# GLUCONEOGENESIS
# THE PENTOSE PHOSPHATE PATHWAY & URONIC ACID PATHWAY

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# BIOMEDICAL IMPORTANCE OF GLUCONEOGENESIS

- **Gluconeogenesis** is the process of synthesizing glucose from non-carbohydrate precursors.
- Some tissues, such as the *brain, red blood cells, kidney medulla, lens and cornea of the eye, testes, and exercising muscle*, require a continuous supply of glucose as a metabolic fuel.
- Liver glycogen can meet these needs for only 10–18 hours in the absence of dietary intake of carbohydrate.
- During a prolonged fast, however, hepatic glycogen stores are depleted, and glucose is formed from precursors such as **lactate, pyruvate, glycerol,** and **a-ketoacids**.
- During an overnight fast, approximately 90% of gluconeogenesis occurs in the liver, with the kidneys providing 10% of the newly synthesized glucose molecules.
- However, during prolonged fasting, the kidneys become major glucose-producing organs, contributing an estimated 40% of the total glucose production.

# SUBSTRATES FOR GLUCONEOGENESIS

- Gluconeogenic precursors are molecules that can be used to produce a net synthesis of glucose.
- They include intermediates of glycolysis and the TCA cycle.
- **Glycerol**, **lactate**, and the a-keto acids obtained from the transamination of **glucogenic amino acids (e.g., alanine)** are the most important gluconeogenic precursors.

# REACTIONS SPECIAL TO GLUCONEOGENESIS

- Seven glycolytic reactions are reversible and are used in the synthesis of glucose from lactate or pyruvate.
- However, three of the reactions are irreversible and must be circumvented by four alternate reactions that energetically favor the synthesis of glucose.

# Carboxylation of pyruvate

- In gluconeogenesis, pyruvate is first carboxylated by **pyruvate carboxylase** (requires **biotin**) to oxaloacetate (OAA), which is then converted to phosphoenolpyruvate (PEP) by the action of **PEP-carboxykinase**.
- Pyruvate carboxylase is allosterically activated by acetyl CoA and **at low levels of acetyl CoA, pyruvate carboxylase is predominantly inactive**.

# Dephosphorylation of fructose 1,6-bisphosphate

- Hydrolysis of fructose 1,6-bisphosphate by **fructose 1,6-bisphosphatase** bypasses the irreversible phosphofructokinase-1 reaction, and provides an energetically favorable pathway for the formation of fructose 6-phosphate.

# Dephosphorylation of glucose 6-phosphate

- Hydrolysis of glucose 6-phosphate by **glucose 6-phosphatase** bypasses the irreversible hexokinase reaction, and provides an energetically favorable pathway for the formation of **free glucose**.
- Liver and kidney are the only organs that release free glucose from glucose 6-phosphate.
- This process actually requires two proteins: glucose 6-phosphate translocase, which transports glucose 6-phosphate across the endoplasmic reticulum (ER) membrane, and the ER enzyme, glucose 6-phosphatase (found only in gluconeogenic cells), which removes the phosphate, producing free glucose.
- These proteins are also required for the final step of glycogen degradation.
- ***Remember that muscle lacks glucose 6-phosphatase, and therefore muscle glycogen can not be used to maintain blood glucose levels***.

# REGULATION OF GLUCONEOGENESIS

- Glucagon (favors gluconeogenesis by 3 mechanisms):
  - *lowers the level of fructose 2,6-bisphosphate,*
  - *converts hepatic pyruvate kinase to its inactive form,*
  - *induces PEP-carboxykinase.*
- Substrate availability
- Allosteric activation by acetyl CoA
- Allosteric inhibition by AMP

# PENTOSE PHOSPHATE PATHWAY

- The pentose phosphate pathway is an alternative route for the metabolism of glucose.
- The pentose phosphate pathway (also called the hexose monophosphate pathway or shunt) occurs in the cytosol of the cell.
- It does not lead to formation of ATP but has two major functions:
  - the formation of **NADPH** for synthesis of fatty acids and steroids, and maintaining reduced glutathione for antioxidant activity,
  - the synthesis of **ribose** for nucleotide and nucleic acid formation.

# The pentose phosphate pathway

- It includes two irreversible oxidative reactions followed by a series of reversible sugar–phosphate interconversions.
- **No ATP is directly consumed or produced in the cycle**.
- **Carbon 1 of glucose 6-phosphate is released as $CO_2$**, and two NADPH are produced for each glucose 6-phosphate molecule entering the oxidative part of the pathway.
- The rate and direction of the reversible reactions of the pentose phosphate pathway are determined by the supply of and demand for intermediates of the cycle.

# Irreversible Oxidative Reactions

- The oxidative portion of the pentose phosphate pathway consists of three reactions that lead to the formation of ribulose 5-phosphate, $CO_2$, and two molecules of NADPH for each molecule of glucose 6-phosphate oxidized.
- Glucose 6-phosphate dehydrogenase (**G6PD**) catalyzes an irreversible oxidation of glucose 6-phosphate to 6-phosphogluconolactone in a reaction that is specific for $NADP^+$ as its coenzyme.
- The pentose phosphate pathway is regulated primarily at the G6PD reaction.
- NADPH is a potent competitive inhibitor of the enzyme.
- Insulin upregulates expression of the gene for G6PD.

# Irreversible Oxidative Reactions

- 6-Phosphogluconolactone is hydrolyzed by 6-phosphogluconolactone hydrolase. The reaction is irreversible and not rate-limiting.
- The oxidative decarboxylation of 6-phosphogluconate is catalyzed by 6-phosphogluconate dehydrogenase.
- This irreversible reaction produces a pentose sugar–phosphate (ribulose 5-phosphate), $CO_2$ (from carbon 1 of glucose), and a second molecule of NADPH.

# Reversible Non-oxidative Reactions

- The non-oxidative reactions of the pentose phosphate pathway occur in all cell types synthesizing nucleotides and nucleic acids.
- These reactions catalyze the interconversion of sugars containing three to seven carbons.
- These reversible reactions permit ribulose 5-phosphate (produced by the oxidative portion of the pathway) to be converted either to ribose 5-phosphate (needed for nucleotide synthesis) or to intermediates of glycolysis—fructose 6-phosphate and glyceraldehyde 3-phosphate.
- For example, many cells that carry out reductive biosynthetic reactions have a greater need for NADPH than for ribose 5-phosphate. In this case, **transketolase** (*which transfers two-carbon units in a thiamine pyrophosphate (TPP)-requiring reaction*) and **transaldolase** (*which transfers three-carbon units*) convert the ribulose 5-phosphate to glyceraldehyde 3-phosphate and fructose 6-phosphate, which are intermediates of glycolysis.

# Reversible Non-oxidative Reactions

- Under conditions in which the demand for ribose for incorporation into nucleotides and nucleic acids is greater than the need for NADPH, the non-oxidative reactions can provide the biosynthesis of ribose 5-phosphate from glyceraldehyde 3-phosphate and fructose 6-phosphate in the absence of the oxidative steps.

# G6PD DEFICIENCY

- G6PD deficiency is an inherited (X-linked) disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents.
- It is the most common disease-producing enzyme abnormality in humans, affecting more than 400 million individuals worldwide.
- In red blood cells, the pentose phosphate pathway is the sole source of NADPH for the reduction of oxidized glutathione catalyzed by glutathione reductase.
- Diminished G6PD activity impairs the ability of the cell to form the NADPH that is essential for the maintenance of the reduced glutathione pool.
- This results in a decrease in the cellular detoxification of free radicals and peroxides formed within the cell.

# Precipitating factors in G6PD deficiency

- Most individuals who have inherited one of the many G6PD mutations do not show clinical manifestations, that is, they are asymptomatic.
- However, some patients with G6PD deficiency develop hemolytic anemia if they are treated with an oxidant drug, ingest fava beans (*favism*), or develop a severe infection.

# GLUCURONATE, A PRECURSOR OF PROTEOGLYCANS & CONJUGATED GLUCURONIDES, IS A PRODUCT OF THE URONIC ACID PATHWAY

- In liver, the **uronic acid pathway** catalyzes the conversion of glucose to glucuronic acid, *ascorbic acid* (***except in human beings and other species for which ascorbate is a vitamin, vitamin C***), and pentoses.
- It is also an alternative oxidative pathway for glucose that, like the pentose phosphate pathway, does not lead to the formation of ATP.
- Glucose-6-phosphate is isomerized to glucose-1-phosphate, which then reacts with uridine triphosphate (UTP) to form uridine diphosphate glucose in a reaction catalyzed by **UDP-Glucose pyrophosphorylase,** as occurs in glycogen synthesis.
- UDP-Glucose is oxidized at carbon 6 by NAD dependent **UDP-Glucose dehydrogenase** in a two-step reaction to yield UDP-glucuronate.

# REFERENCES


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