Section A
Carbohydrates and their Metabolism

1

Carbohydrate Chemistry

1. WHAT IS CARBOHYDRATE?/DEFINE CARBOHYDRATES

Carbohydrates are aldehyde or keto-derivatives of polyhydroxy alcohols or substances which yield such compounds on hydrolysis.

2. CLASSIFICATION OF CARBOHYDRATES

Carbohydrates are classified based on a number of individual monosaccharide units derived from the complete hydrolysis of the carbohydrate compound.

Accordingly, they are classified into the following four major groups:

- Monosaccharides
- Disaccharides
- Oligosaccharides
- Polysaccharides

Key Notes

Table 1.1: Monosaccharides		
General formula	**Aldosugar**	**Ketosugar**
Triose	Glyceraldehyde or Glycerose	Dihydroxyacetone
Tetrose	Erythrose	Erythrulose
Pentose	Ribose (Xylose, Arabinose)	Ribulose, Xylulose
Hexose	Glucose, Galactose, Mannose	Fructose
Heptose	Glucoheptose	Sedoheptulose
Nanose	Sialic acid (NANA)	—

Table 1.2: List of disaccharides			
Disaccharides	**Reducing (R) or nonreducing (NR)**	**Individual monosaccharide units**	**Bonds**
Sucrose α-D-glucopyranosyl β-D-fructofuranoside	Nonreducing	Glucose + Fructose	α-1, β-2
Trehalose	Nonreducing	Glucose + Glucose	α-1,1-glycosidic
Maltose	Reducing	Glucose + Glucose	α-1,4-glycosidic
Isomaltose	Reducing	Glucose + Glucose	α-1,6-glycosidic
Lactose	Reducing	Glucose + Galactose	β-1,4-glycosidic
Lactulose	Reducing	Fructose + Galactose	β-1,4-glycosidic

Key Notes

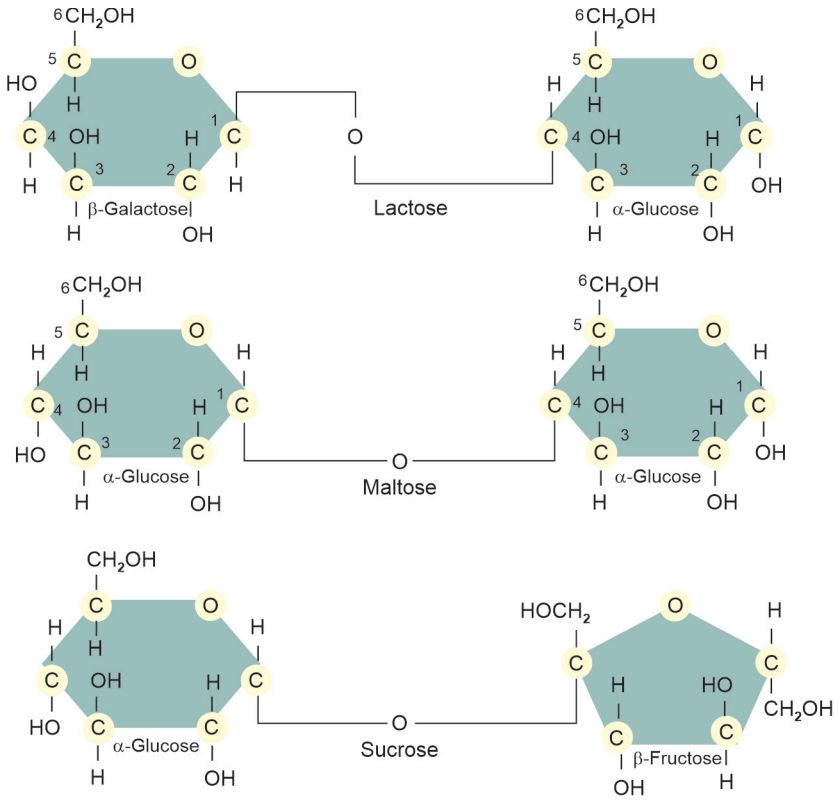


Fig. 1.1: Disaccharides

Oligosaccharides

They have 3–10 residues of monosaccharide linked together
Examples are: Limit dextrin, maltotriose

Polysaccharides

They have more than ten monosaccharide residues attached. These monosaccharides may be the same or different, accordingly, they are known as homopolysaccharides or heteropolysaccharides.

Key Notes

Homopolysaccharides

Table 1.3: List of homopolysaccharides

Homopolysaccharides	Units of monosaccharides	Bonds
Starch	Glucose	α-1,4- and α-1,6-glycosidic bond
Glycogen	Glucose	α-1,4- and α-1,6-glycosidic bond
Cellulose	Glucose	β-1,4-glycosidic bond
Inulin	Fructose	β-1,2-glycosidic bond
Dextran	Glucose	α-1,6-glycosidic bond α-1,4-glycosidic bond α-1,3-glycosidic bond
Chitin	N-acetyl-D-glucosamine [NAG]	β-1,4-glycosidic bond

Heteropolysaccharides

Agar, agarose, pectin, gum, blood group antigen, and mucopolysaccharides are examples of heteropolysaccharides (HPS). MPS are also known as glycosaminoglycans (GAG).

3. STEREOISOMERS OF CARBOHYDRATE

Compounds having the same molecular formula but different structure formulas are known as structural isomers/stereoisomers of each other.

A. Aldo–keto isomer

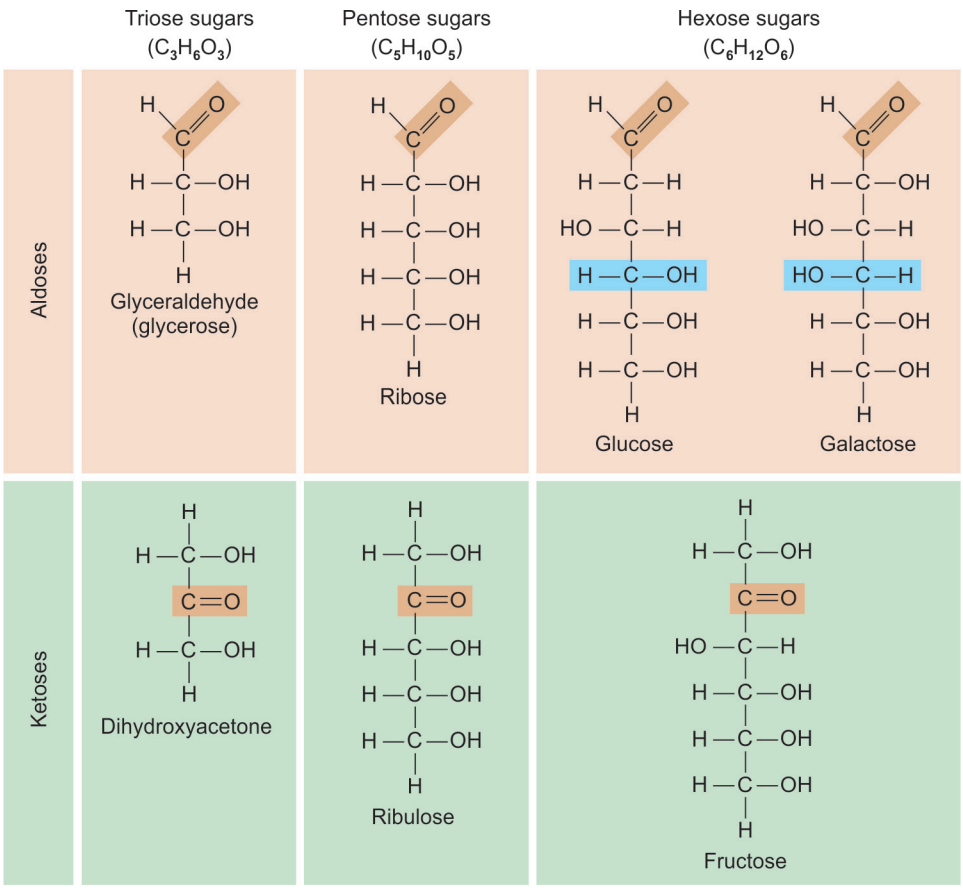


Fig. 1.2: Aldo–keto isomers

B. Epimers

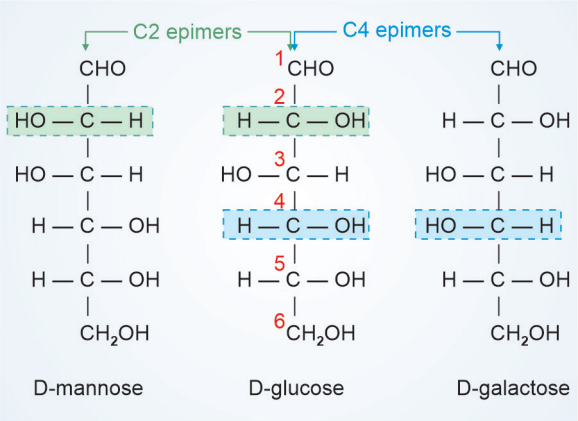


Fig. 1.3: C2 and C4 epimers of glucose

C. Pyranose–furanose type of isomers

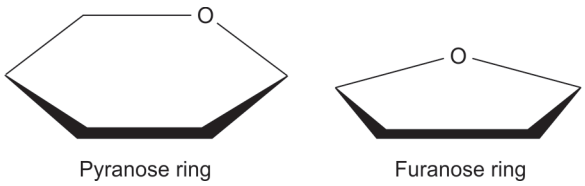


Fig. 1.4: Pyranose and furanose rings

D. Anomers (alpha and beta)

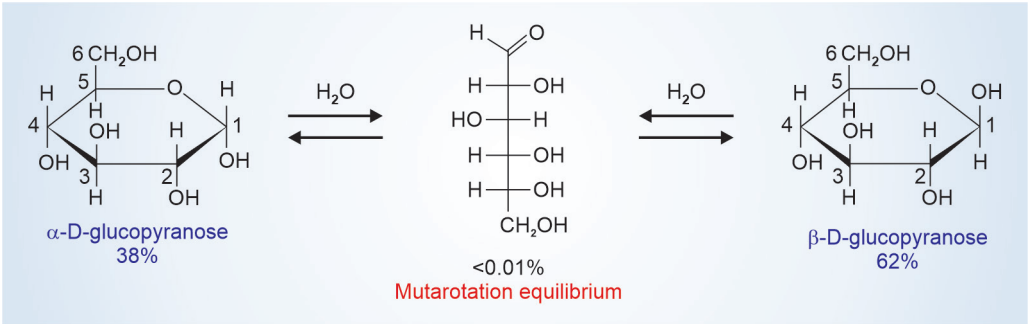


Fig. 1.5: Mutarotation equilibrium (in glucose)

E. D and L isomers [enantiomer]

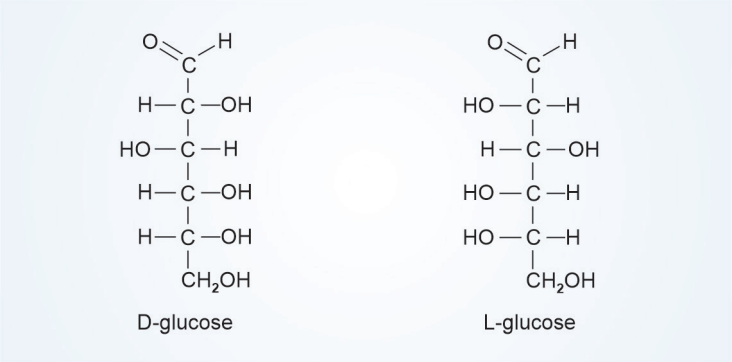


Fig. 1.6: D and L isomers of glucose

4. CLINICAL CORRELATION

Lactose intolerance

a. Enzyme deficiency: Lactase
b. Clinical presentation: Abdominal discomfort, bloating, cramps, diarrhea on consumption of milk and dairy products
c. Food to avoid: Milk and dairy products

5. CLINICAL UTILITY

a. Lactulose: Being used to induce osmotic diarrhea
b. Sucralose: Used as artificial sweetener

6. MUCOPOLYSACCHARIDES

Characteristics

- Made up of repeating units of amino sugar and uronic acid
- Most of them are highly sulfated (the exception is hyaluronic acid, which is not sulfated)
- They are negatively charged
- They are hygroscopic

Examples of mucopolysaccharides are

1. Hyaluronic acid
2. Heparin
3. Heparan sulfate
4. Chondroitin sulfate
5. Dermatan sulfate
6. Keratan sulfate I
7. Keratan sulfate II

Key Notes

2

Glucose Oxidation

Key concept of glucose oxidation
Main purpose of glucose oxidation is production of ATP.

Aerobic glucose oxidation comprises 3 stages

- Aerobic glycolysis
- PDH complex activity
- TCA cycle

Anaerobic glucose oxidation comprises only 1 stage

- Anaerobic glycolysis

GLYCOLYSIS

Also called the Embden Meyerhof pathway

Both aerobic and anaerobic glycolysis is cytosolic pathway
End product of aerobic glycolysis: Pyruvate
End product of anaerobic glycolysis: Lactate

ATP Production

- Aerobic glycolysis: Total 9, Net 7
- Anaerobic glycolysis: Total 4, Net 2
- PDH complex: 2.5 ATP from 1 pyruvate
- TCA cycle: 10 ATP from 1 acetyl-CoA

Key Notes

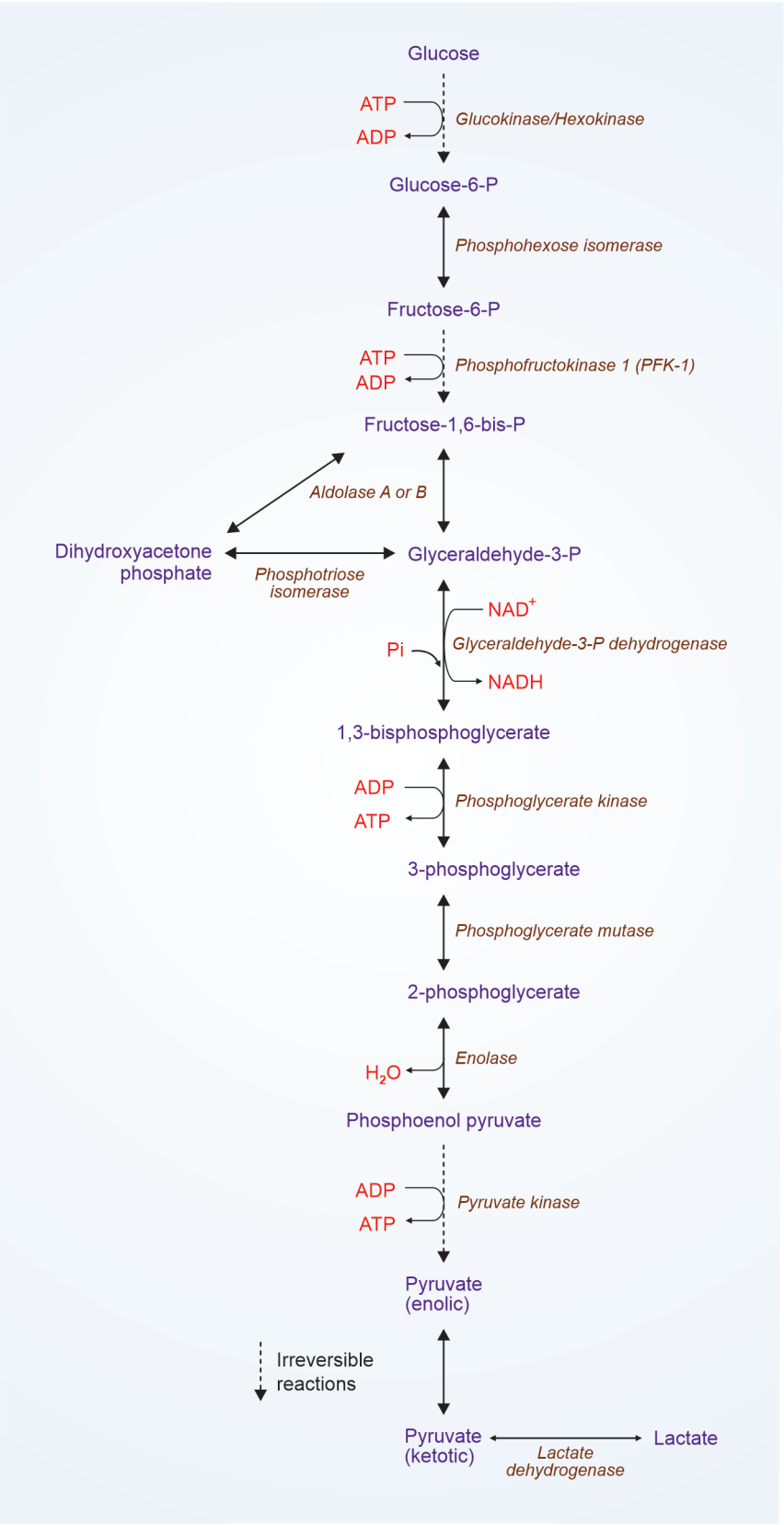


Fig. 2.1: Steps of glycolysis

Clinical Correlation

- For estimation of blood/plasma glucose, blood is collected in uoride vacutainer (grey cap) to prevent glycolysis in the collected blood as to give true reflection of blood glucose. Fluoride inhibits enolase enzyme and prevents glycolysis.
- Pyruvate kinase is one of those enzymes whose deficiency results in hemolysis
- *Crabtree effect:* Excess glycolysis in limited oxygen supply results in anaerobic glycolysis and hence lactic acid production.

Rate-limiting Step: PFK-1 (Phosphofructokinase 1)

1. Regulation of PFK-1

- Phosphofructokinase 1 (PFK-1) is a major regulatory enzyme of glycolysis.
- Phosphofructokinase 1 is an allosteric enzyme which has got its positive and negative allosteric factors.

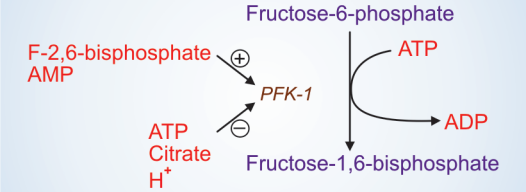


Fig. 2.2: Positive and negative allosteric modifiers of phosphofructokinase enzyme

Key point for PFK-1

Positive factors for PFK-1

- Fructose 2,6-bisphosphate 5′AMP

Negative factors for PFK-1

- ATP
- Citrate
- Protons

Table 2.1: Differences between hexokinase and glucokinase

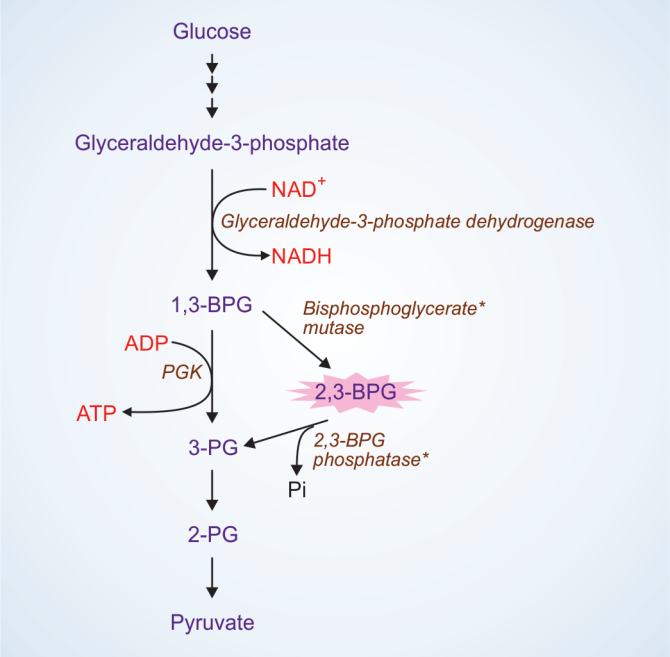
	Hexokinase	Glucokinase
Site	All tissues except liver	Only in liver, β-cell of pancreas
Substrate	Glucose, fructose or galactose	Only glucose
Induction	Noninducible	Inducible
K_m for glucose	Low (0.05 mmol/L or 0.9 mg/dl)	High (10 mmol/L or 180 mg/dl)
Inhibition by glucose-6-phosphate	Inhibited	Not inhibited
Effect of feeding and insulin	No change in activity	Increased activity as well as rate of synthesis

Key Notes

Rapoport-Luebering Shunt (RL Shunt)

Key concepts for Rapoport-Luebering shunt

- RL shunt occurs in mature RBC for the purpose of production of 2,3-bisphosphoglycerate
- 2,3-bisphosphoglycerate helps in release of oxygen from the hemogobin, which facilitates delivery of oxygen to the tissues.
- Two key enzymes of Rapoport-Luebering shunt are:
  a. 1,3-bisphosphoglycerate mutase
  b. 2,3-bisphosphoglycerate phosphatase



(*BPG mutase and BPG phosphatase are bifunctional enzymes which means one polypeptide has two catalytic domains)

Fig. 2.3: Rapoport-Luebering cycle (RL shunt)

Key Notes

PDH COMPLEX

Key concept of PDH complex

- Pyruvate is oxidatively decarboxylated to produce acetyl-CoA.

Enzymes of PDH complex

There are three enzymes in PDH complex which act in a sequential manner with the help of various coenzymes.

a. Pyruvate dehydrogenase (E1)

b. Dihydrolipoyl transacetylase (E2)

c. Dihydrolipoyl dehydrogenase (E3)

Coenzymes of PDH complex

- Thiamine pyrophosphate (TPP)
- Lipoate
- CoA-SH (coenzyme A-SH)
- FAD
- NAD

Energetics

- 1 NADH is produced when 1 pyruvate is converted to acetyl-CoA, simultaneously generating 2.5 ATP

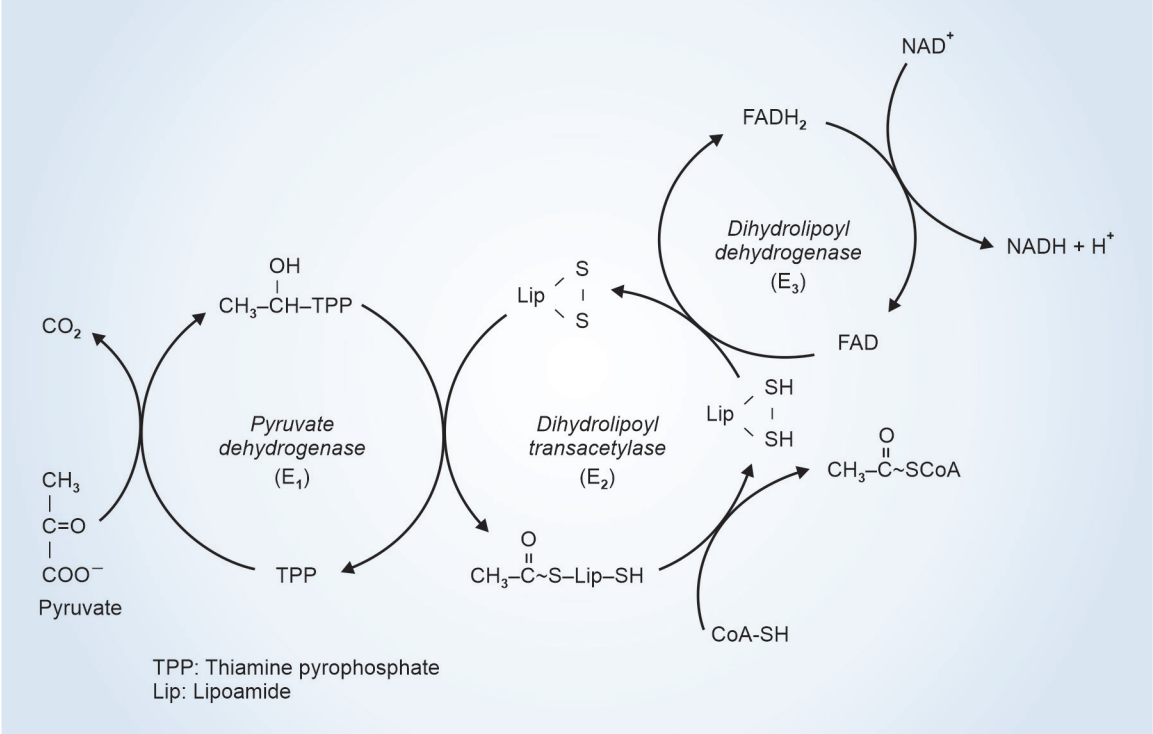


Fig. 2.4: PDH complex

Clinical Correlation

- In deficiency of vitamin B_1 or in case of mutation of any of the enzyme of PDH complex, lactic acidosis results due to diversion of pyruvate to lactate by LDH enzyme.
- Babies belonging to low socio-economic strata often present with features of B_1 deficiency (beriberi) where lactic acidosis is an important finding.

CITRIC ACID CYCLE (KREBS' CYCLE OR TCA CYCLE)

Key concepts

- ***TCA cycle:*** It is a series of enzyme catalyzed reactions that form a common pathway for final oxidation of acetyl-CoA coming from all metabolic fuels (carbohydrate, free fatty acids, ketone bodies and amino acids).
- ***Location:*** All the enzymes of TCA cycle (except succinate dehydrogenase) is dispersed in mitochondrial matrix. Succinate dehydrogenase is found at inner mitochondrial membrane.
- ***Bioenergetics*:** One molecule of acetyl-CoA produces 10 ATPs in a complete turn of citric acid cycle.
  TCA cycle is an amphibolic pathway which has role to play in catabolism of acetyl-CoA and various anabolic pathways of system.

Key Notes

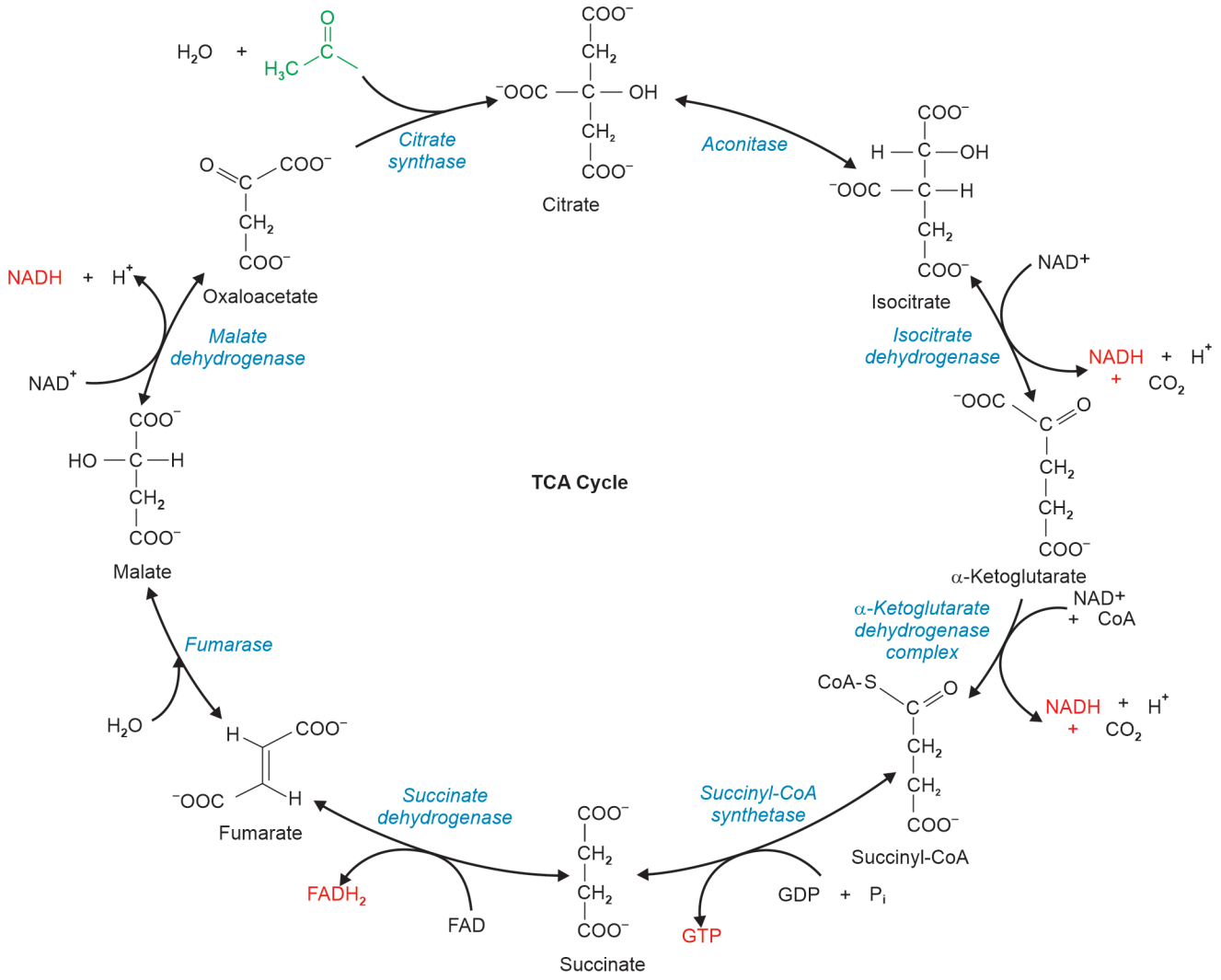


Fig. 2.5: TCA cycle

Key Notes

3

Gluconeogenesis

What is gluconeogenesis?

This is the process of formation of glucose from noncarbohydrate substances.

Substrate of gluconeogenesis

- *Glucogenic amino acid*
- *Lactate*
- *Pyruvate*
- *Propionate*
- *Glycerol*
- *Fumaric acid*.

Key concept for the process of gluconeogenesis

Reversible steps of the glycolysis are used in reverse direction and irreversible steps of glycolysis (pyruvate kinase, phosphofructokinase, glucokinase) are bypassed by exclusive reactions of gluconeogenesis.

Key Notes

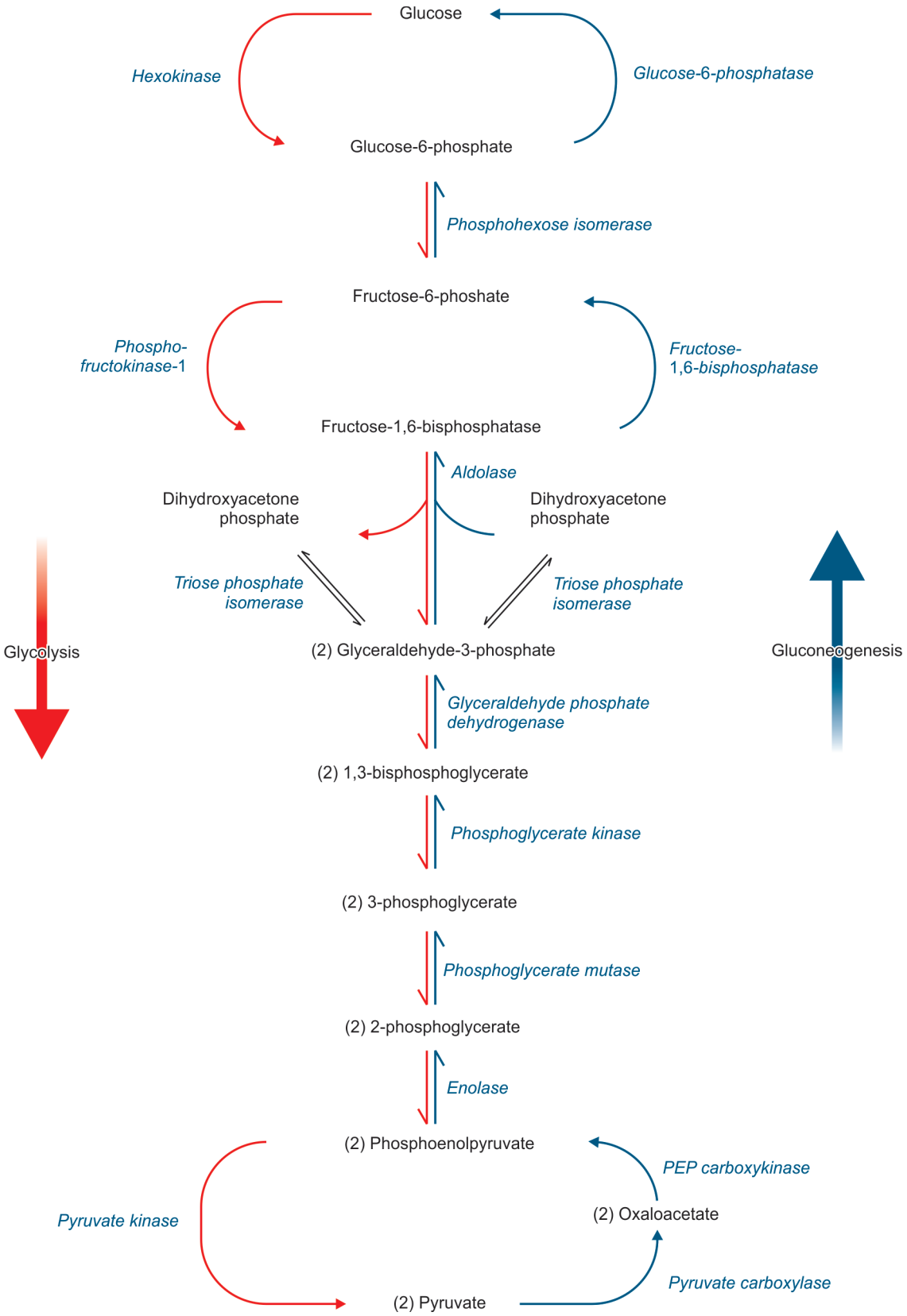


Fig. 3.1: Steps of glycolysis and gluconeogenesis

The above diagram shows how the reversible steps of glycolysis are used in a reverse direction and how irreversible steps of glycolysis are bypassed by new reactions during gluconeogenesis.

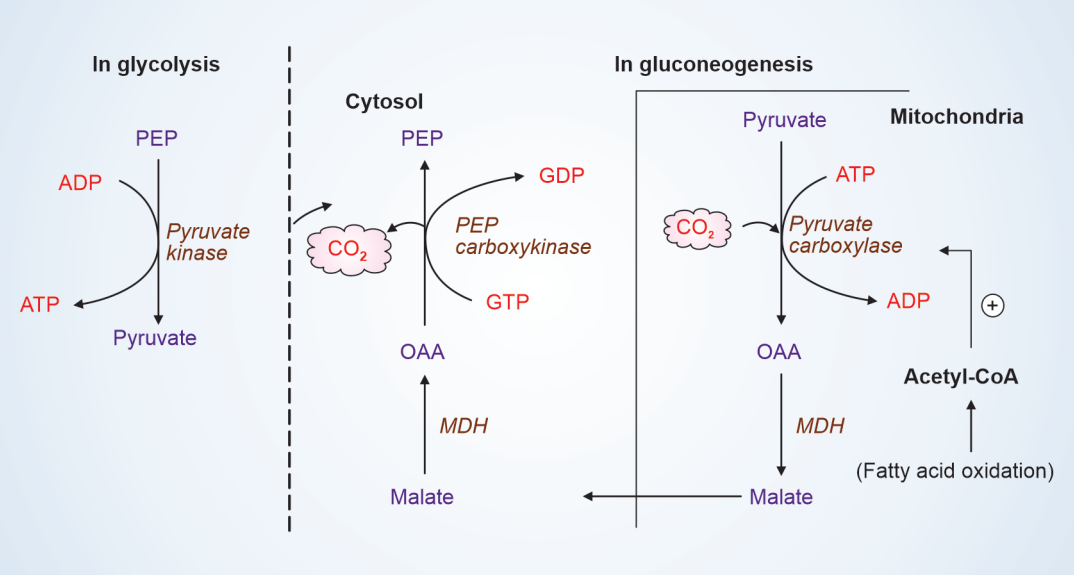


Fig. 3.2: Reversal of pyruvate kinase reaction

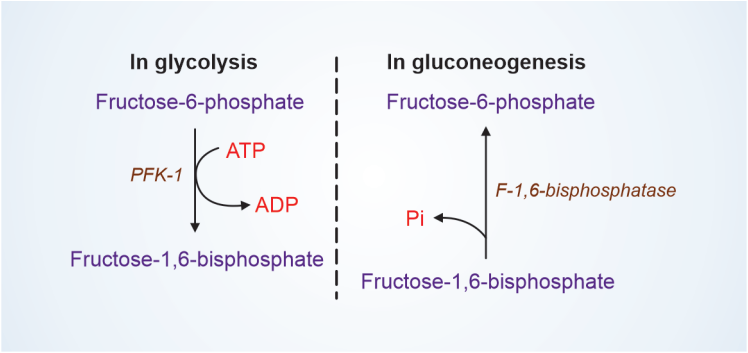


Fig. 3.3: Reversal of PFK-1 reaction

Fig. 3.4: Reversal of glucokinase/hexokinase reaction

Regulation of Gluconeogenesis

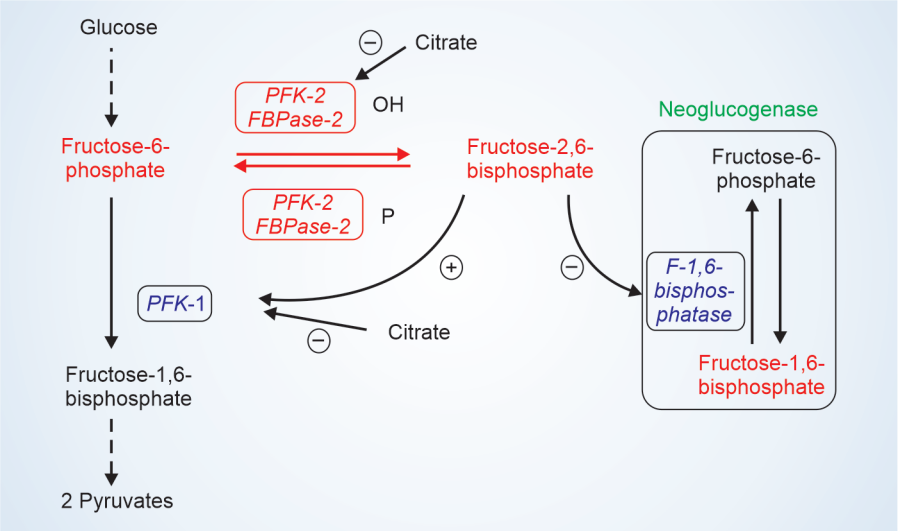


Fig. 3.5: Simultaneous regulation of PFK-1 and F-1,6-bisphosphatase by F-2,6-bisphosphate

Key Notes

CORI CYCLE

Key concept for Cori cycle

- Cori cycle is also known as glucose–lactate cycle.
- Anaerobic glycolysis in skeletal muscle during exercise and gluconeogenesis in liver constitute Cori cycle.
- During prolonged exercise muscle pain is due to accumulation of lactate, which gets diffused to blood on resting.

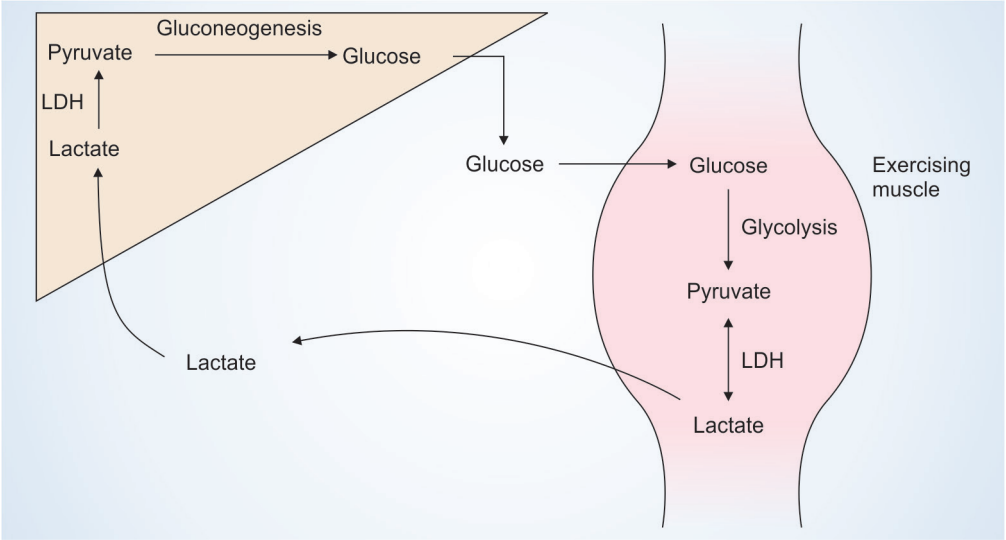


Fig. 3.6: Cori cycle (glucose–lactate cycle)

Key Notes

4 Glycogen Metabolism

GLYCOGENESIS

Key concepts

- Synthesis of highly branched polymer of glucose in a multistep process, where UDP glucose is the donor of glucose is known as glycogenesis.
- Organs involved in the process of glycogen metabolism
  - *Liver*
  - *Skeletal muscle*

SYNTHESIS OF UPD GLUCOSE AND OVERVIEW OF GLYCOGEN SYNTHESIS

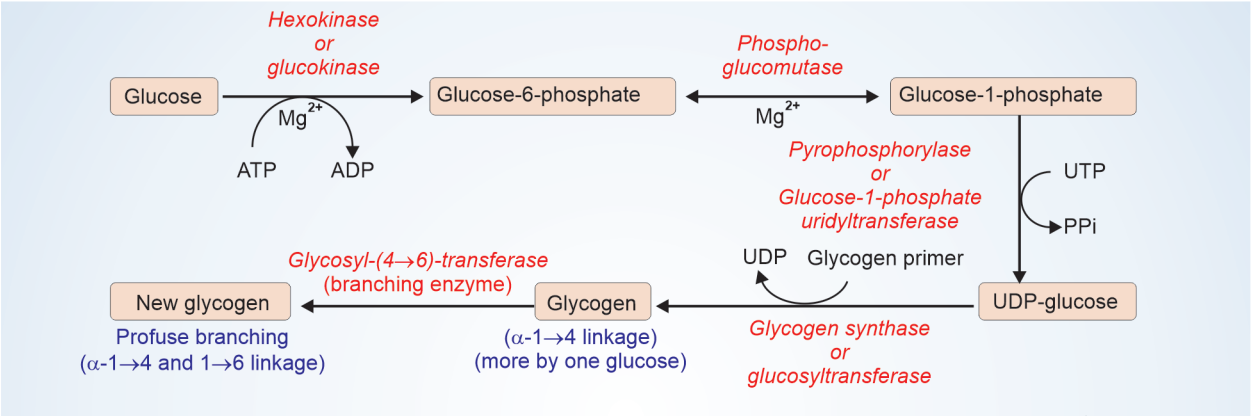


Fig. 4.1: Mechanism of glycogenesis

Key Notes

ACTION OF GLYCOGEN SYNTHASE AND BRANCHING ENZYME DURING GLYCOGENESIS

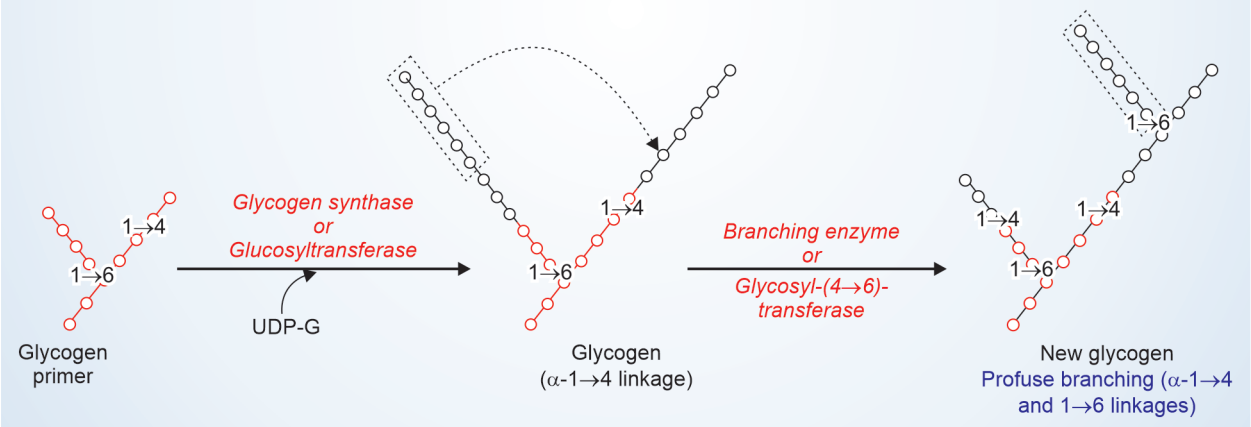


Fig. 4.2: Mechanism of glycogenesis

Key Notes

GLYCOGENOLYSIS

Key concepts

Purpose of glycogenolysis

- In liver: to maintain the hypoglycemia by releasing free glucose.
- In skeletal muscle: to provide glucose 6 phosphate which is used in glycolysis in muscle itself for ATP production to sustain the exercise.

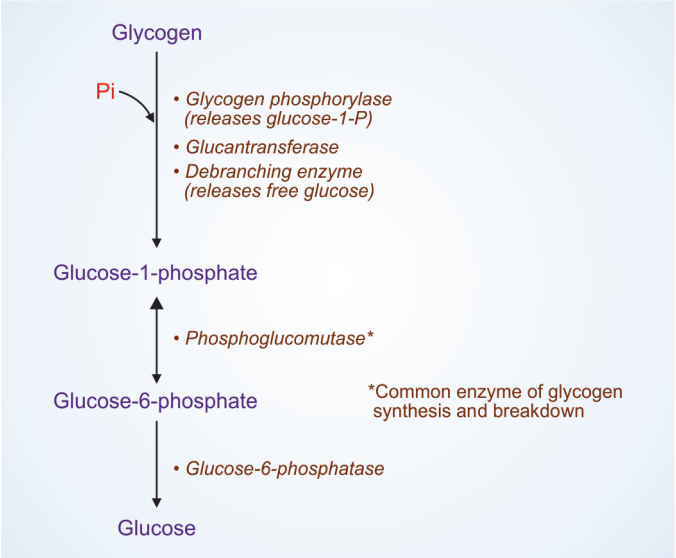


Fig. 4.3: Glycogen degradation (glycogenolysis)

Key Notes

Clinical Correlation

Glycogen Storage Diseases

Table 4.1: Glycogen storage disorders

Glyco-genesis	Name	Cause of disorder	Characteristics
Type 0	—	Glycogen synthase	Hypoglycemia, hyperketonemia, early death
Type Ia	Von Gierke disease	Deficiency of glucose-6-phosphatase	Hypoglycemia, lactic acidemia, ketosis, hyperlipemia
Type Ib	—	Endoplasmic reticulum glucose-6-phosphate transporter	As type Ia; neutropenia and impaired neutrophil function leading to recurrent infections
Type II*	Pompe disease	Deficiency of lysosomal α-1,4 and α-1,6-glucosidase	Fatal, accumulation of glycogen in lysosomes, skeletal and cardiac muscle involved, liver spared
Type IIIa	Cori/Forbes disease/ Limit dextrinosis	Absence of debranching enzyme in muscle and liver	Accumulation of characteristic branched polysaccharide in both
Type IIIb	Limit dextrinosis	Liver debranching enzyme is deficient	Accumulation of characteristic branched polysaccharide in liver alone
Type IV	Andersen disease, amylopectinosis	Absence of branching enzyme	Death due to cardiac or liver failure in the first year of life
Type V*	McArdle syndrome	Absence of muscle phosphorylase	Diminished exercise tolerance; muscles have abnormally high glycogen content
Type VI	Hers disease	Deficiency of liver (hepatic)	High glycogen content in liver, tendency towards hypoglycemia
Type VII*	Tarui's disease	Deficiency of muscle and RBC phospho-fructokinase	As in type V
Type VIII	—	Liver phosphorylase kinase	Hepatomegaly
Type IX	—	Liver and muscle phosphorylase kinase	Hepatomegaly
Type X	—	cAMP-dependent protein kinase A	Hepatomegaly
Type XI	Fanconi-Bickel disease	GLUT-2 in liver is affected	—

*Liver spared in: GSD type II, V, VII; muscle spared in: GSD type 0, Ia, Ib, IIIb, VI, VIII, IX, X

Key Notes

5

Galactose Metabolism

GALACTOSE METABOLISM

Key concepts

- Metabolism of galactose occurs only in the liver
- Galactokinase, galactose-1-phosphate uridyl transferase, 4-epimerase are the exclusive enzyme for galactose metabolism
- Any metabolic error in galactose metabolism results in increased level of galactose in the plasma which is excreted in the urine (galactosuria). Benedict's test will be positive in urine as galactose is the reducing sugar.

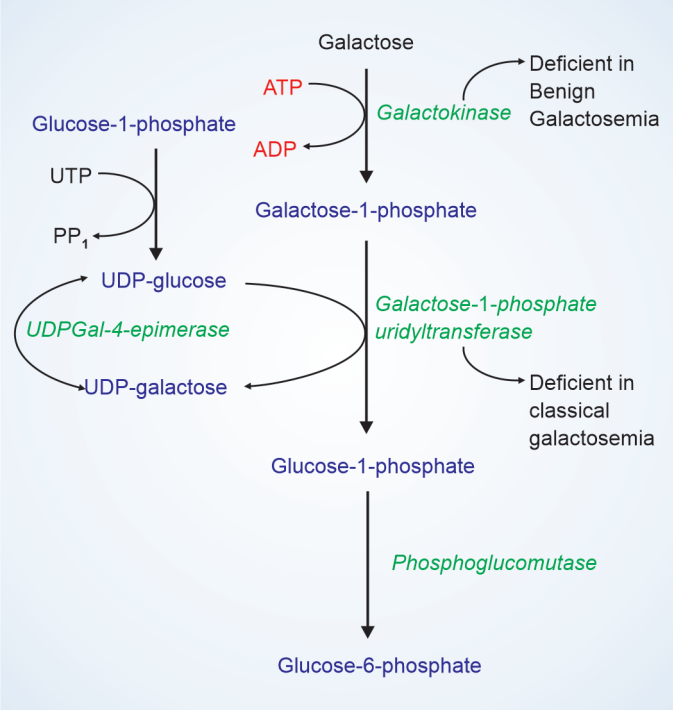


Fig. 5.1: Galactose metabolism

Key Notes

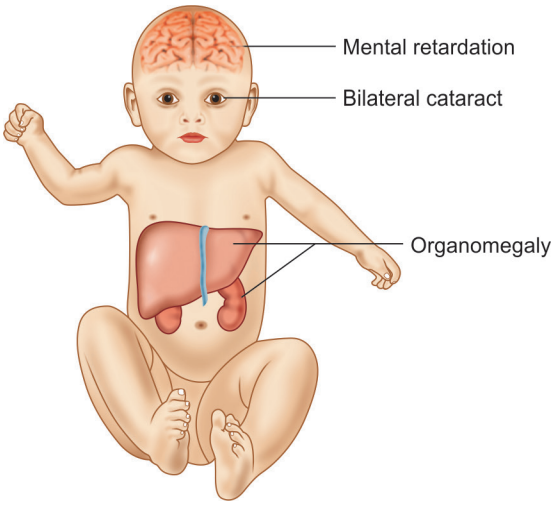


Fig. 5.2: A child with galactosemia

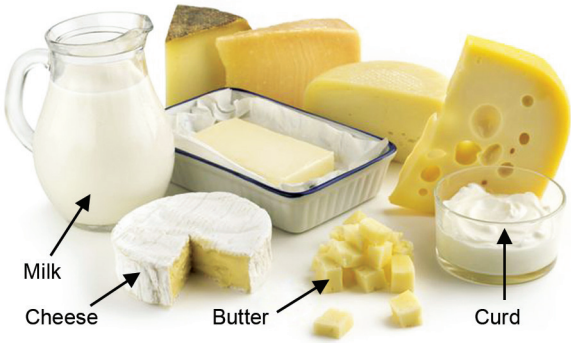


Fig. 5.3: Lactose-containing diet should be avoided in galactosemia

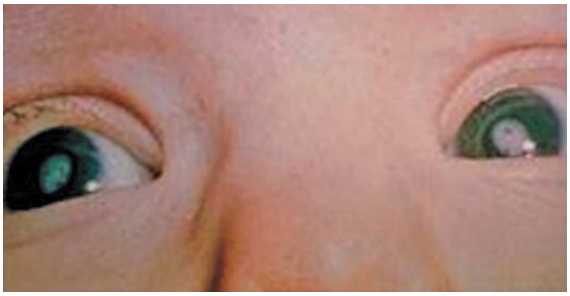


Fig. 5.4: Bilateral cataract in galactosemia

Clinical Correlation

Classical galactosemia

Enzyme deficiency: Galactose-1-phosphate uridyltransferase is deficient in classical galactosemia.

Clinical presentation: Bilateral cataract, mental retardation (due to repeated hypoglycemia), liver enlargement (hepatomegaly).

Benign galactosemia

Enzyme deficiency: Galactokinase is deficient in benign galactosemia.

Clinical presentation: Bilateral cataract.

Key Notes

6

Fructose Metabolism

Key concepts

- Fructose is metabolized in liver as well as extrahepatic tissues.
- Pathway in liver requires **fructokinase** enzyme which converts fructose to fructose-1-phosphate, and in extrahepatic cell **hexokinase** converts fructose to fructose-6-phosphate.
- Ultimate fate of fructose during its metabolism is glycolytic steps where pyruvate is produced.

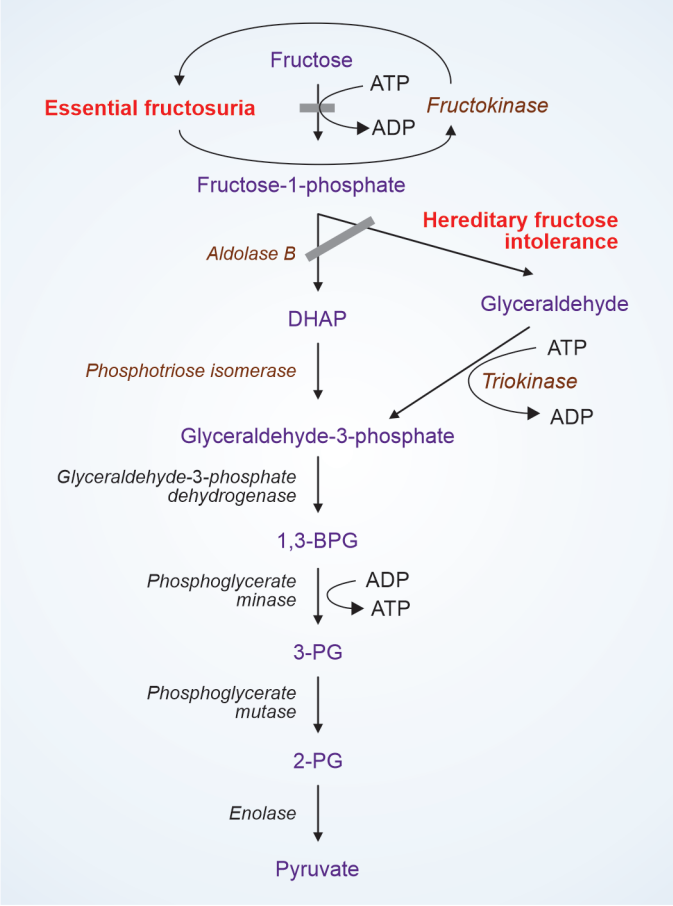


Fig. 6.1: Fructose metabolism in liver

Enzyme Defect in Fructose Catabolism

- *Hereditary fructose intolerance:* Enzyme defect is aldolase B.
- *Benign fructosuria:* Enzyme defect is fructokinase.

Key Notes

7

HMP Shunt Pathway

HEXOSE MONOPHOSPHATE SHUNT

Also known as pentose phosphate pathway (PPP)/Dickens-Horecker pathway/phosphogluconate oxidative pathway.

Key concepts for HMP shunt pathway

- HMP shunt pathway is the cytosolic pathway for glucose oxidation
- Significance of HMP shunt pathway
  - HMP shunt pathway is utilized for production of NADPH and ribose-5 phosphate.
  - NADPH is utilized for reductive biosynthesis and is important to tackle free radicals.
  - Ribose-5-phosphate is needed for synthesis of purine and pyrimidine nucleotide.

Location: Erythrocytes, liver, lactating mammary gland, adipose tissue, adrenal cortex (cytosol).

Clinical Correlation of HMP Shunt Pathway

- Deficiency of G6PD enzyme results in hemolytic anemia due to free radical damage of RBC membrane.

Key Notes

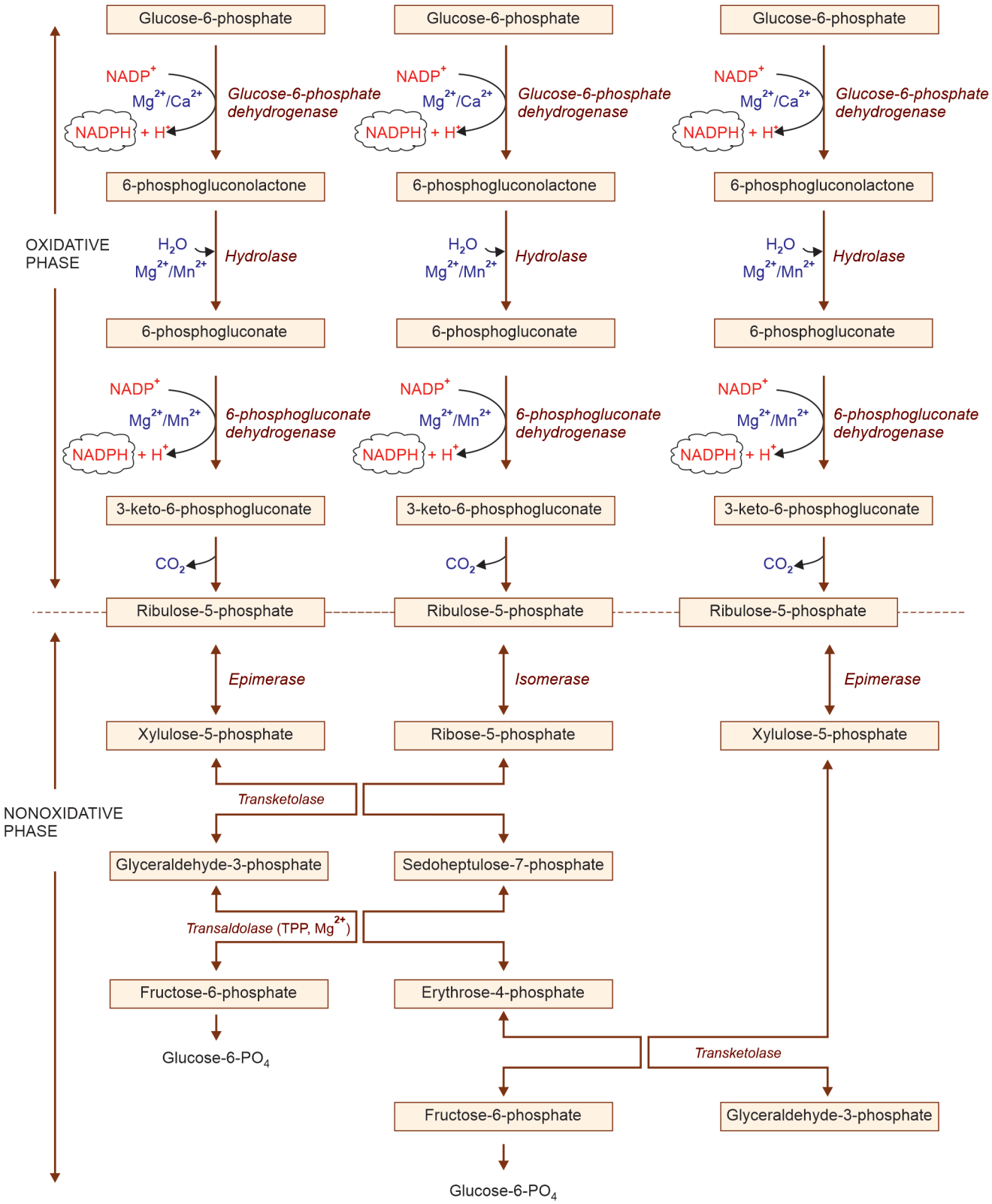


Fig. 7.1: Steps of HMP pathway

8

Uronic Acid Pathway

Key concepts

- Uronic acid pathway occurs in liver.
- Here glucose is oxidized for production of glucuronic acid which is a conjugating agent.
- Unlike lower primates, human is incapable of producing ascorbic acid in uronic acid pathway.
- This is due to absence of L-gulonolactone oxidase enzyme.

Clinical Correlation

- Essential pentosuria is due to deficiency of enzyme xylitol dehydrogenase, which results in excretion of L-xylulose in the urine.

Key Notes

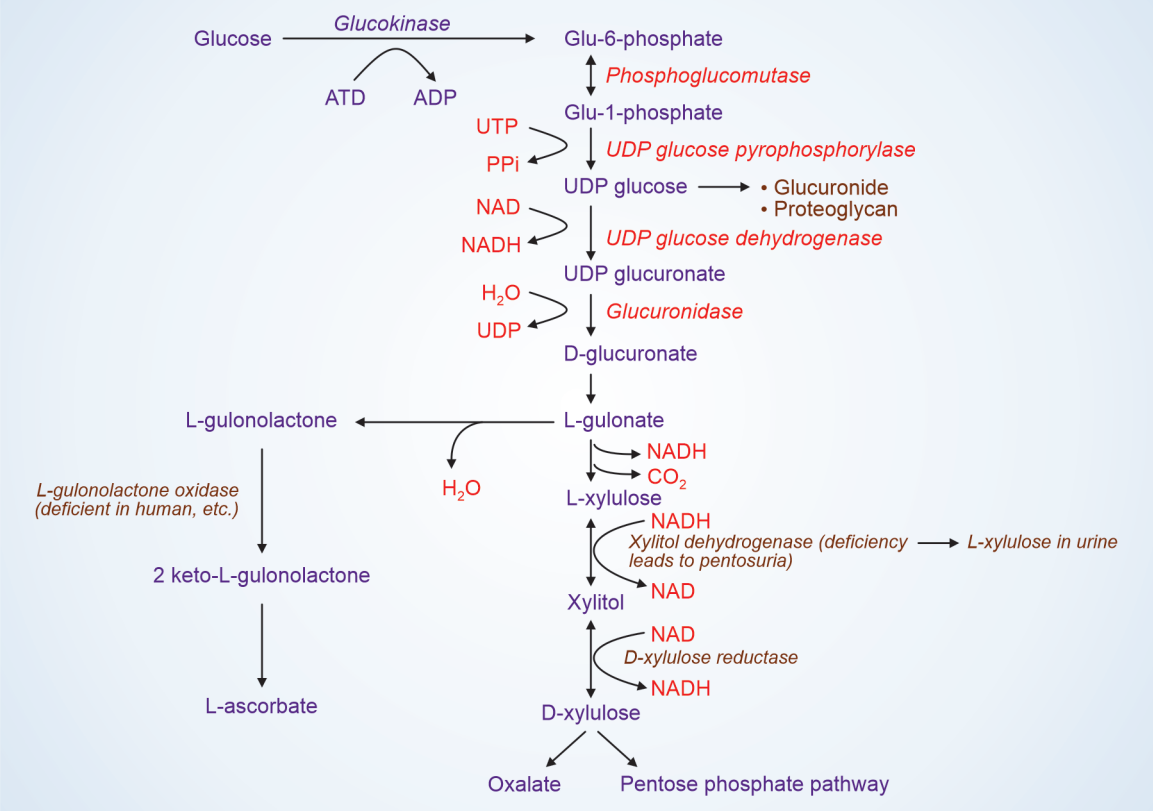


Fig. 8.1: Uronic acid pathway

Key Notes

Key Notes

Key Notes