation of glycogen synthetase as well as by the increased concentration of glucose that is entering the cells from the hepatic portal vein.

-The inactive, phosphorylated form of glycogen synthetase is dephosphorylated, and the enzyme becomes active.

2. Factors that Promote Glycogen Synthesis in Muscle:

After a meal, muscle will have low levels of cAMP, AMP, and Ca^{2+} if it is not contracting and epinephrine is low. Consequently, muscle glycogen degradation will not occur.

Glycogen synthesis will be stimulated by insulin. In addition, insulin stimulates the uptake of glucose by muscle.

6. Glycogen storage disease:

A. Type I (von Gierke's disease):
This is a disease characterised by a deficiency of glucose 6-phosphatase in liver. The symptoms include:
a) Fasting hypoglycemia.
b) Lactic acidemia,
c) Hyperlipidemia,
d) Hyperuricemia (with gouty arthritis),

B. Other types:
These are summarized in Table.

GLUCONEOGENESIS

(Synthesis of "new" glucose)

1. Definition:

Gluconeogenesis is the synthesis of glucose from compounds that are not carbohydrates. In humans, the major precursors for gluconeogenesis are lactate, amino acids, and glycerol.

2. Site:

Partly in cytosol and partly in the mitochondria.(mainly in the liver)

3. Reactions of Gluconeogenesis:

Gluconeogenesis is not a reversal of glycolysis. A number of different enzymatic steps are required.

A. Conversion of Pyruvate to Phosphoenolpyruvate:

Pyruvate (derived from lactate or amino acids such as alanine) is converted to phosphoenolpyruvate in a series of steps that require the enzymes

pyruvate carboxylase and phosphoenolpyruvate carboxykinase.

B. Conversion of Fructose 1,6-Bisphosphate to Fructose 6-Phosphate:

Fructose 1,6-bisphosphate is converted to fructose 6-phosphate by fructose 1,6-bisphosphatase, which releases inorganic phosphate.

C. Conversion of Glucose 6-Phosphate to Glucose:

Glucose 6-phosphatase cleaves inorganic phosphate from glucose 6-phosphate, and free glucose is released into the blood.

4 Precursors for Gluconeogenesis:

A. Lactate:

Lactate is oxidized by NAD^+ in a reaction catalyzed by lactate dehydrogenase to form pyruvate, which may be converted to glucose.

-Sources of lactate include red blood cells and exercising muscle.

B. Amino Acids:

Amino acids for gluconeogenesis come from muscle. They may be derived by degradation of muscle protein.

-Alanine may also be formed by transamination of pyruvate that is derived by oxidation of glucose.

-Amino acids from muscle travel to the liver and provide carbon for gluconeogenesis.

C. Glycerol:

Glycerol, which is derived from adipose triglycerides, enters the gluconeogenic pathway in the liver.

-Glycerol reacts with ATP to form glycerol 3-phosphate, which is oxidized to dihydroxyacetone phosphate and converted to glucose.

5. Energy Requirements for Gluconeogenesis:

Two moles of pyruvate are required for the synthesis of one mole of glucose.

-A total of **six** moles of ATP are required for the synthesis of one mole of glucose from two moles of pyruvate.

- Only **two** moles of ATP are required to synthesize one mole of glucose from two moles of glycerol.

6. Regulation of Gluconeogenesis:

Under fasting conditions, glucagon is elevated and stimulates gluconeogenesis.

A. Regulation of Pyruvate Dehydrogenase:

Glucagon stimulates the release of fatty acids from adipose tissue.

Fatty acids travel to the liver and are oxidized, producing acetyl CoA, NADH, and ATP, which cause inactivation of pyruvate dehydrogenase.

B. Regulation of Pyruvate Kinase:

Glucagon, via cAMP and protein kinase, causes pyruvate kinase to be phosphorylated and inactivated.

C. Regulation of Phosphofructokinase:

Phosphofructokinase is relatively inactive because the concentrations of its activators, AMP and fructose 2,6-bisphosphate, are low and its inhibitor, ATP, is high.

D. Regulation of Glucokinase and Hexokinase:

-Glucokinase is relatively inactive because it has a high Km for glucose and, under conditions that favor gluconeogenesis, the glucose concentration is low.

-Hexokinase is inhibited by glucose 6-phosphate.

E. Induction of Enzymes:

When glucagon is elevated, phosphoenolpyruvate carboxykinase fructose 1,6-bisphosphatase, and glucose 6-phosphatase are induced.

7. Functions of gluconeogenesis:

1. During fasting gluconeogenesis is important in maintaining blood glucose level.
2. During severe exercise, the gluconeogenic pathway allows the use of lactate from glycolysis and of glycerol from fat breakdown.
3. Gluconeogenesis also allows the use of dietary protein in carbohydrate pathways.

MAINTENANCE OF BLOOD GLUCOSE LEVELS

(Glucose homeostasis)

Blood glucose levels are maintained within a very narrow range even though the nature of the diet varies widely and the normal human eats periodically during the day and fasts between meals and at night.

Blood glucose conenctration is narrowly regulated becuase:

1.Brain is dependent on glucose: If blood glucose falls, brain function is impaired. This will result in coma and if prolonged will cause death.

2.Osmotic and chemical properties of glucose:

Osmotic properties: High blood glucose levels have the effect of dehydrating tissues which leads to loss of importrant ions.

Chemical properties: High blood glucose react nonenzymatically with exposed amino groups of proteins (one of the process of protein aging). Hemoglobin, collagen, proteins of the lens of the eye and others all suffer glucose modification in proportion to the concentration of glucose in the circulation.

Normal fasting level is 5 mM (90 mg/100 ml) or 80-100 mg%.

Normal level after heavy carbohydrate meal is always below 10mM (180 mg%) ,about 120-130 mg%.

Hypoglycaemia: It is the decrease of blood glucose below 50mg%

Hyperglycaemia: It is the increase of blood glucose above renal threshold (180 mg%), after which glucose appears in urine.

Mechanism of control of blood glucose concentration:

After a meal, blood glucose is supplied by dietary carbohydrate.

-The liver converts glucose to glycogen and triglycerides.

-Muscle converts glucose to glycogen.

-Adipose tissue converts glucose to the glycerol moiety of triglycerides.

-Tissues such as brain and red blood cells oxidize glucose for energy.

During fasting, blood glucose is maintained by the liver by the processes of glycogenolysis and gluconeogenesis.

-Within the first few hours of fasting, glycogenolysis is primarily responsible for maintaining blood glucose levels.

-After an overnight fast, as glycogen stores decrease, gluconeogenesis serves as an imporant additional source of blood glucose.

-After 30 hours, when liver glycogen stores are depleted, gluconeogenesis becomes the only source of blood glucose.

All cells use glucose for energy, however, the production of glucose during fasting is particularly important for tissues such as the brain and red blood cells.

-During exercise, blood glucose is also maintained by liver glycogenolysis and gluconeogenesis.

Medical problems associated with control of blood glucose level:

1.Hyperglcemia (Diabetes Mellitus)
High blood glucose levels occur due either to :

- deficiency of insulin
- inability of tissues such as adipose and muscle to take up glucose in the presence of normal amounts of insulin.

2.Hypoglycemia
Low blood sugar is caused by:

- an impairment of glycogenolysis or gluconeogenesis.
- excessive alcohol ingestion can cause hypoglycemia (inhibits gluconeogenesis.
- insulin-secreting tumors
- administration of high doses of insulin or sulfonylureas.

PENTOSE PHOSPHATE PATHWAY
(Pentose shunt)

The pentose phosphate pathway generates:

- NADPH for reductive biosynthesis and protection against oxidative damage
- Ribose 5-phosphate for nucleotide production.

1. Site: Like glycolysis: it is present in every cell in the cytosol

2. The Reactions of the Pentose Phosphate Pathway:

A.The Oxidative Reactions:

In the oxidative reactions, glucose 6-phosphate is oxidatively decarboxylated. CO_2 is released, NADPH is generated, and ribulose5-phosphate is produced.

1. Glucose 6-phosphate is converted to 6-phosphogluconolactone and $NADP^+$ is reduced to NADPH + H^+.

- Enzyme: glucose 6-phosphate dehydrogenase.

2. 6-Phosphogluconolactone is hydrolyzed to 6-phosphogluconate.

- Enzyme: gluconolactonase.

3. 6-Phosphogluconate is oxidatively decarboxylated. CO_2 is released and a second NADPH + H^+ is generated from $NADP^+$. The remaining carbons form ribulose 5-phosphate.

- Enzyme: 6-phosphogluconate dehydrogenase.

B.The Nonoxidative Reactions:

In the nonoxidative reactions of the pathway, ribulose 5-phosphate, produced in the oxidative reactions, is converted to ribose 5-phosphate, which may be used for nucleotide biosynthesis.

Ribulose 5-phosphate, in addition to forming ribose 5-phosphate, may also form xylulose 5-phosphate.

-These pentose phosphates may undergo a series of reactions catalyzed by transketolase and transaldolase, which transfer carbons from one compound to another. Ultimately, the glycolytic intermediates, fructose 6-phosphate and glyceraldehyde 3-phosphate, are formed.

1.Ribulose 5-phosphate may be isomerized to ribose 5-phosphate.

- Enzyme: phosphoriboisomerase.

2.Ribulose 5-phosphate may be epimerized to xylulose 5-phosphate.

- Enzyme: ribulose phosphate epimerase.

3.A two-carbon unit may be transferred from xylulose 5-phosphate to ribose 5-phosphate to form sedoheptulose 7-phosphate. Glyceraldehyde

3-phosphate is formed from the remaining 3 carbons of the xylulose 5-phosphate.

- Enzyme: **transketolase**.
- Transketolase, which transfers two-carbon unit, requires **thiamine pyrophosphate.**

4. A three-carbon unit may be transferred from sedoheptulose 7-phosphate to glyceraldehyde 3-phosphate to form fructose 6-phosphate. The four remaining carbons of the sedoheptulose 7-phosphate form erythrose 4-phosphate.

- Enzyme: **transaldolase**.

5. A two-carbon unit stransferred from xylulose 5-phosphate to erythrose 4-phosphate to form another fructose 6-phosphate. Glyceraldehyde 3-phosphgate is formed from the remaining carbons of the xylulose 5-phosphate.

- Enzyme: **transketolase.**

3. <u>Functions of pentose shunt</u>:

1.Serves as source of NADPH for fatty acid synthesis, reduction of glutathione and others.

2.Source of pentoses for nucleic acid synthesis.

4. <u>Regulation of the pathway</u>:

The celular concentration of NADPH is the major controlling factor; its availability regulates the rate-limiting G6PD reaction.

- When NADPH levels are low, the oxidative reaction of the pathway may be used to generate ribose 5-phosphate for nucleotide biosynthesis.
- When NADPH levels are high, the reversible nonoxidative portion of the pathway can be used to generate ribose 5-phosphate for nucleotide biosynthesis from fructose 6-phosphate and glyceraldehyde 3-phosphate.

5. <u>Medical problem associated with pentose shunt</u>:

<u>Glucose 6-Phosphate Dehydrogenase Deficiency</u>:

1. Red blood cells depend upon the pentose phosphate pathway for the formation of NADPH.

2. A deficiency of glucose 6-phosphate dehydrogenase causes insufficient amounts of NADPH to be produced. As a result, glutathione is not reduced and, in turn is not available to reduce H_2O_2. Red blood cells lyse and a **hemolytic anemia** may occur. (Figure)

Fructose Metabolism

The major dietary source of fructose is sucrose (table sugar).

A. MajorPathway (Conversion of Fructose to Glycolytic Intermediates):

Fructose is metabolized mainly in the liver where it is converted to pyruvate or, under fasting conditions to glucose.

-Fructose is phosphorylated by ATP to form fructose 1-phosphate. The enzyme is fructokinase.

-Fructose 1-phosphate is cleaved by fructose 1-phosphate aldolase to form dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is phosphorylated by ATP to form glyceraldehyde 3-phosphate.

- DHAP and glyceraldehyde 3-phosphate are intermediates of glycolysis.

-Glyceraldehyde may also be reduced ty glycerol, which is phosphoryulated to glycerol 3-phosphate and used in lipid synthesis.

B. Specialized pathway:

1.Fructose formation from glucose:

Sorbitol is produced from glucose by aldose reductase which reduces the aldehyde group to an alcohol.

Sorbitol is then reoxidized by sorbitol dehydrogenase to form fructose.

-These reactions are particularly important in seminal vesicles, which produce the fructose that serves as the major energy source for sperm cells.

2.Sorbitol formation from glucose in diabetes:

-The formation of sorbitol from glucose proceeds rapidly in the lens of the eye and in the Schwann cells of the nervous system.

-Sorbitol cannot pass through the cell membrane, and in diabetic individuals, sorbitol levels build up in these cells because the rate of oxidation of sorbitol to fructose is decreased.

-It is thought that the elevated sorbitol concentration causes an increase in osmotic pressure, which might be a causative factor in the development of the lens cataracts and the neural dysfunction that occur in diabetes.

C. Medical problems associated with fructose metabolism:

1.Essential Fructosuria:

- Fructokinase is deficient,
- Blood fructose levels rise, and fructose may appear in the urine.

2.Fructose Intolerance:

- Fructose 1-phosphate aldolase is deficient.
- Fructose 1-phosphate accumulates and inhibits glucose production, causing severe hypoglycemia if fructose is ingested.

Galactose Metabolism

The major dietary source of galactose is lactose found in milk

A.Conversion of Galactose to UDP-Galactose:

Galactokinase utilizes ATP to phosphorylate galactose to galactose 1-phosphate.

Galactose 1-phosphate reacts with UDP-glucose. Glucose 1-phosphate is released, and UDP-galactose is formed. The enzyme is galactose 1-phosphata uridyl transferase.

-UDP-galactose supplies galactose moieties for the synthesis of glycoproteins, glycolipids, and proteoglycans.

- The enzyme that adds galactose units to growing polysaccharide chains is galactosyl transferase.

-UDP-galactose may react with glucose in the mammary gland to produce the milk sugar lactose.

-The modifier protein, α- lactalbumin, reacts with galactosyl transferase, causing its Km for glucose to be lowered so that it adds galactose (from UDP-galactose) to glucose, forming lactose.

B. Conversion of UDP-Galactose to UDP-Glucose:

UDP-galactose is epimerized to UDP-glucose in a reaction that is readily reversible.

C. Conversion of Galactose to Intermediates of Glucose Metabolism:

Galactose is phosphorylated to galactose 1-phosphate.

Galactose 1-phosphate reacts with UDP-glucose to form UDP- galactose and glucose 1-phosphate.

Epimerization of UDP-galactose produces UDP-glucose.

This sequence of reactions is repeated with the result that galactose enters the cell, is phosphorylated, and then converted to UDP-glucose and glucose 1-phosphate.

-These glucose derivatives may be converted to blood glucose or to glycogen by the liver.

D. Conversion of Galactose to Galactitol:

Aldose reductase reduces galactose to galactitol (dulcitol).

E. Medical problems associated with Galactose Metabolism:

Galactosemia: (high concentration of galactose in the blood)

may be due to a galactokinase deficiency or to a uridyl transferase deficiency. In both conditions, excess galactose may be reduced to galaclitol, which can produce cataracts. The uridyl transferase deficiency

is more severe, causing elevation of galactose 1-phosphate which inhibits phosphoglucomutase, interfering with glycogen synthesis and degradation.