Carbohydrate Metabolism

Learning Objectives

- Describe pathway of Glycolysis, its regulation in liver & muscles, significance and energetics.

- Describe the disorders associated with glycolysis like pyruvate kinase deficiency, hexokinase deficiency, lactic acidosis and discuss the role of glycolysis in cancer cells.

- Describe the pathway of Gluconeogenesis, its regulation and significance.
- Describe the glycogen synthesis (Glycogenesis), its significance and allosteric & hormonal regulation in liver & muscles.
- Describe the glycogen breakdown (Glycogenolysis), its significance and allosteric & hormonal regulation in liver & muscles.

- Describe various glycogen storage diseases associated with the synthesis & breakdown of glycogen

- Describe the Pentose Phosphate Pathway/Hexose Monophosphate (HMP) shunt, its significance, regulation and associated disorders

- Outline the Uronic acid pathway, its significance and associated disorder

- Describe the Galactose metabolism, its significance and disorder galactosemia.

- Describe the metabolism of Fructose and Sorbitol/Polyol pathway, and associated disorders

Digestion, Absorption and Transport of Carbohydrates

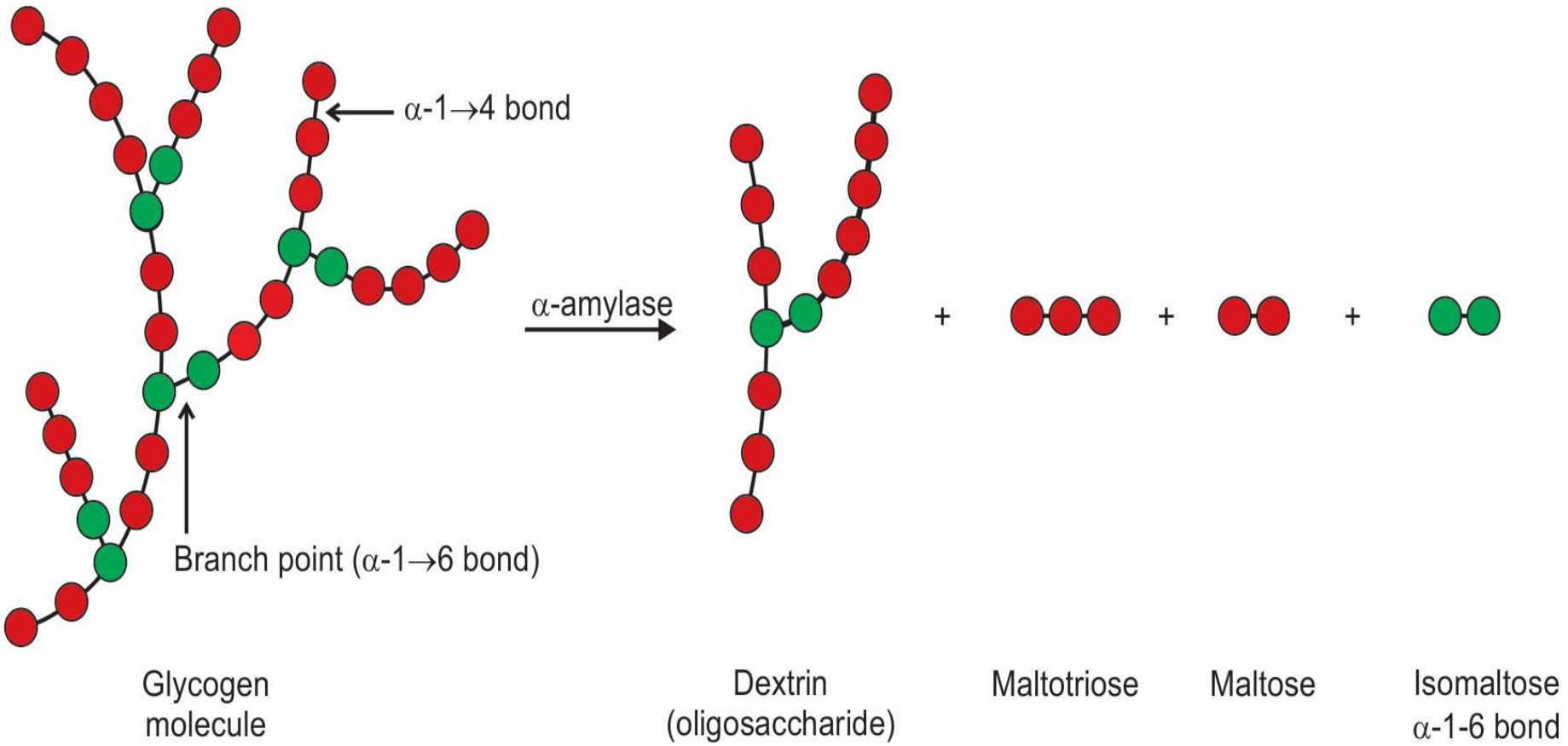
The dietary carbohydrate consists of:

- Polysaccharides: Starch, glycogen and cellulose
- Disaccharides: Sucrose, maltose and lactose
- Monosaccharides: Mainly glucose and fructose

Digestion in Mouth

- Salivary glands secrete α-*amylase*.
- Acts briefly on dietary starch and glycogen breaking some α-(1 → 4) bonds.
- α-amylase hydrolyzes starch into dextrins.

Figure 10.2: Action of α-amylase on starch or glycogen



Digestion in Stomach

Carbohydrate digestion halts temporarily in stomach.

Digestion in Intestine

There are two phases of intestinal digestion:

1. Digestion due to pancreatic α-amylase

2. Digestion due to intestinal enzymes :

   Sucrase

   Maltase

   Lactase

   Isomaltase

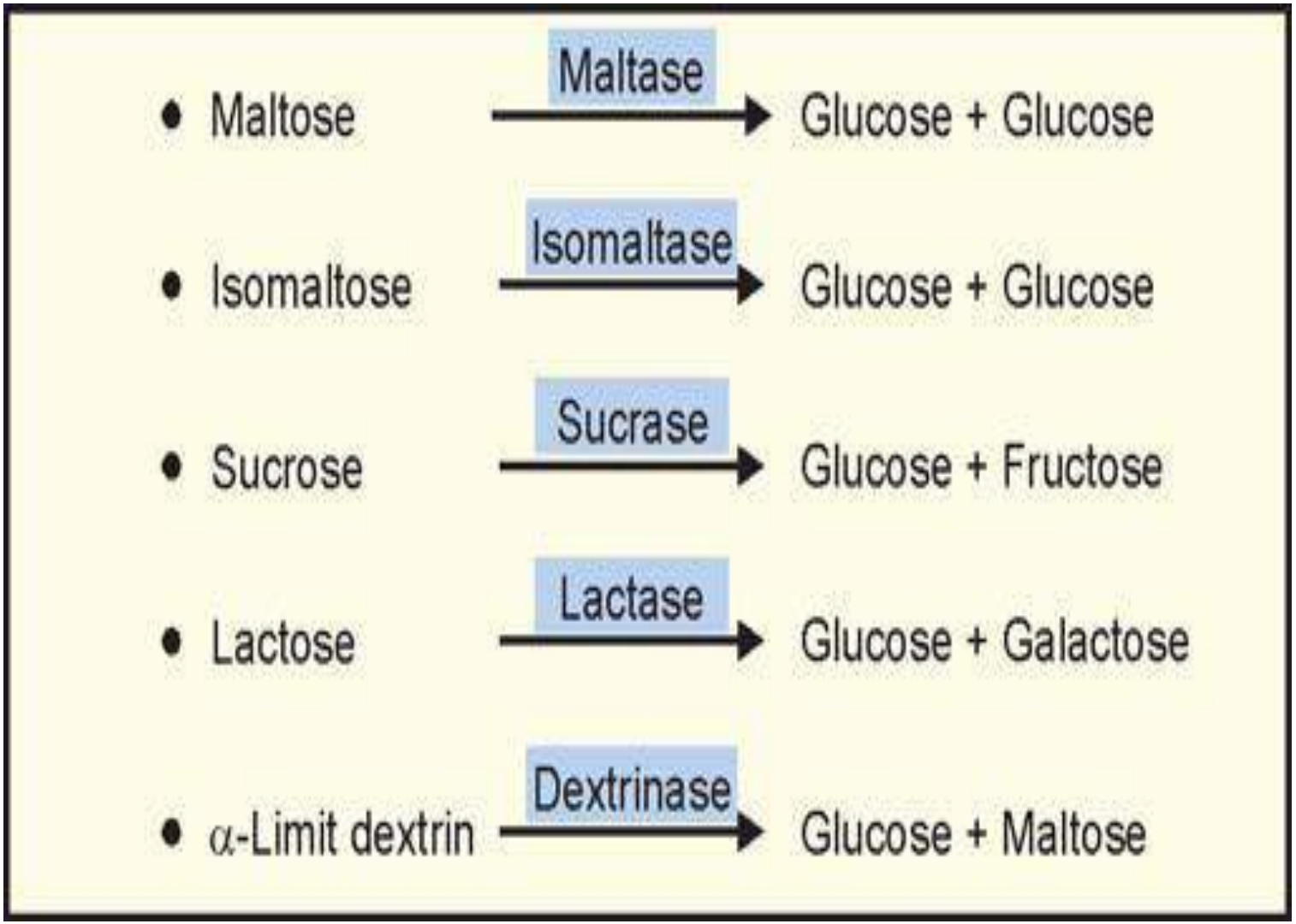
Digestion due to pancreatic α-amylase

- Pancreatic α-amylase degrades dextrins further into a mixture of :

  Maltose, Isomaltose and α-limit dextrin.

- The α-limit dextrins are smaller oligosaccharides containing 3 to 5 glucose units.

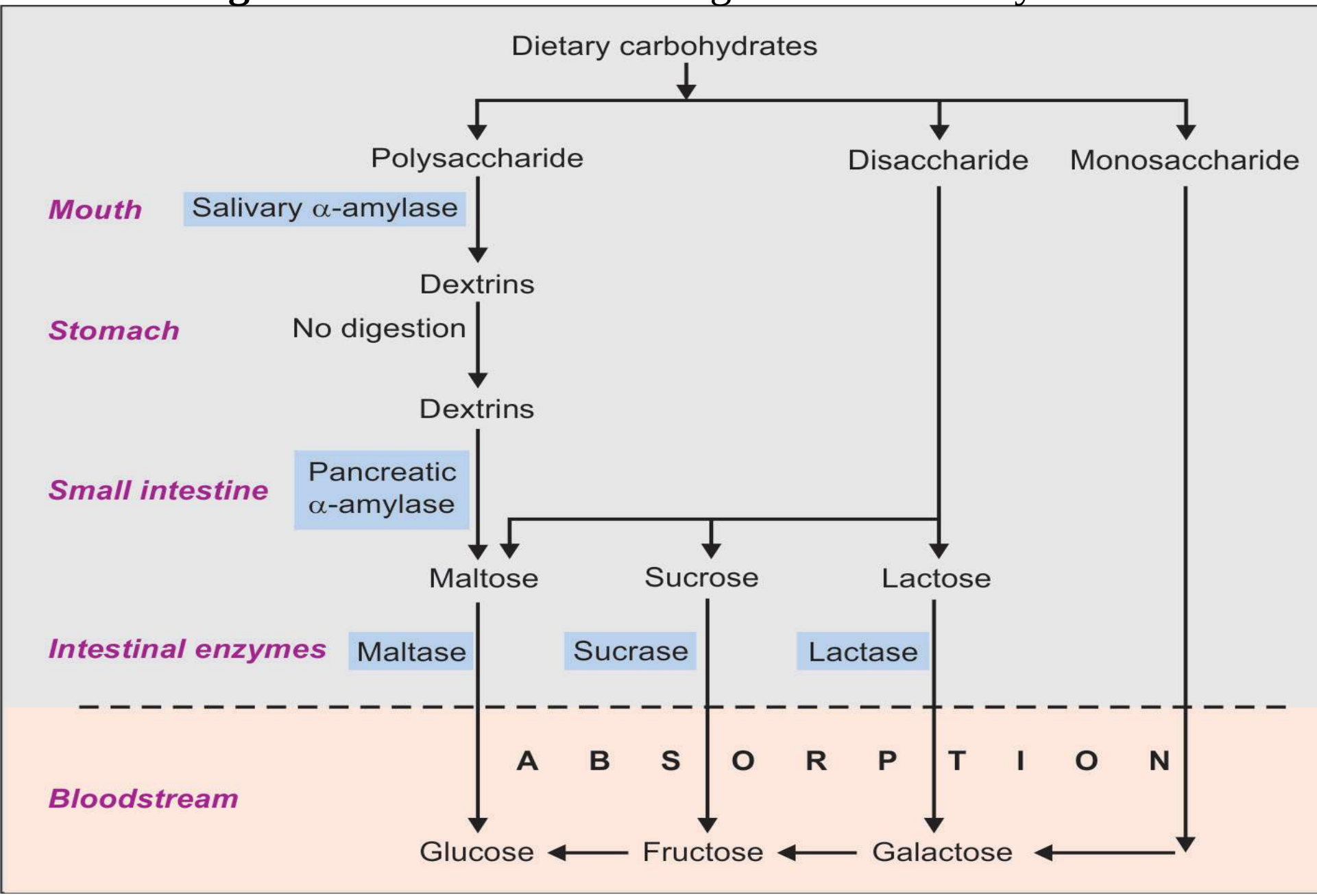
Digestion due to intestinal enzymes



The end products of carbohydrate digestion are:

- Glucose
- Fructose
- Galactose

Figure 10.1: Flow sheet of digestion of carbohydrates.



Absorption of Carbohydrates

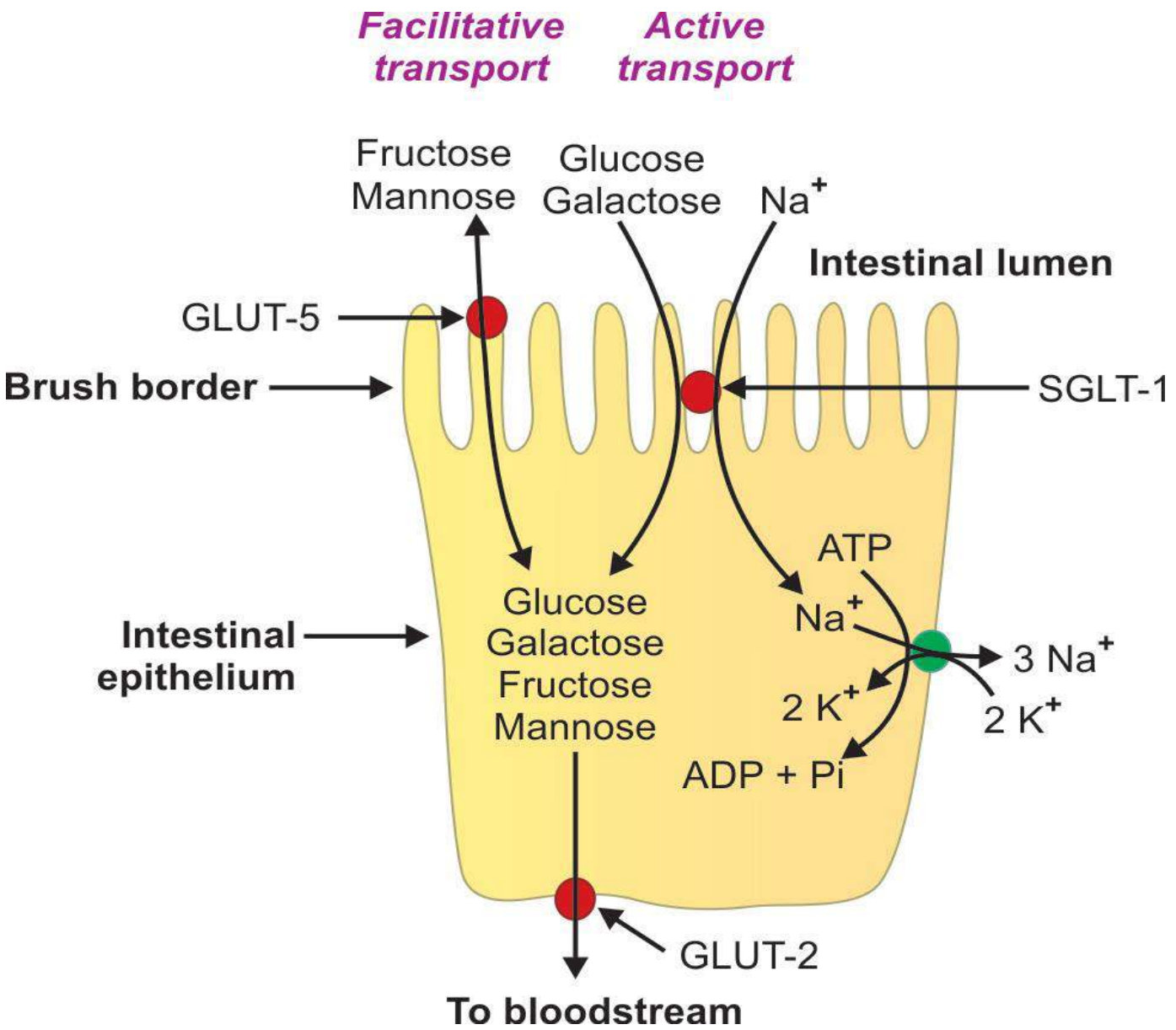
Two mechanisms are responsible for the absorption of monosaccharides:

1. Active transport against a concentration gradient, from a low glucose concentration to a higher concentration.
2. Facilitative transport, with concentration gradient , from a higher concentration to lower conc.

Active Transport

- The transport of glucose and galactose occurs by an active transport.
- Active transport requires:
  - Energy
  - A specific transport protein
  - Presence of sodium ions

Figure 10.3: Transport of glucose, fructose, galactose, mannose.



Facilitative Transport

- *Fructose* and *mannose* are transported by a Na+ independent facilitative diffusion process, requiring specific glucose transporter, GLUT-5.

- Movement of sugar in facilitative diffusion is strictly from a higher concentration to a lower one until it reaches an equilibrium.

Transport of Carbohydrates

- Sodium independent transporter, GLUT-2 facilitates transport of sugars out of the mucosal cells.
- Through portal circulation transported to the liver.

Lactose Intolerance

- Intolerance to lactose (the sugar of milk).
- Due to deficiency of enzyme *lactase.*
- lactose undergoes bacterial fermentation with the production of:
    - H_2 and CO_2 gases
    - acetic acid , propionic acid and butyric acid

- Abdominal cramps and flatulence results from the:

  -- Accumulation of gases

  -- Osmotically active products that draw water from the intestinal cells into the lumen resulting in *diarrhoea* and *dehydration*.

- Treatment for this disorder is simply to remove lactose from the diet.

GLYCOLYSIS

Embden Meyerhof pathway.

Definition

Glycolysis is the sequence of reactions that converts glucose into pyruvate in the presence of oxygen (aerobic) or lactate in the absence of oxygen (anaerobic) with the production of ATP.

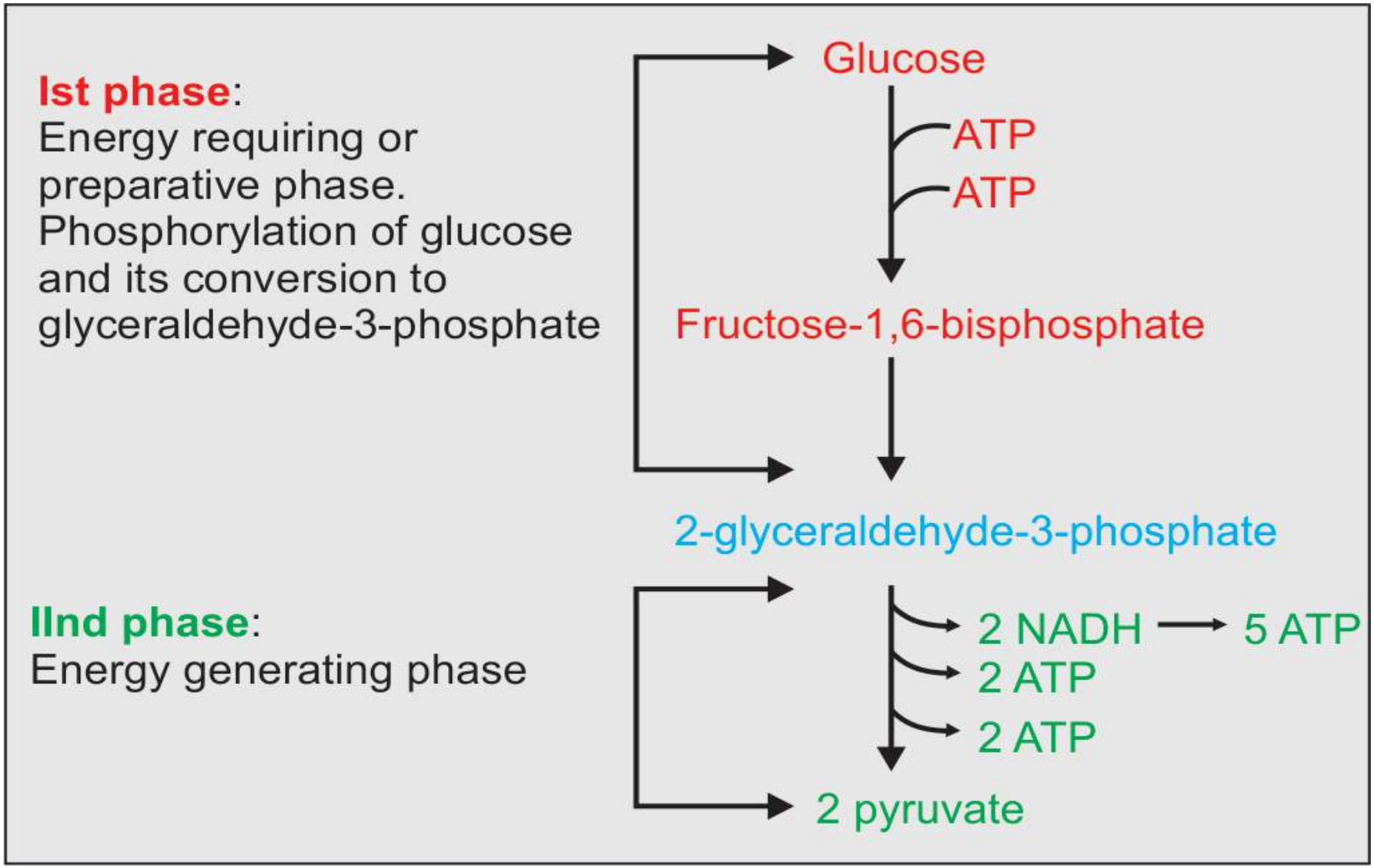
Location

Glycolysis is found in cytosol of all cells.

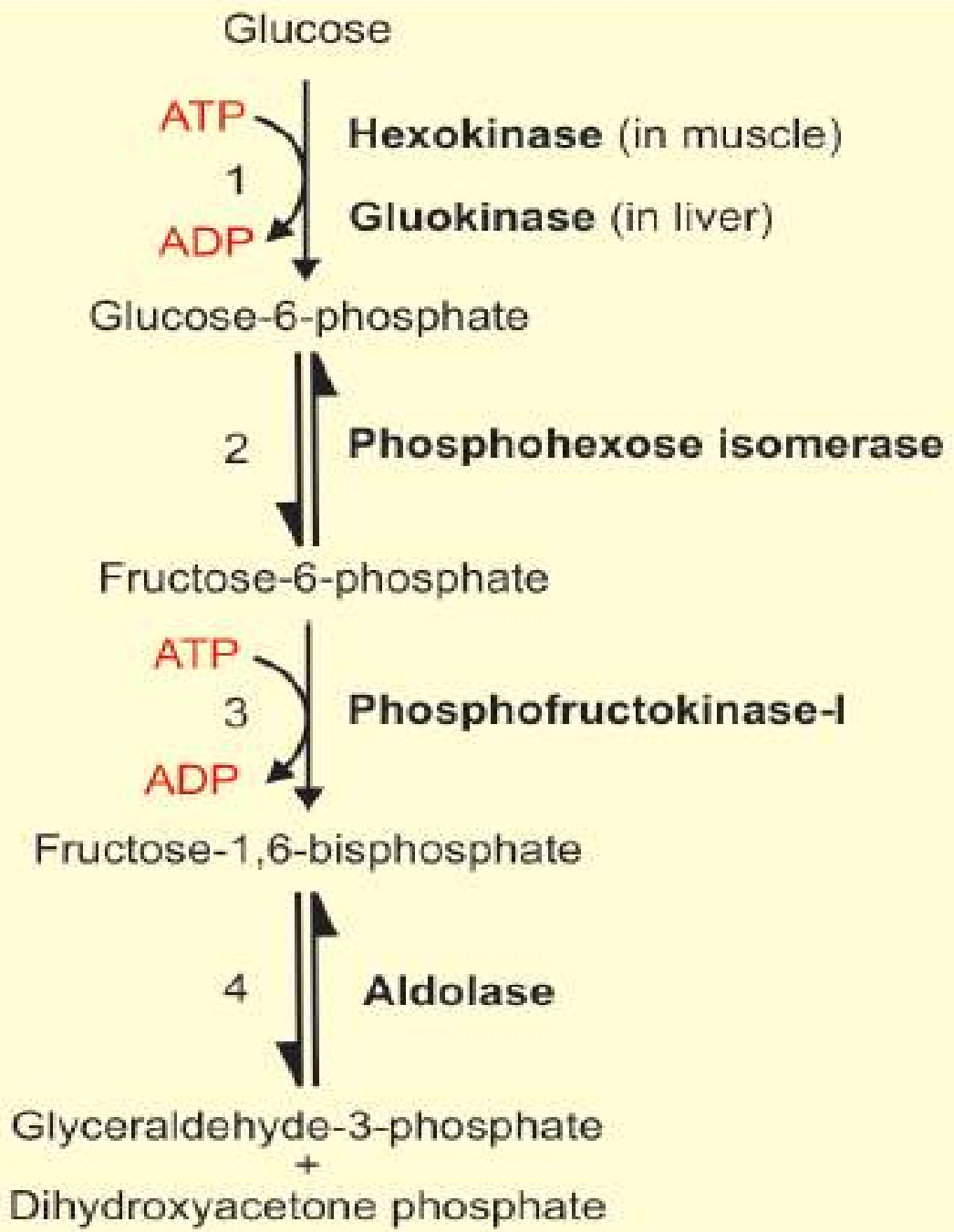
Reactions Of Glycolysis

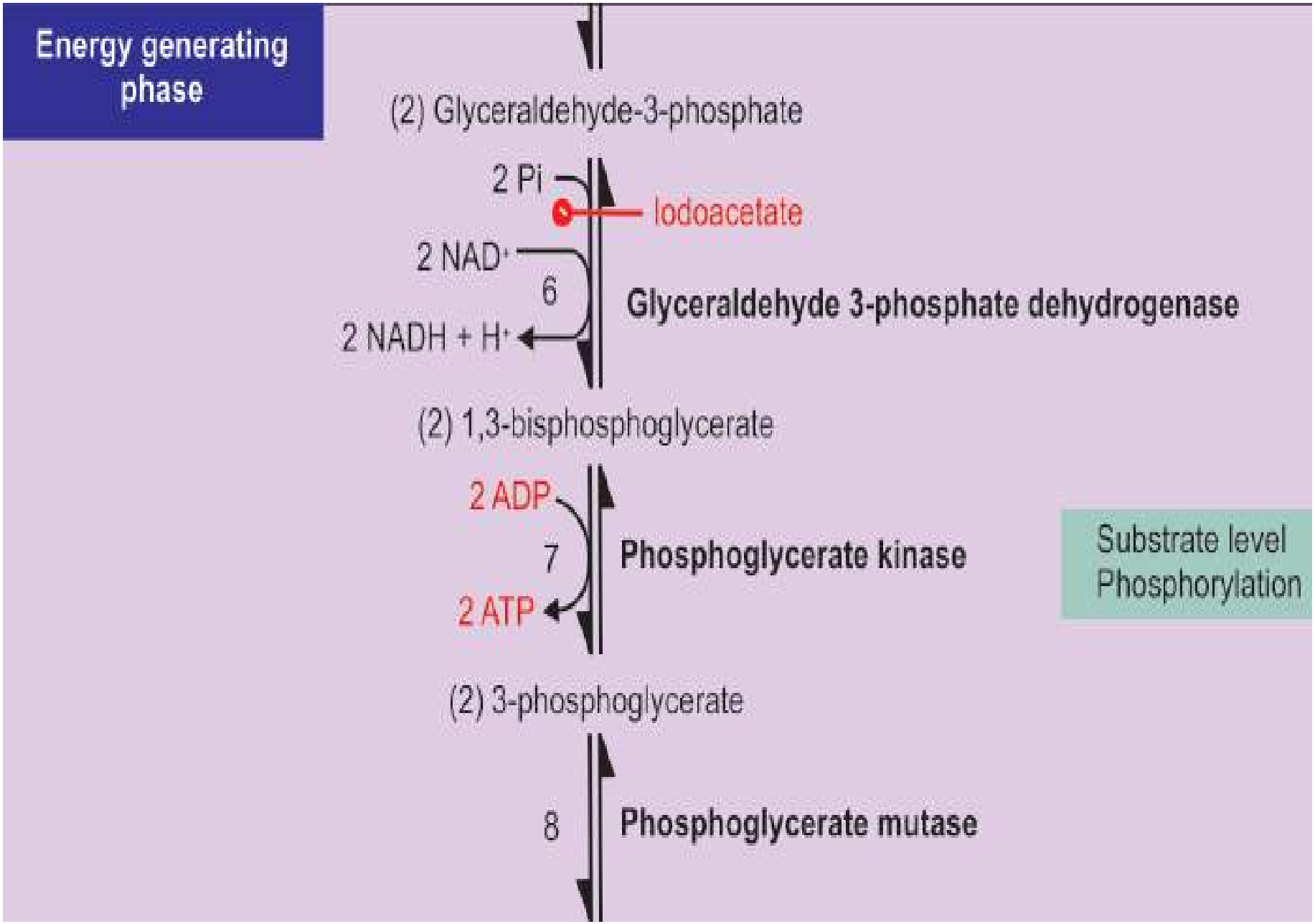
- I st phase: Energy requiring phase.
- II nd phase: Energy generating phase.

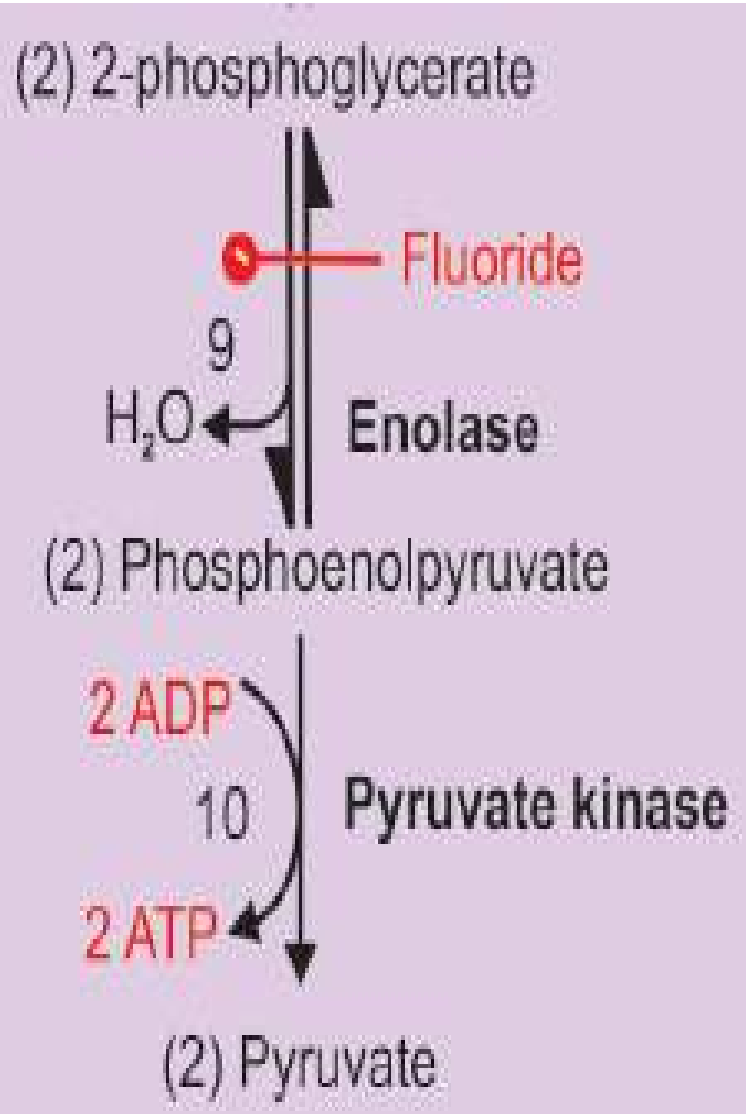
Figure 10.5: Phases of the glycolytic pathway.



Preparatory phase



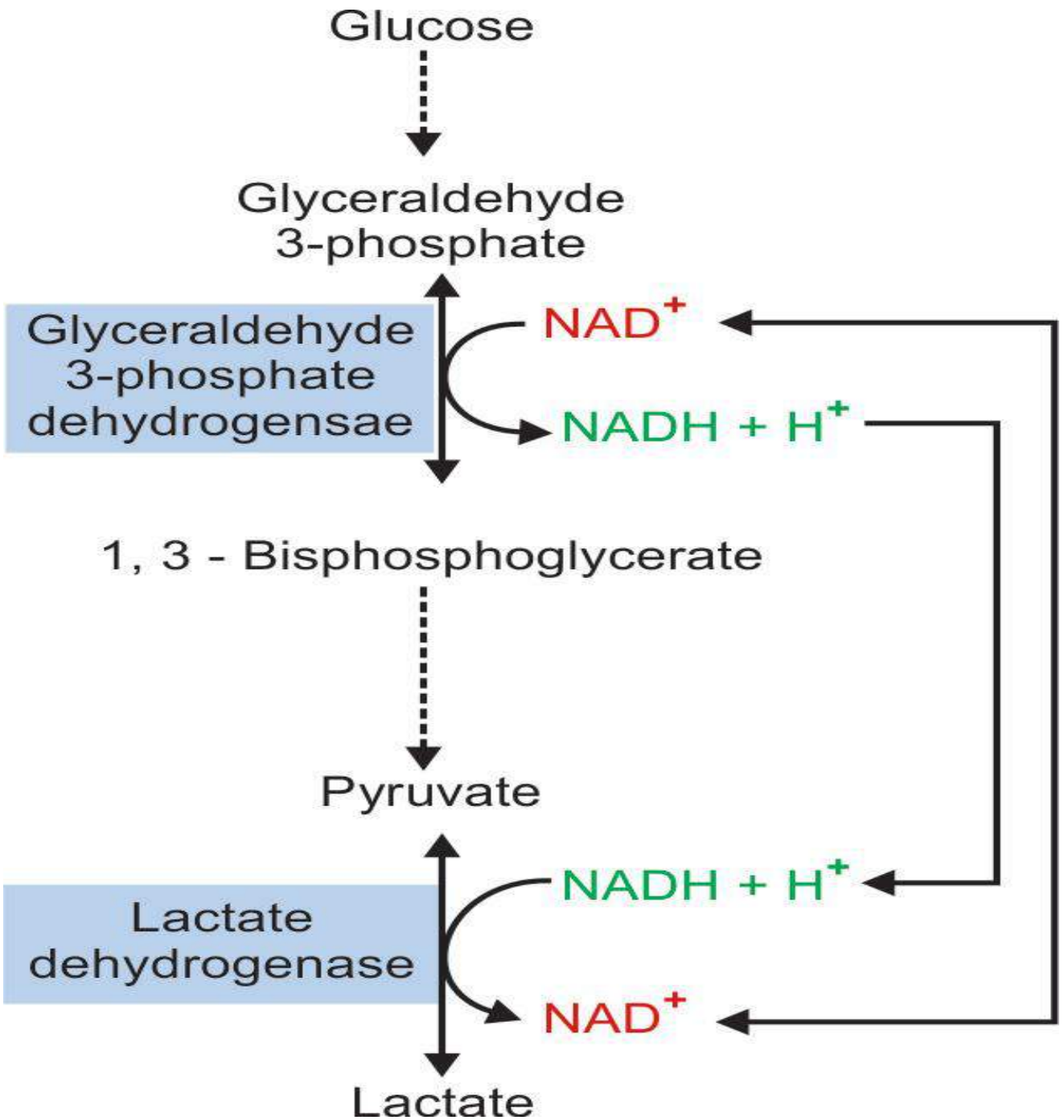

Energy generating phase
(2) Glyceraldehyde-3-phosphate
2 Pi
Iodoacetate
2 NAD+
6
2 NADH + H+
Glyceraldehyde 3-phosphate dehydrogenase
(2) 1,3-bisphosphoglycerate
2 ADP
7
2 ATP
Phosphoglycerate kinase
Substrate level Phosphorylation
(2) 3-phosphoglycerate
8
Phosphoglycerate mutase



Substrate level Phosphorylation

Anaerobic Glycolysis

- The re-oxidation of NADH by conversion of pyruvate to lactate by lactate dehydrogenase
- Tissues that function under hypoxic conditions produce lactate, e.g. skeletal muscle, smooth muscle and erythrocytes.


Glucose
Glyceraldehyde 3-phosphate
Glyceraldehyde 3-phosphate dehydrogensae
NAD+
NADH + H+
1, 3 - Bisphosphoglycerate
Pyruvate
Lactate dehydrogenase
NADH + H+
NAD+
Lactate

Regulation of Glycolysis

Glycolysis is regulated at 3 irreversible steps.These reactions are catalysed by:

1. Hexokinase and glucokinase
2. Phosphofructokinase-I
3. Pyruvate kinase

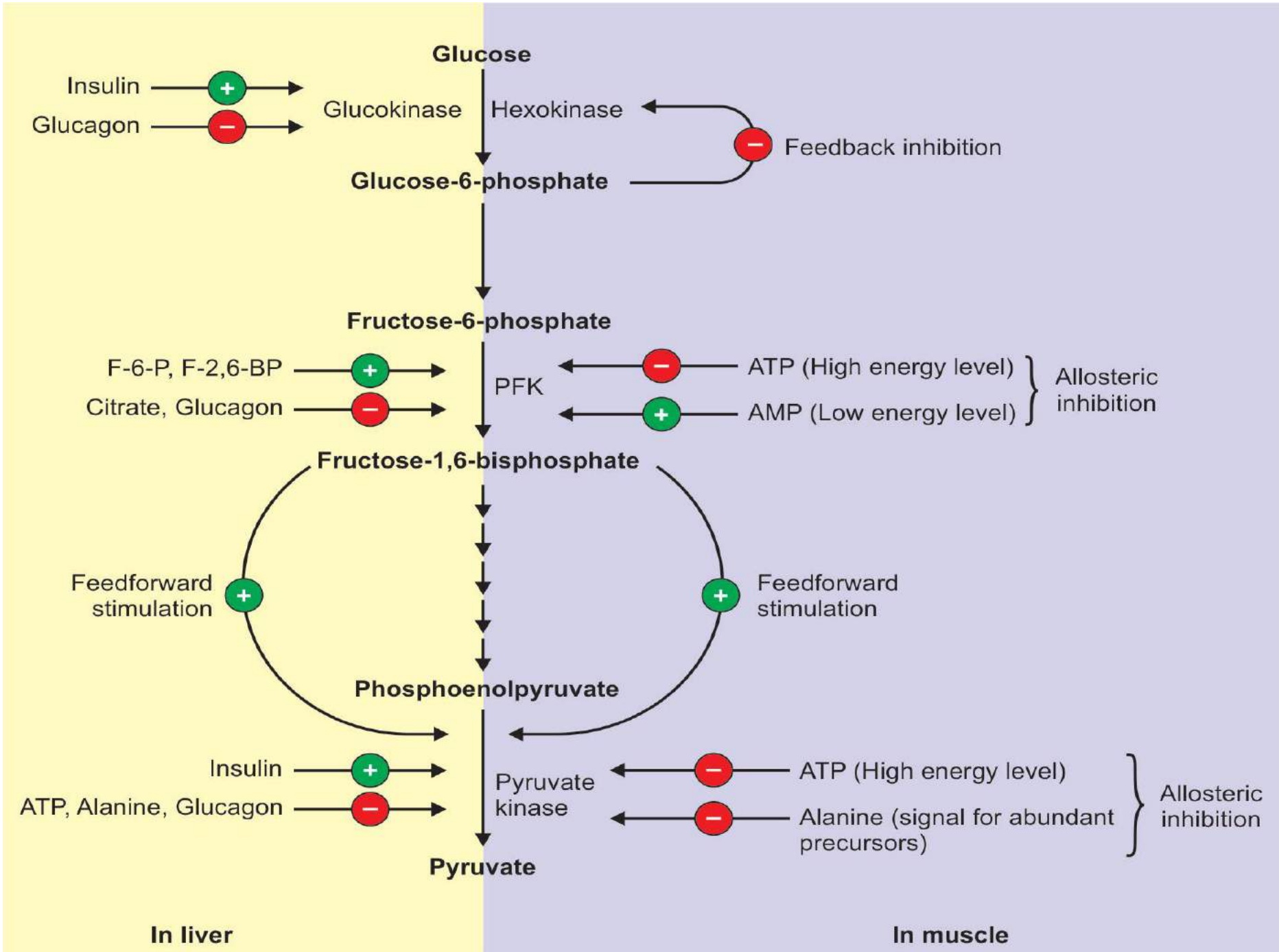

Glucose
Insulin
Glucagon
Glucokinase
Hexokinase
Feedback inhibition
Glucose-6-phosphate
Fructose-6-phosphate
F-6-P, F-2,6-BP
Citrate, Glucagon
PFK
ATP (High energy level)
AMP (Low energy level)
Allosteric inhibition
Fructose-1,6-bisphosphate
Feedforward stimulation
Feedforward stimulation
Phosphoenolpyruvate
Insulin
ATP, Alanine, Glucagon
Pyruvate kinase
ATP (High energy level)
Alanine (signal for abundant precursors)
Allosteric inhibition
Pyruvate
In liver
In muscle

Figure 10.9: Regulation of phosphofructokinase by fructose-2,6-bisphosphate

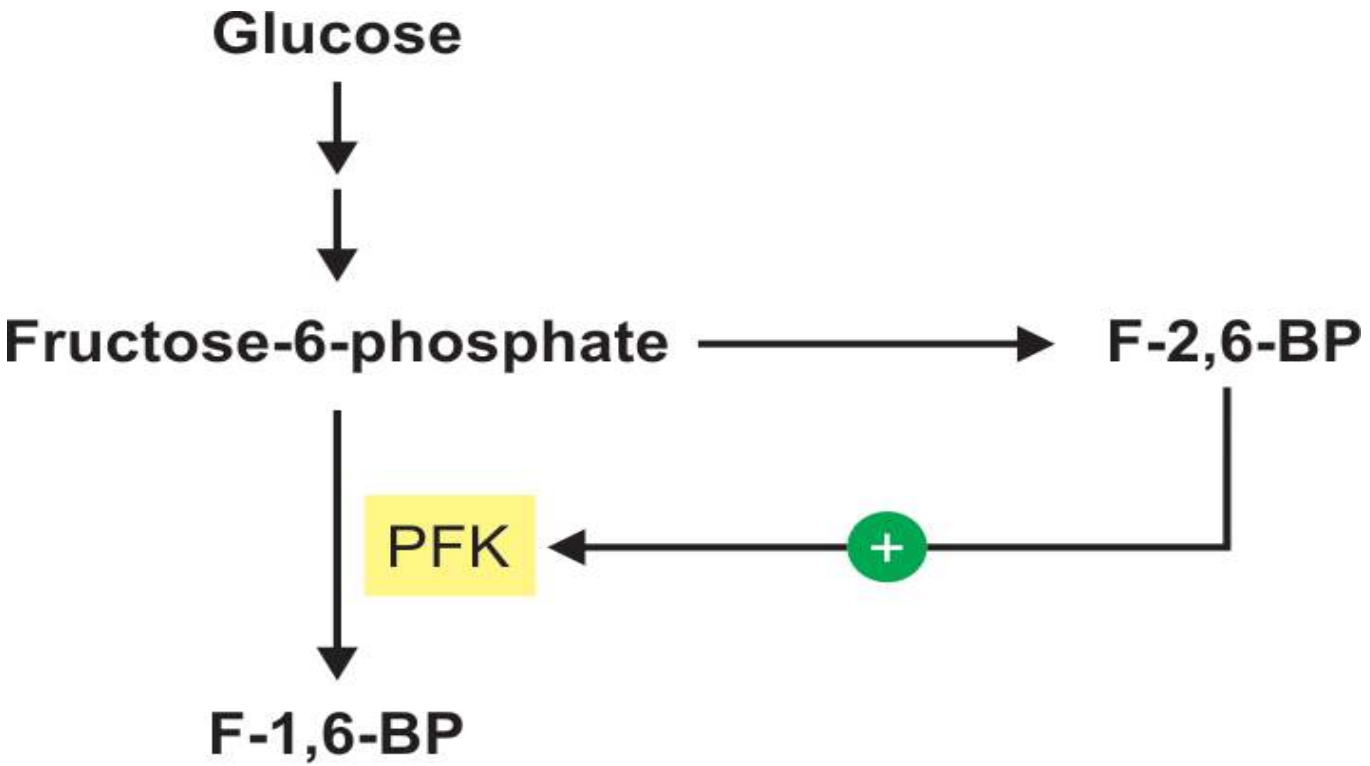
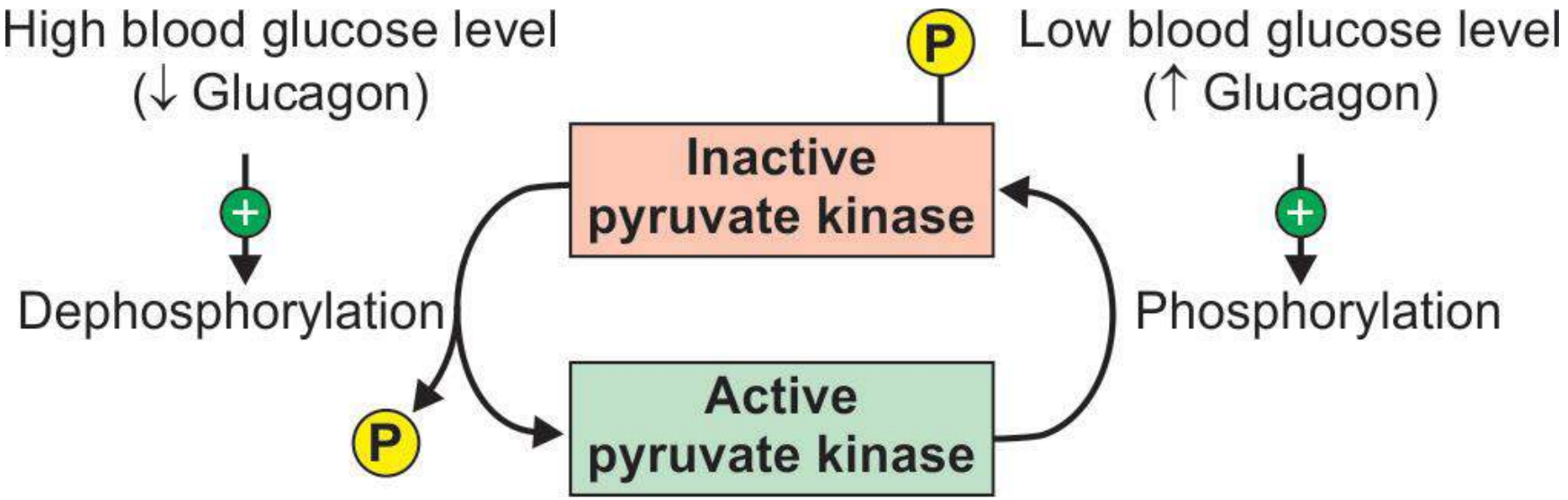


Figure 10.10: Regulation of liver pyruvate kinase.



Significance of Glycolysis

- Glycolysis is the principal route for glucose metabolism for the production of ATP molecules.
- Glycolysis provide ATP in the absence of oxygen and allows tissues to survive anoxic episodes.
- In erythrocytes, glycolysis supplies 2,3-BPG which is required for transport of oxygen by Hb.

- Generates precursors for biosynthetic pathway:
  - Pyruvate transaminated to amino acid alanine.
  - Pyruvate provides substrate acetyl-CoA for fatty acid biosynthesis.
  - Glycerol-3-phosphate, required for synthesis of triacylglycerol is derived from glycolysis.

- It also provide pathway for the metabolism of fructose and galactose derived from diet.
- 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.

Energetic of Glycolysis

- The net reaction of aerobic glycolysis of glucose into two molecules pyruvate generates:
  - 2 molecules of NADH (2.5 x2 = 5)
  - 4 molecules of ATP at subs level phosphorylation

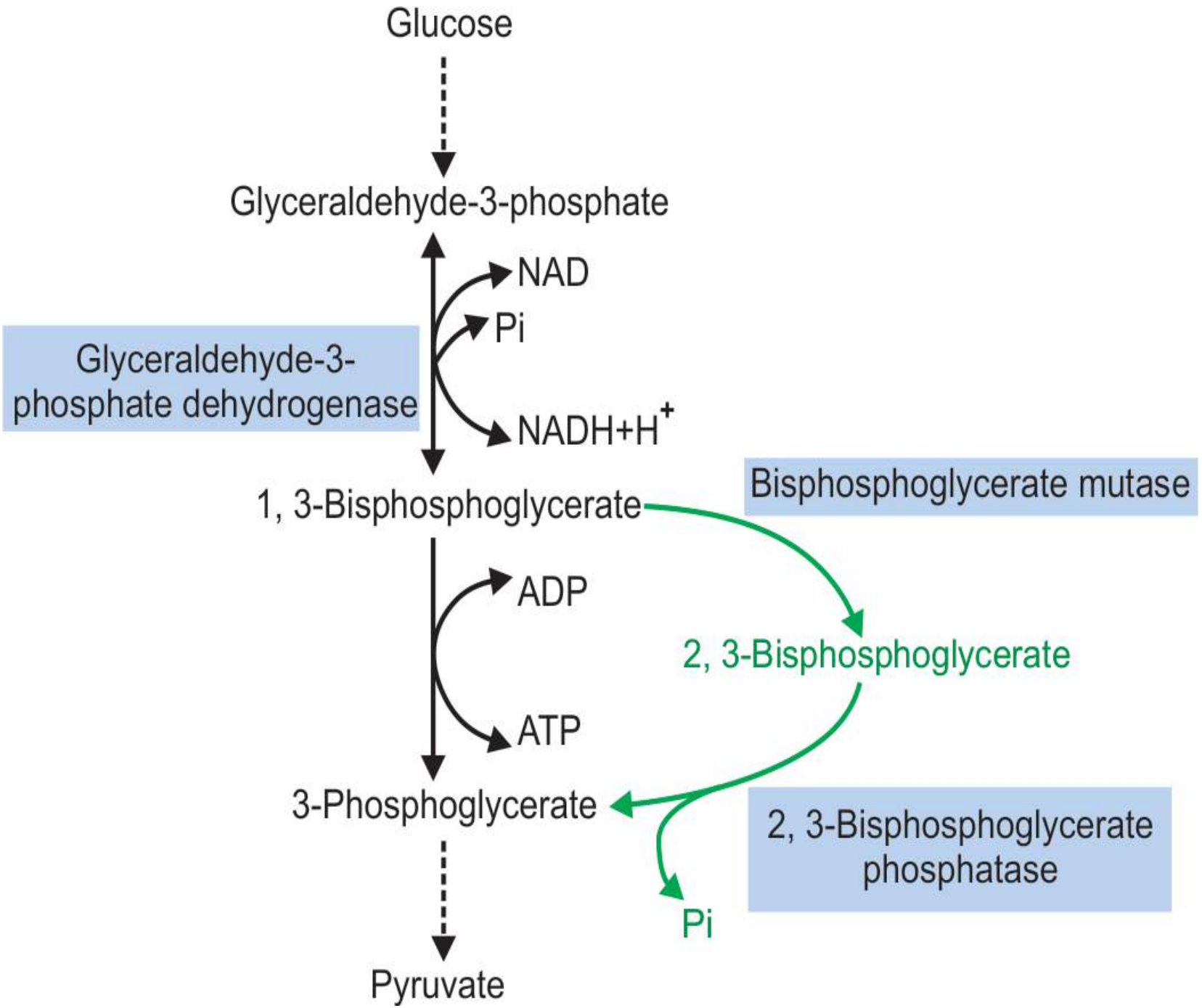
- Two molecules of ATP per mole of glucose are consumed
- The net gain is 7 moles of ATP

- Under aerobic conditions, 7 molecules of ATP are produced.

- In anaerobic glycolysis, on the other hand, only 2 moles of ATP are produced per molecule of glucose.

Rapoport Lubering Cycle

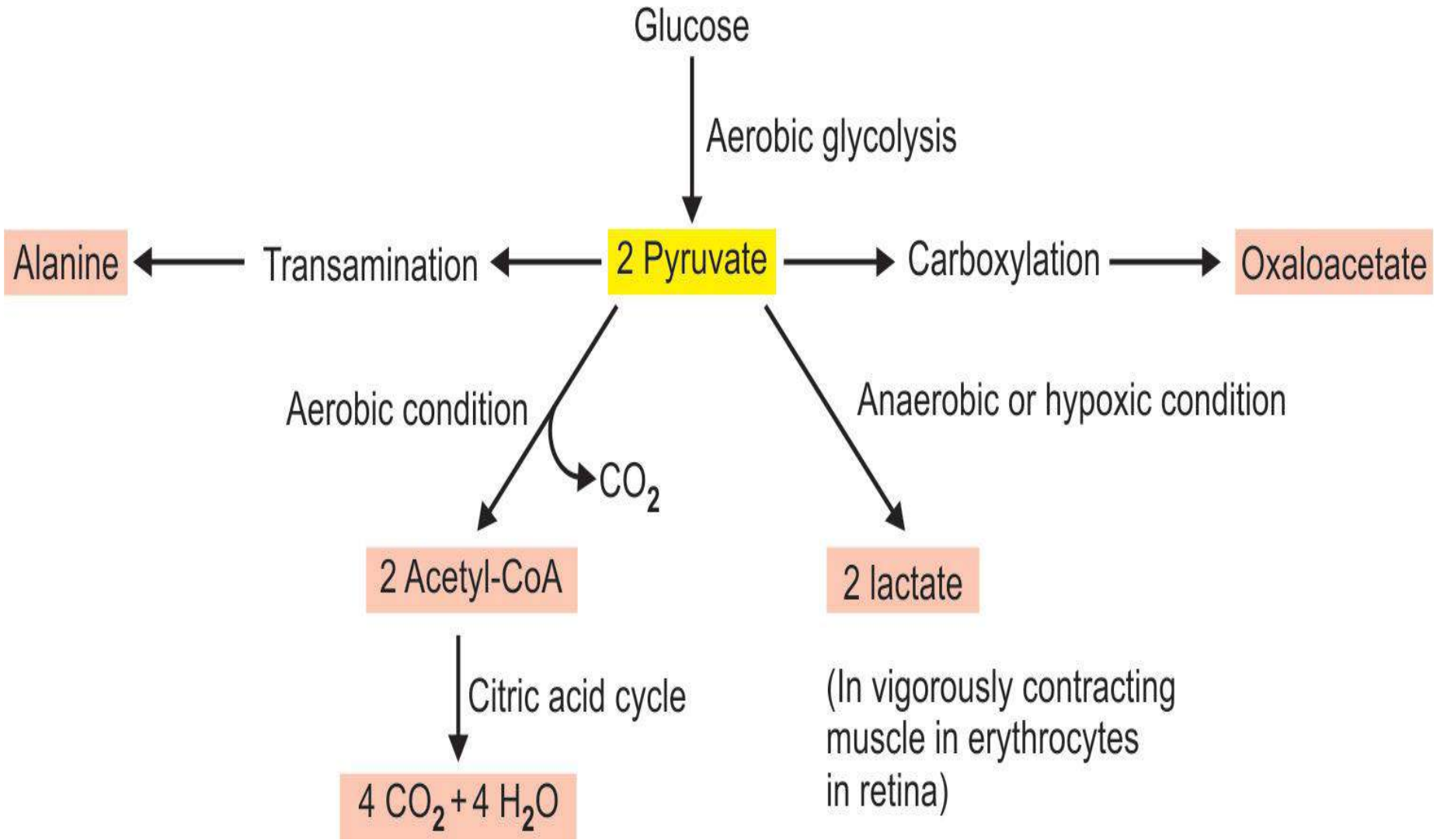
- In Rapoport lubering cycle, production of ATP by substrate phosphorylation from 1,3-BPG to 3-BPG is bypassed in the erythrocyte.
- There is no net production of ATP when glycolysis takes this route.


Glucose
Glyceraldehyde-3-phosphate
NAD
Pi
Glyceraldehyde-3-phosphate dehydrogenase
NADH+H+
1, 3-Bisphosphoglycerate
Bisphosphoglycerate mutase
ADP
2, 3-Bisphosphoglycerate
ATP
3-Phosphoglycerate
2, 3-Bisphosphoglycerate phosphatase
Pi
Pyruvate

Significance of Rapoport Lubering Cycle

- It supplies 2,3-BPG required for transport of oxygen by hemoglobin. 2,3-BPG regulates the binding and release of oxygen from hemoglobin
- 2, 3-BPG present in erythrocytes acts as a buffer.

Figure 10.14: Catabolic fates of pyruvate.

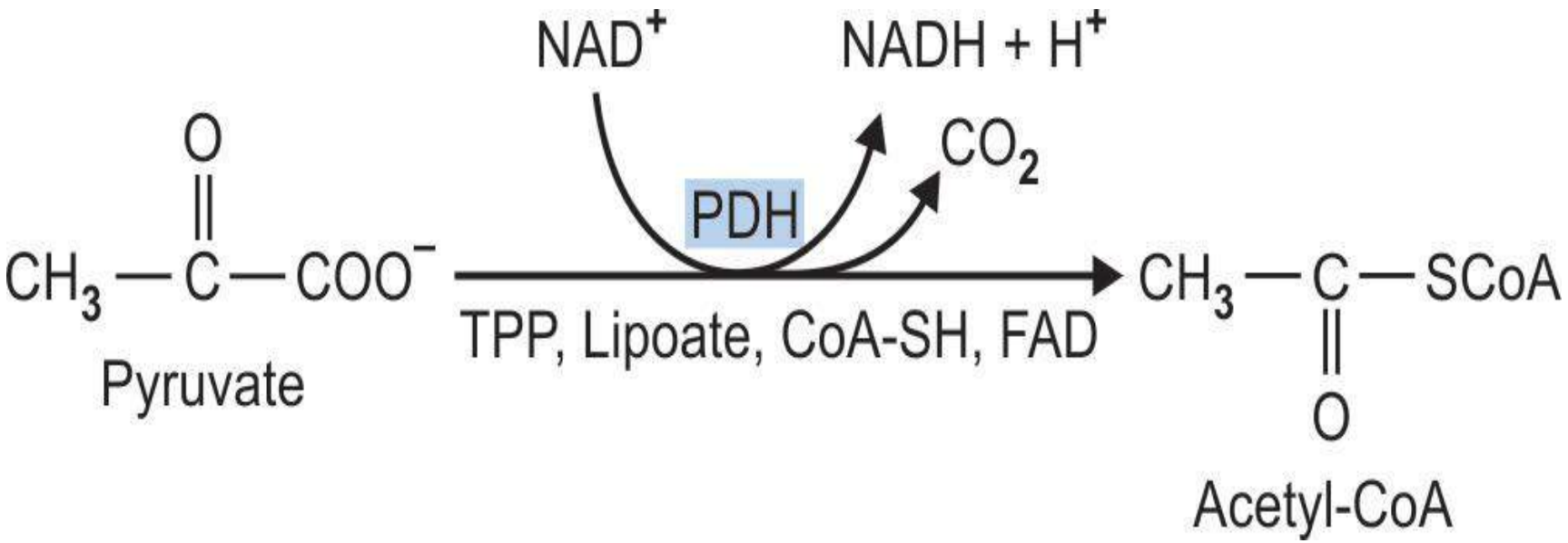


Conversion Of Pyruvate To Acetyl-CoA

- Pyruvate is converted to acetyl CoA by oxidative decarboxylation in mitochondria.
- Irreversible reaction catalyzed by a multienzyme complex pyruvate dehydrogenase (PDH)
- PDH requires five coenzymes :

  thiamine pyrophosphate (TPP), lipoate, coenzyme-A, FAD and NAD+.

Figure 10.15: Oxidative decarboxylation of pyruvate by the pyruvate dehydrogenase complex.



Energetics in conversion of pyruvate to Acetyl Co A

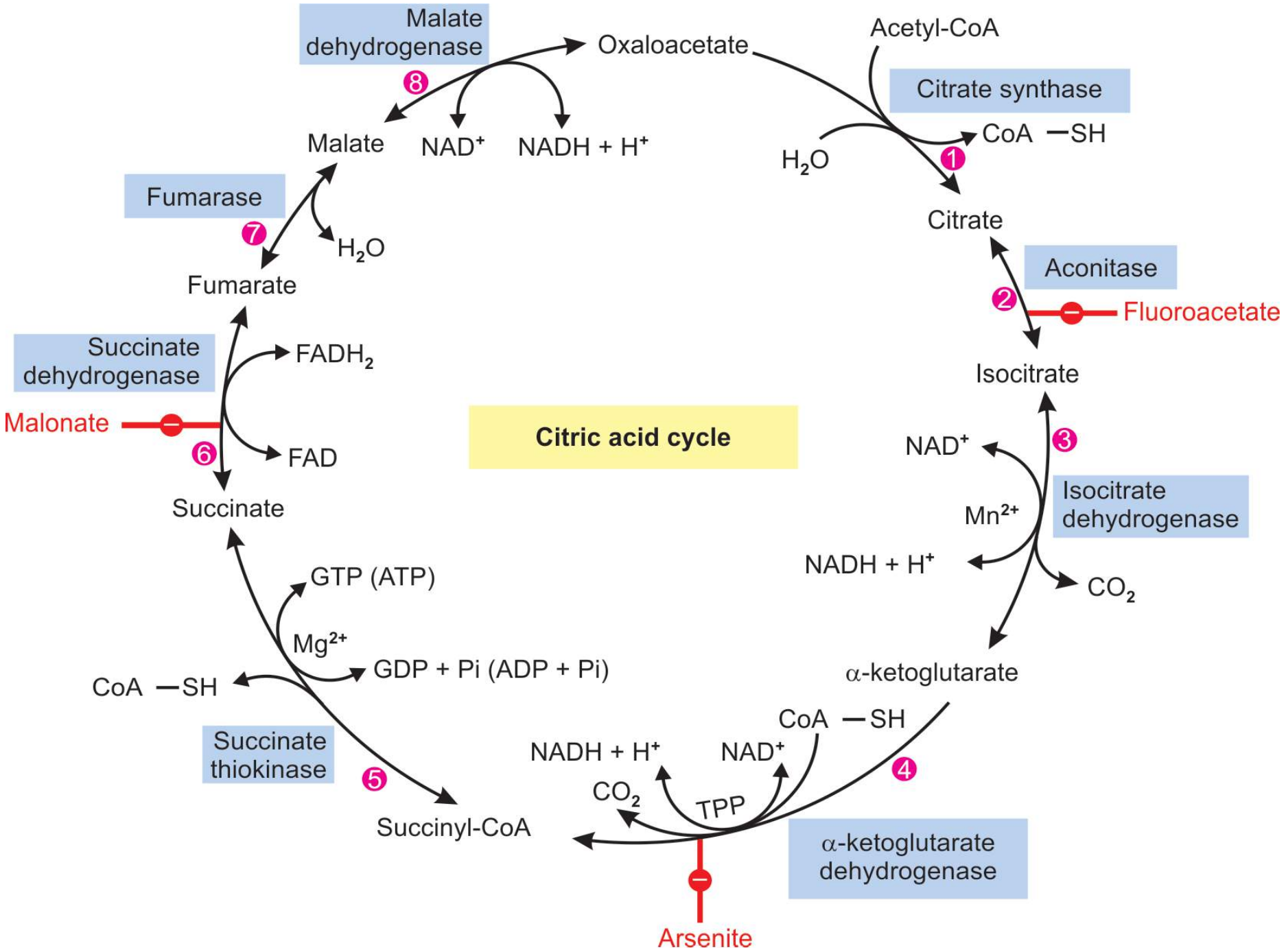
- One molecule of NADH is produced for each molecule of pyruvate.
- Oxidation of NADH by electron transport chain results in synthesis of 2.5 ATP molecules

Citric Acid Cycle

Citric acid cycle or Krebs cycle or tricarboxylic acid (TCA) cycle

Definition

The citric acid cycle is a series of reactions in mitochondria that brings about the catabolism of acetyl-CoA to CO_2 and H_2O with generation of ATP.


Malate dehydrogenase
Oxaloacetate
Acetyl-CoA
Citrate synthase
Malate
NAD+
NADH + H+
CoA —SH
H2O
Fumarase
Citrate
H2O
Aconitase
Fumarate
Fluoroacetate
Succinate dehydrogenase
Isocitrate
FADH2
Malonate
Citric acid cycle
NAD+
Isocitrate dehydrogenase
FAD
Mn2+
Succinate
NADH + H+
CO2
GTP (ATP)
Mg2+
α-ketoglutarate
GDP + Pi (ADP + Pi)
CoA —SH
CoA —SH
Succinate thiokinase
NADH + H+
NAD+
CO2
TPP
Succinyl-CoA
α-ketoglutarate dehydrogenase
Arsenite

Energetics of Citric Acid Cycle

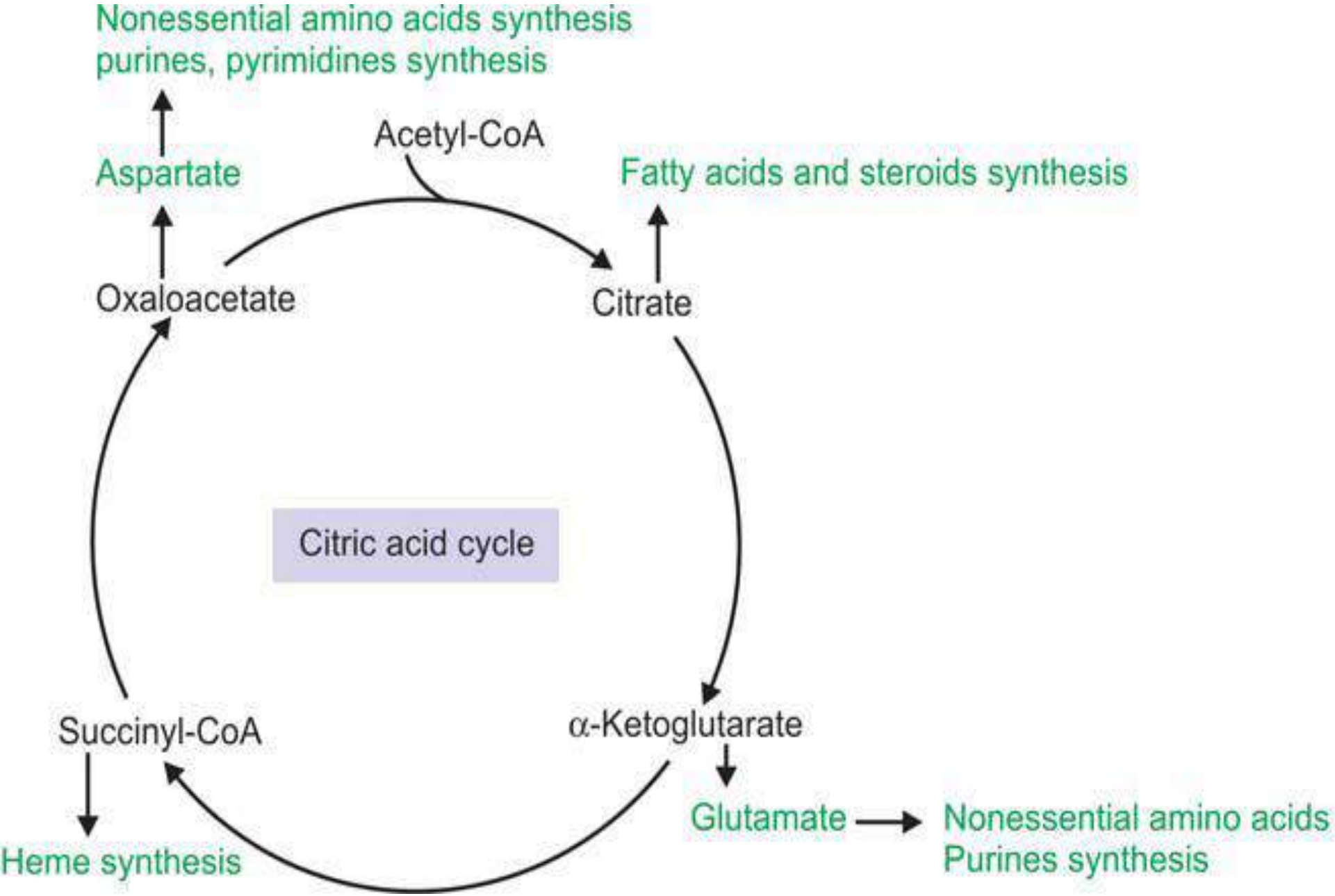
- Three molecules of NADH and one $FADH_2$ are produced
- One molecule of ATP is generated at substrate level during the conversion of succinyl-CoA to succinate.

Total 10 ATP are generated from one mole of acetyl-CoA.

Significance of Citric Acid Cycle

- Provide energy in the form of ATP.
- Final common pathway for the oxidation of carb, lipids, and proteins.
- Amphibolic (catabolic and anabolic) process , has a dual function.

- Pathways originate from the TCA cycle:
  - Gluconeogenesis
  - Transamination
  - Fatty acid synthesis
  - Heme synthesis.



Amphibolic role of the citric acid cycle

Regulation of Citric Acid Cycle

- Citric acid cycle is regulated at three steps by:

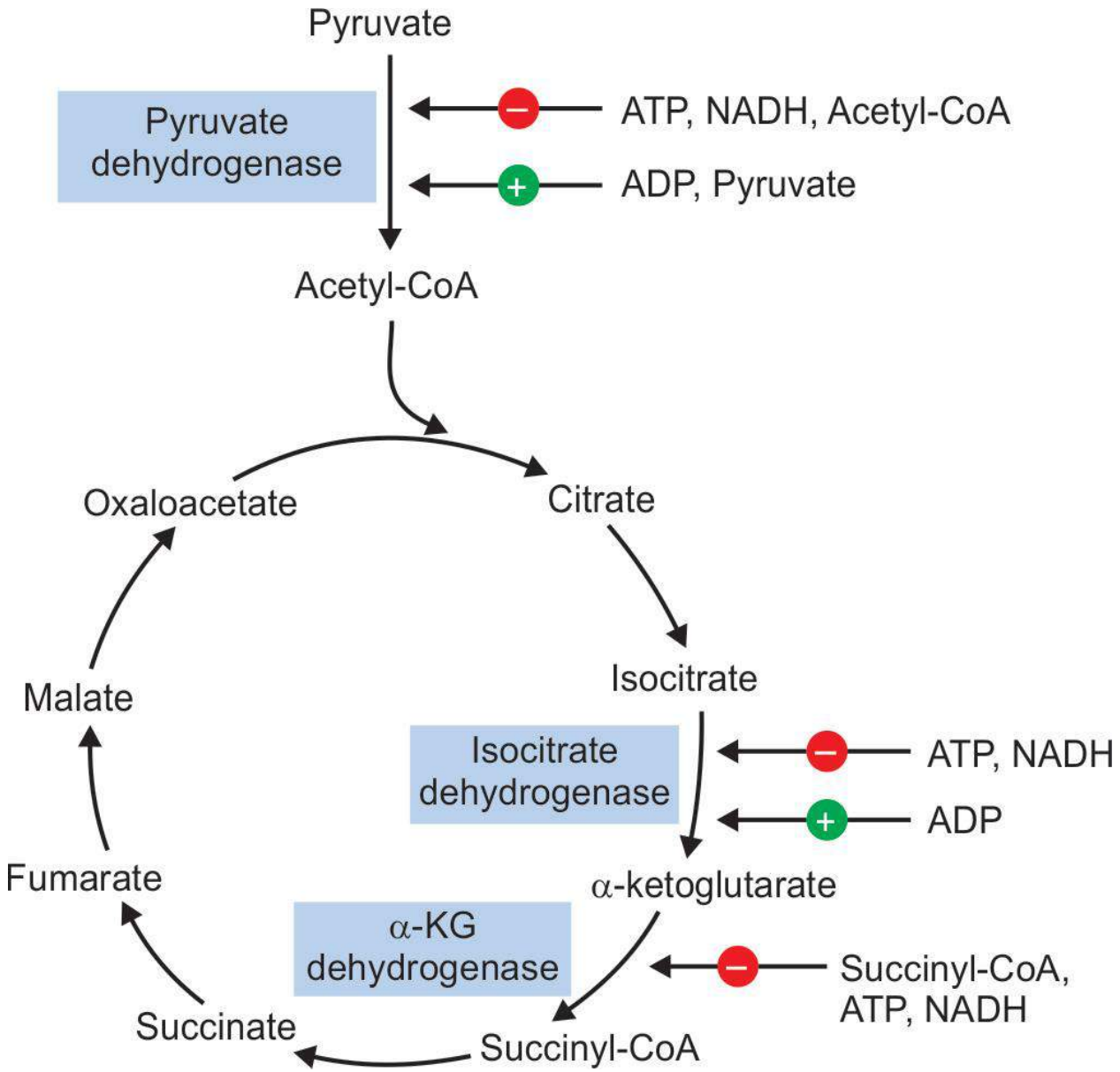
  1. Citrate synthase
  2. Isocitrate dehydrogenase
  3. α-ketoglutarate dehydrogenase.

- Activities of these enzymes are dependent on the energy status of the cycle.

- Excess of ATP, NADH and succinyl-CoA, which signals high energy status of the cell, inhibit these enzymes.

- High level of ADP which signals low energy status of the cell stimulates the operation of the cycle.

Figure 10.20: Regulation of citric acid cycle.



GLUCONEOGENESIS

Synthesis of glucose from non-carbohydrate precursors.

Location of Gluconeogenesis

- Liver is the major tissue
- During starvation, the kidney is also capable of making glucose by gluconeogenesis.

Non-carbohydrate Precursors of gluconeogenesis

- Lactate
- Glycerol
- Glucogenic amino acids
- Propionic acid
- Intermediates of TCA

Figure 10.23: Major non-carbohydrate substrates and their entry points into gluconeogenesis.

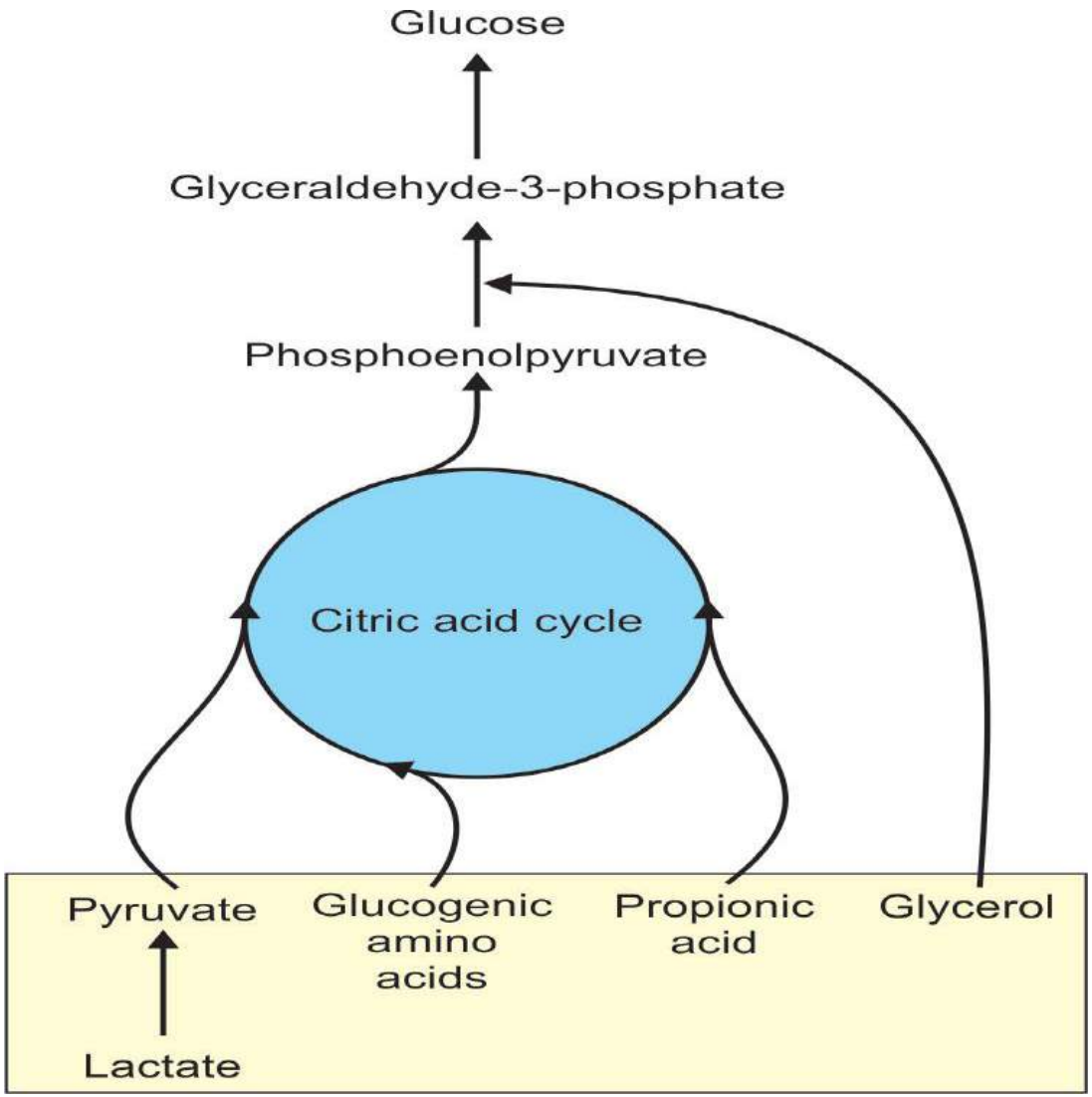


Figure 10.27: Conversion of propionate to succinyl-CoA.

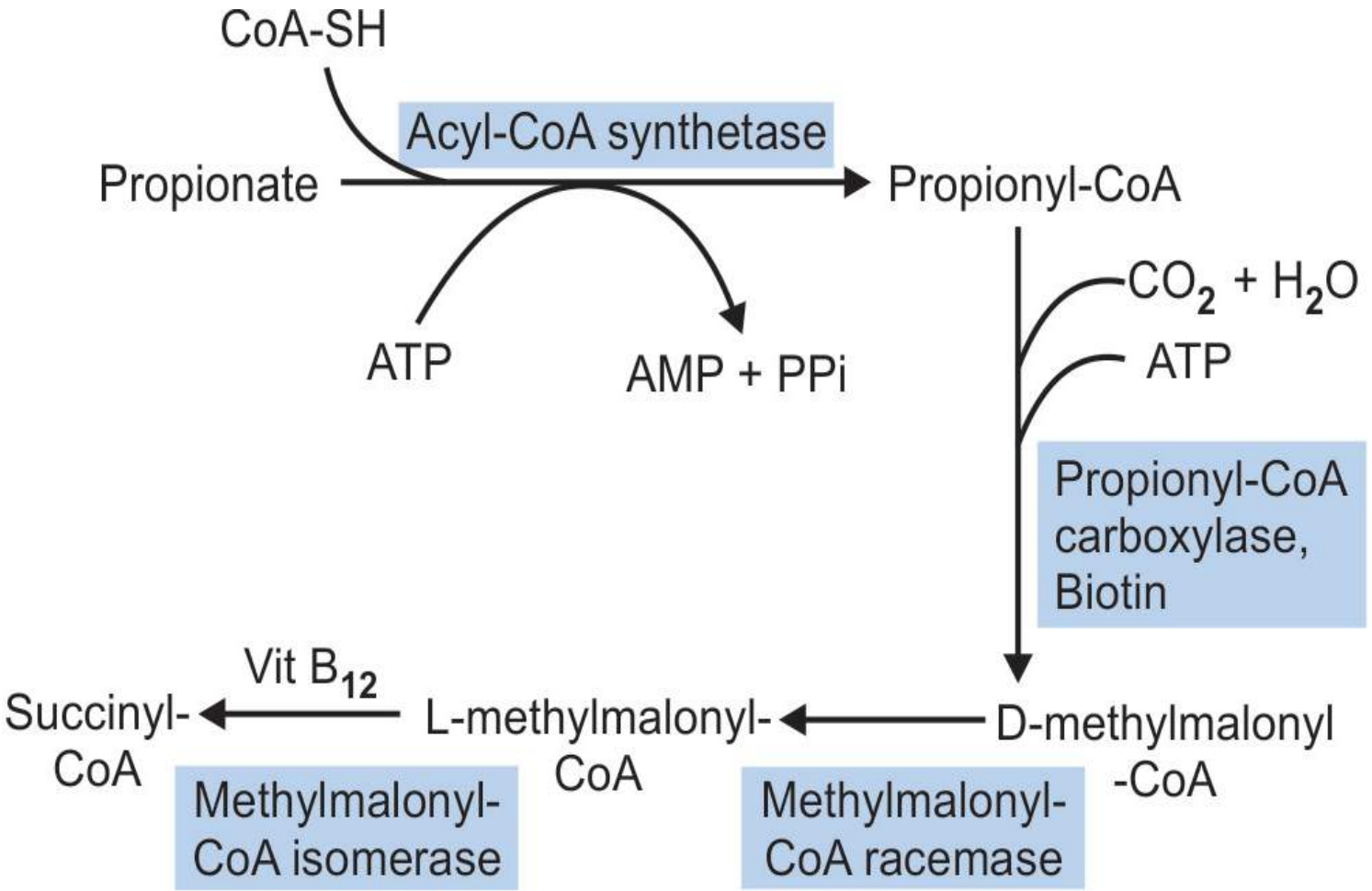


Figure 10.25: Conversion of glycerol to dihydroxyacetone phosphate.

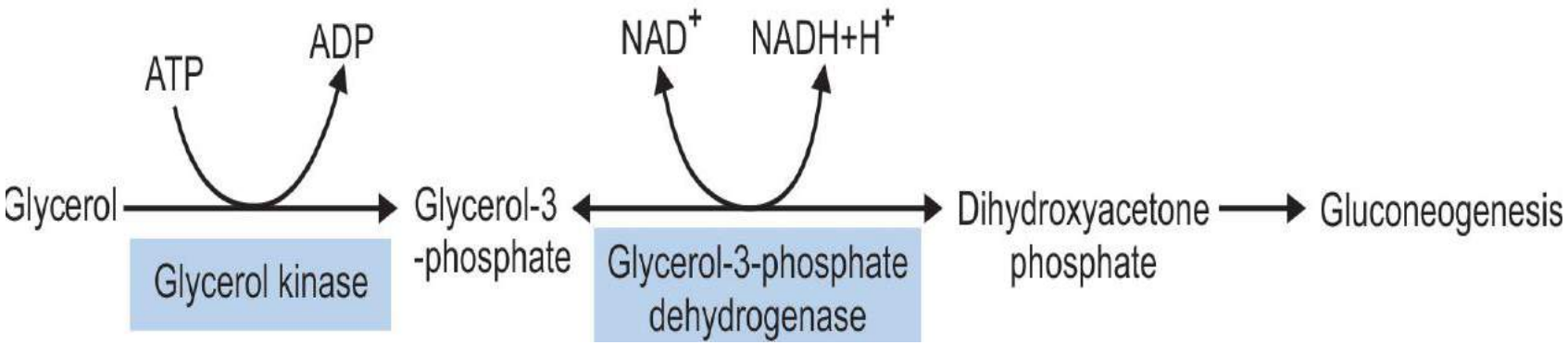


Figure 10.24: Pathway of Cori cycle or lactic acid cycle.

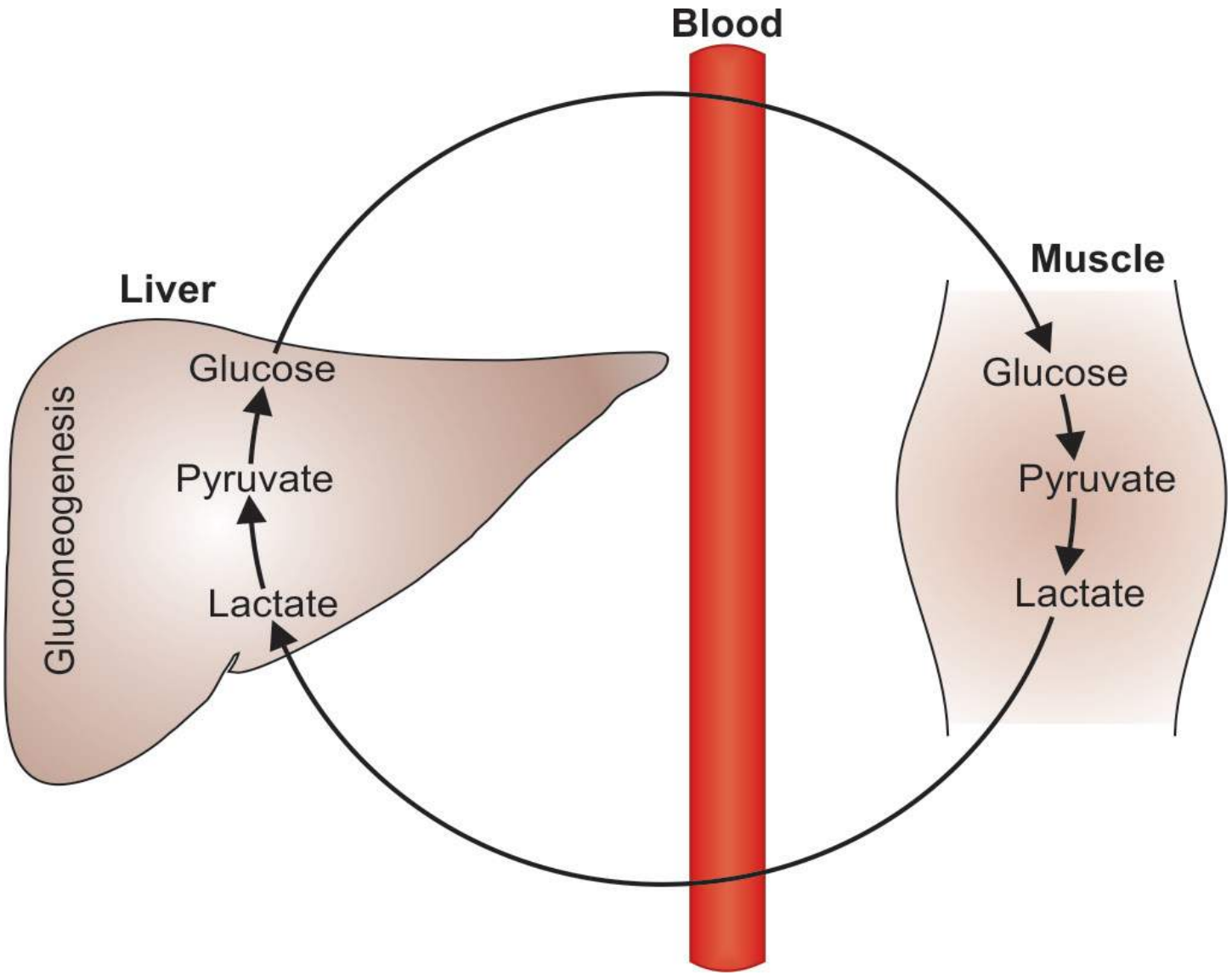
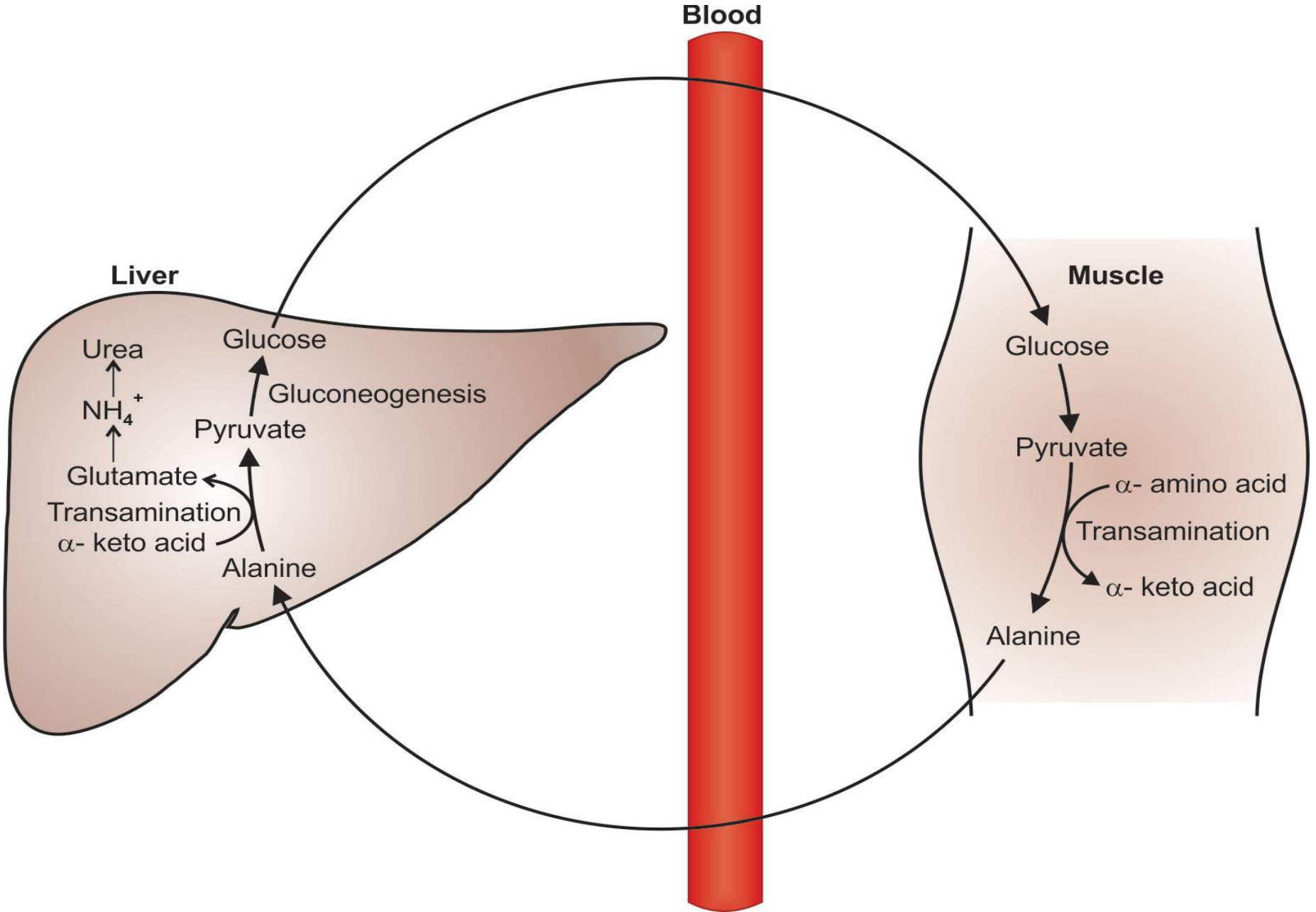
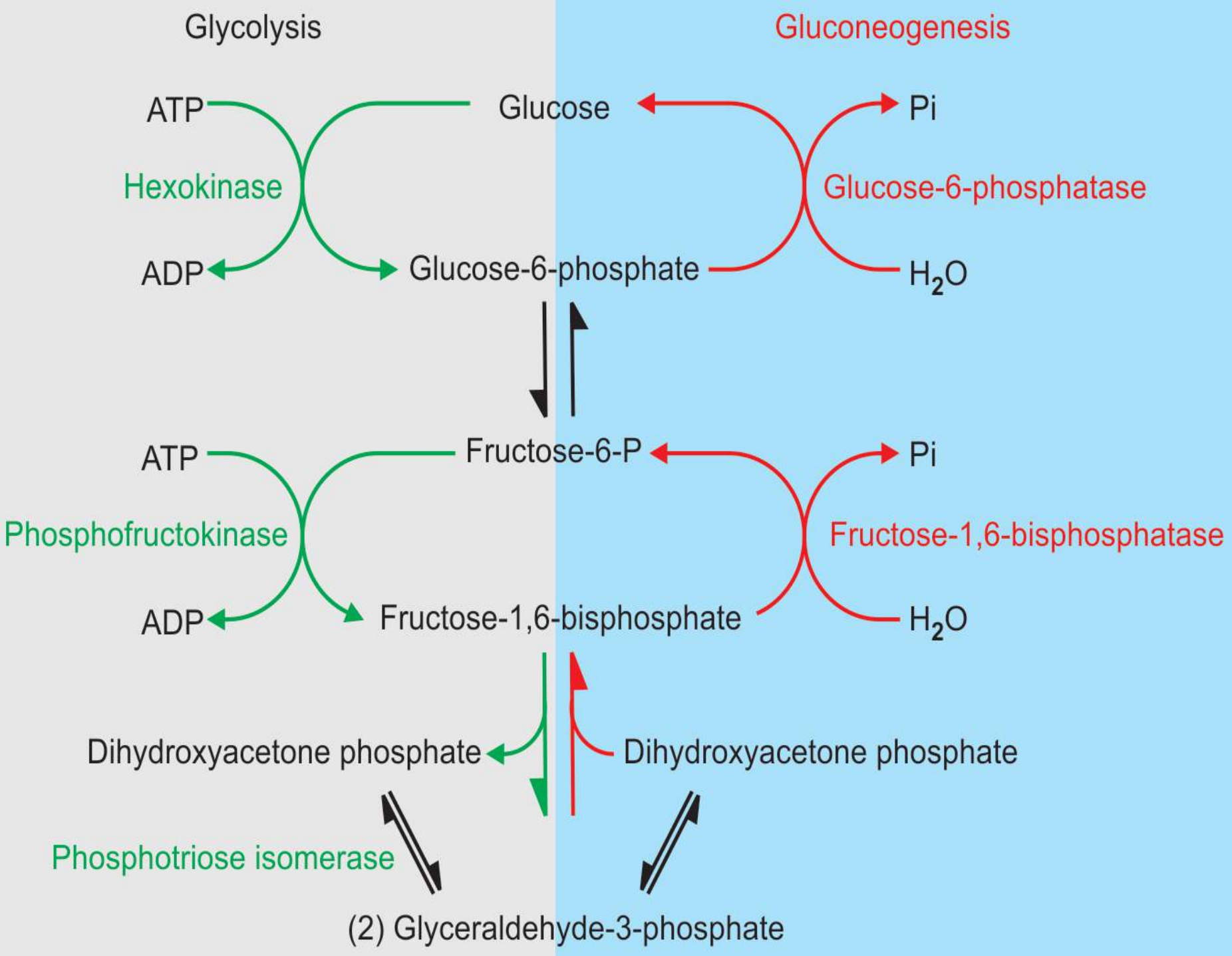


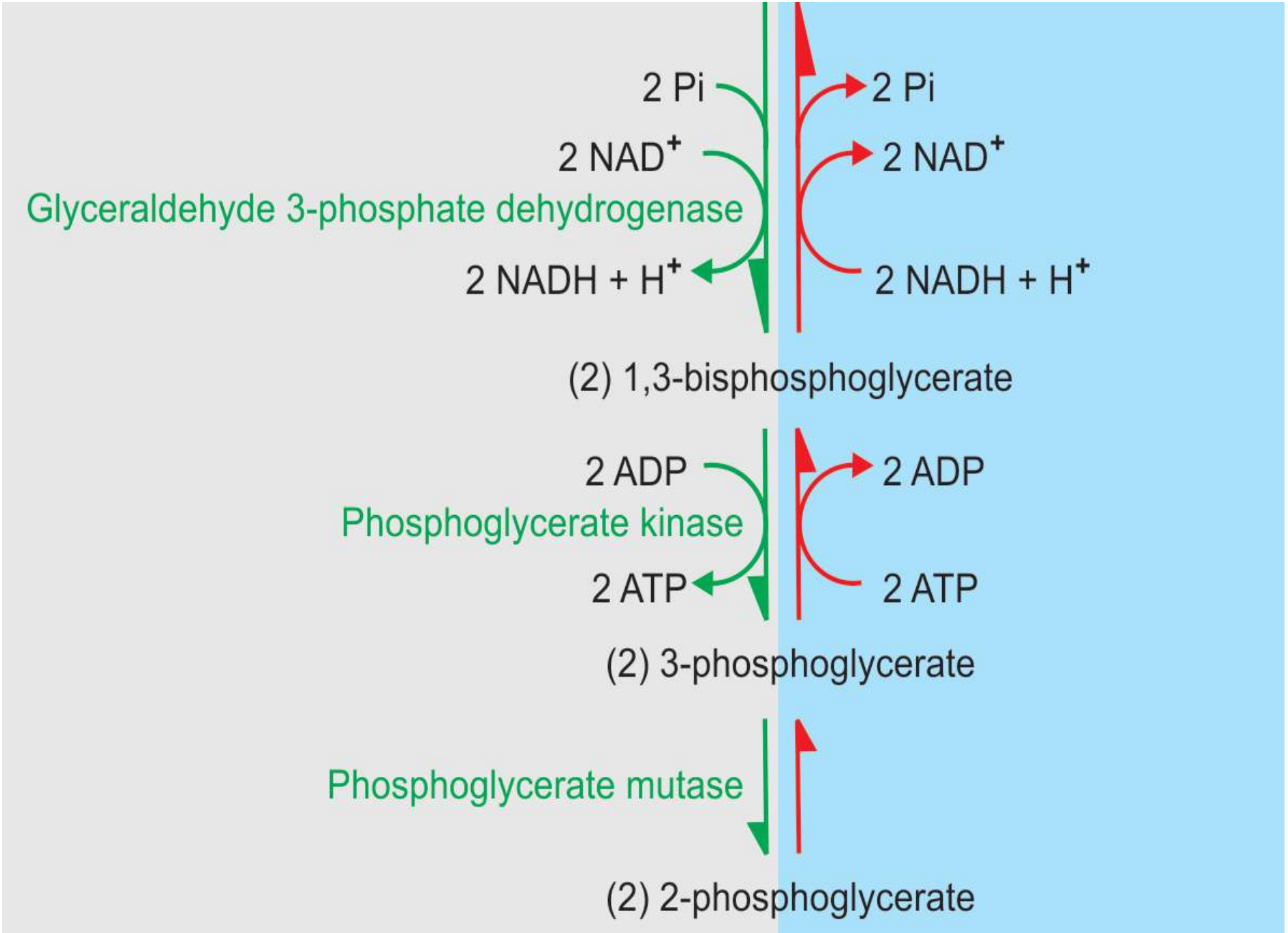
Figure 10.26: Glucose alanine cycle or Cahill cycle.

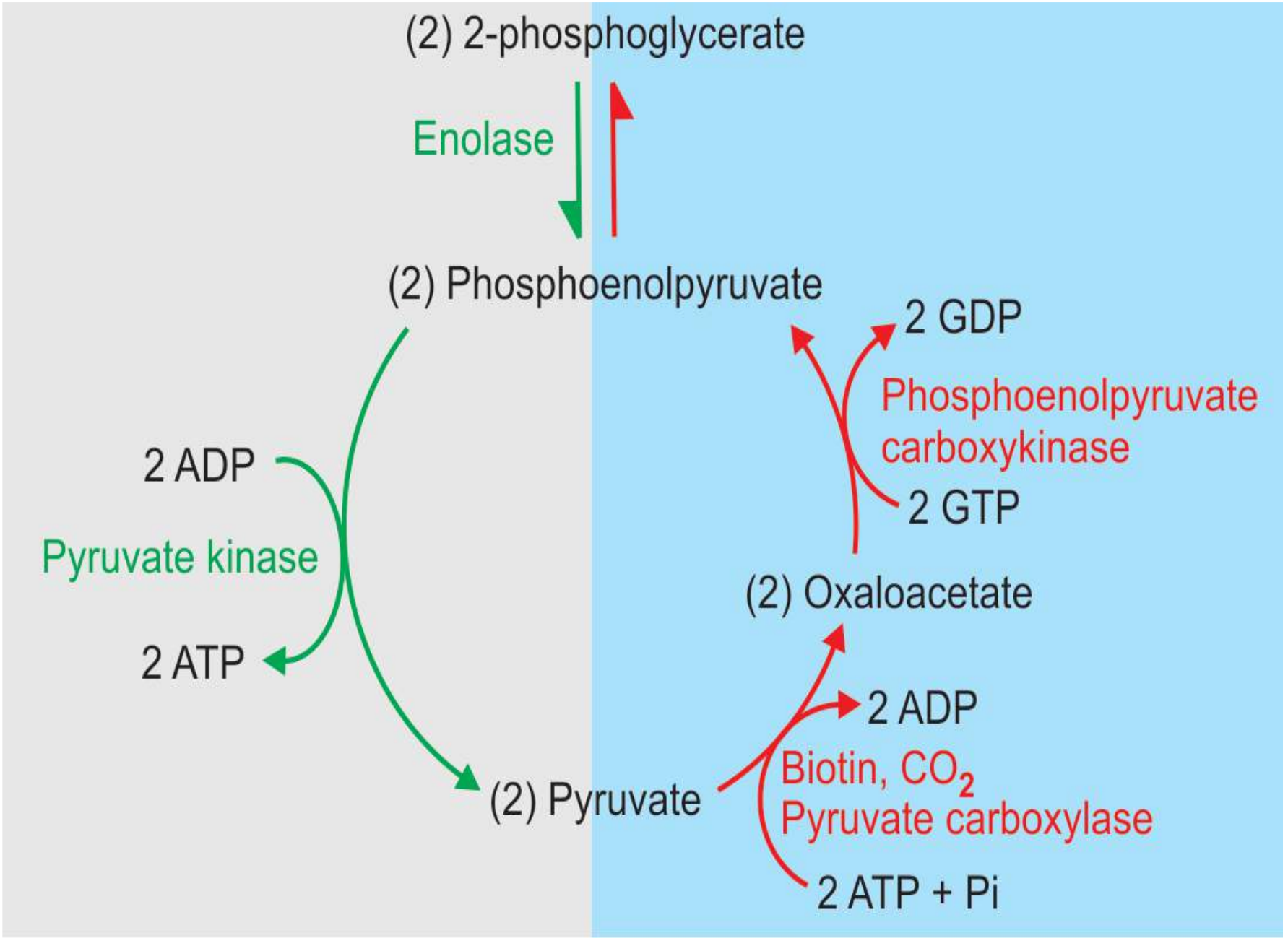


Characteristics of Gluconeogenesis

1. Glycolysis and gluconeogenesis share the same pathway but in opposite direction.
2. Seven reversible reactions of glycolysis are used by gluconeogenesis.
3. Involves glycolysis plus some special reactions.


Glycolysis
Gluconeogenesis
ATP
Glucose
Pi
Hexokinase
Glucose-6-phosphatase
ADP
Glucose-6-phosphate
H_2O
Fructose-6-P
ATP
Pi
Phosphofructokinase
Fructose-1,6-bisphosphatase
ADP
Fructose-1,6-bisphosphate
H_2O
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
Phosphotriose isomerase
(2) Glyceraldehyde-3-phosphate


2 Pi
2 NAD+
Glyceraldehyde 3-phosphate dehydrogenase
2 NADH + H+
2 Pi
2 NAD+
2 NADH + H+
(2) 1,3-bisphosphoglycerate
2 ADP
Phosphoglycerate kinase
2 ATP
2 ADP
2 ATP
(2) 3-phosphoglycerate
Phosphoglycerate mutase
(2) 2-phosphoglycerate


(2) 2-phosphoglycerate
Enolase
(2) Phosphoenolpyruvate
2 GDP
Phosphoenolpyruvate carboxykinase
2 GTP
2 ADP
Pyruvate kinase
2 ATP
(2) Oxaloacetate
2 ADP
Biotin, CO_2
Pyruvate carboxylase
(2) Pyruvate
2 ATP + Pi

Significance of Gluconeogenesis

1. Maintains blood glucose level when carbohydrate is not available in sufficient amounts from the diet.
2. During starvation glucose is provided to the brain and other tissues like erythrocytes, lens, cornea of the eye and kidney

3. Gluconeogenesis is used to clear the products of metabolism of other tissues from blood.

- Lactate, produced by muscle and erythrocytes
- Glycerol produced by adipose tissue
- Propionyl-CoA produced by oxidation of odd carbon number fatty acids and carbon skeleton of some amino acids.

Regulation of Gluconeogenesis

- Gluconeogenesis regulated by four key enzymes:

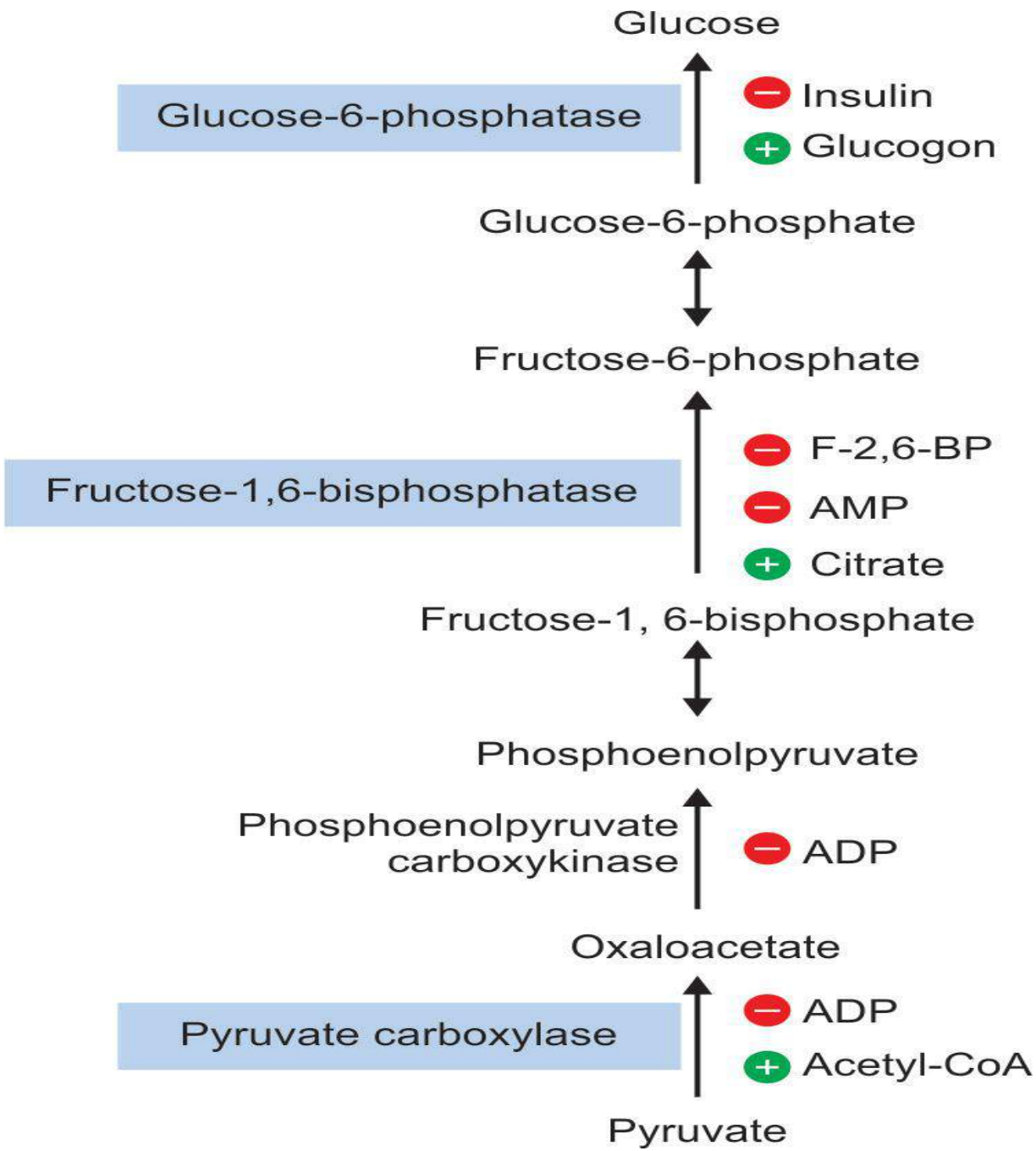
1. Pyruvate carboxylase
2. Phosphoenolpyruvate carboxykinase
3. Fructose-1,6-bisphosphatase
4. Glucose-6-phosphatase

- The hormones glucagon and epinephrine stimulate gluconeogenesis by inducing the synthesis of the key enzymes

- Insulin inhibits the gluconeogenesis by repressing their synthesis.

- During starvation and in diabetes mellitus, high level of glucagon stimulates gluconeogenesis.

- However in well-fed state, insulin suppresses the gluconeogenesis.


Glucose
Glucose-6-phosphatase
Insulin
Glucogon
Glucose-6-phosphate
Fructose-6-phosphate
Fructose-1,6-bisphosphatase
F-2,6-BP
AMP
Citrate
Fructose-1, 6-bisphosphate
Phosphoenolpyruvate
Phosphoenolpyruvate carboxykinase
ADP
Oxaloacetate
Pyruvate carboxylase
ADP
Acetyl-CoA
Pyruvate

Glycogen Metabolism

- Glycogen metabolism includes:

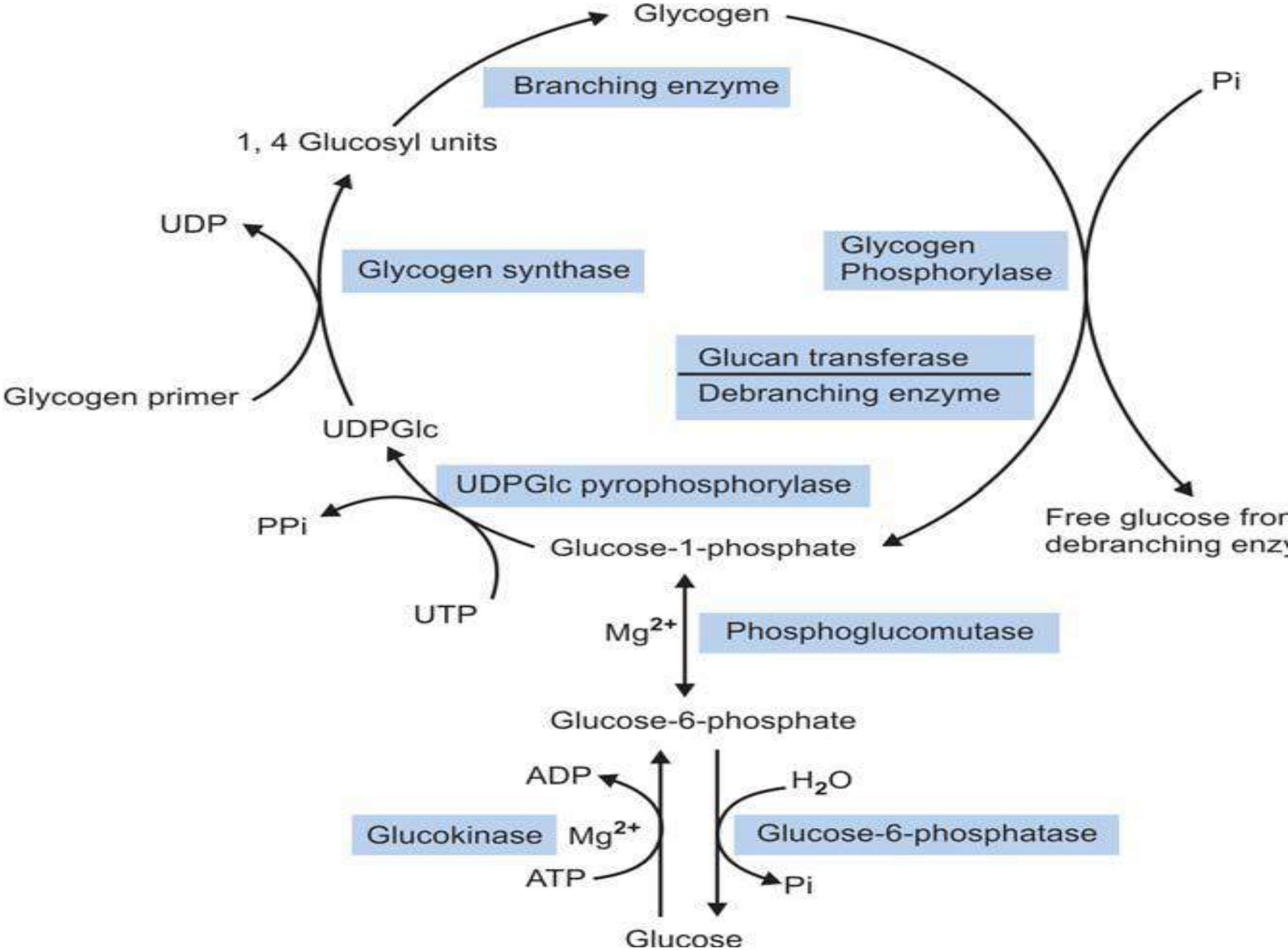
  Glycogenesis

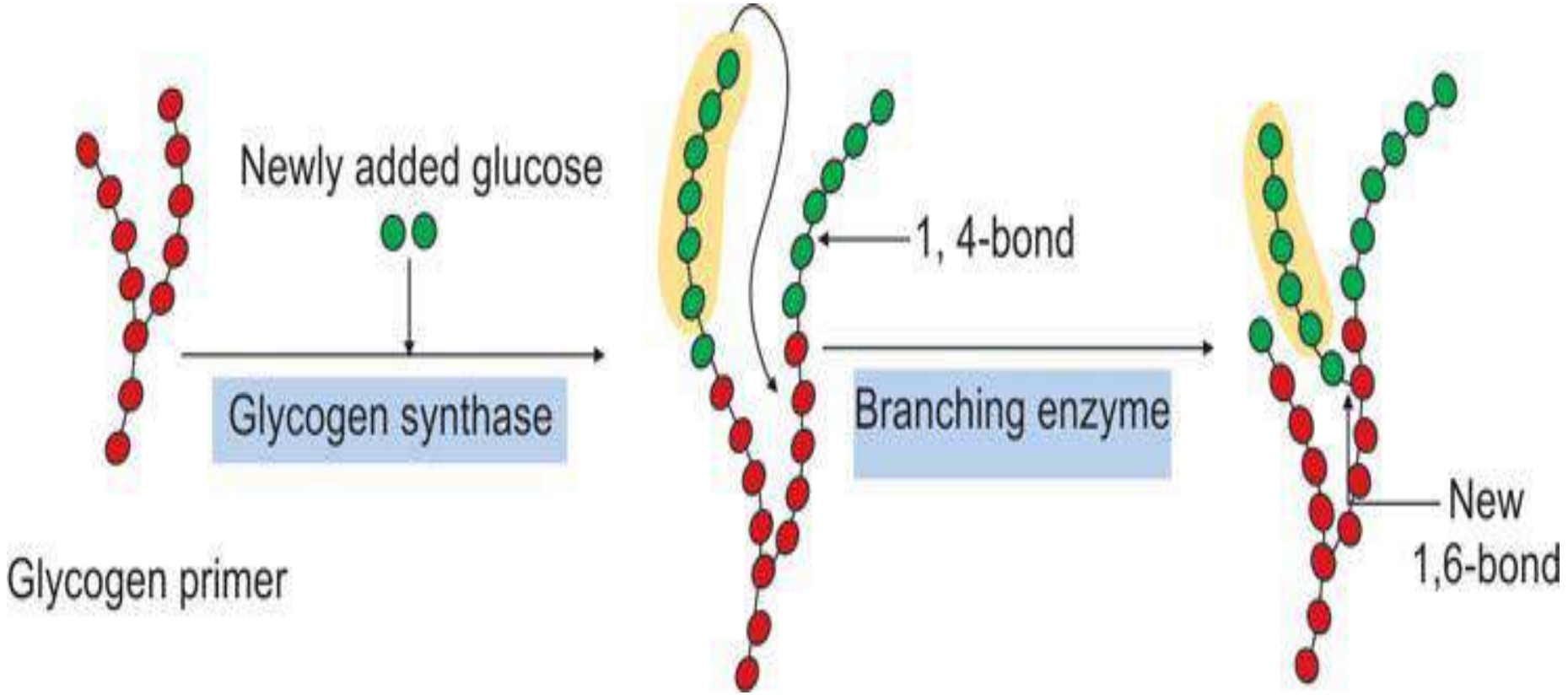
  Glycogenolysis

- Glycogenesis and glycogenolysis are both cytosolic processes.

Glycogenesis

- Glycogenesis is the pathway for the formation of glycogen from glucose.
- This process requires energy, supplied by ATP and uridine triphosphate (UTP).
- It occurs in muscle and liver.

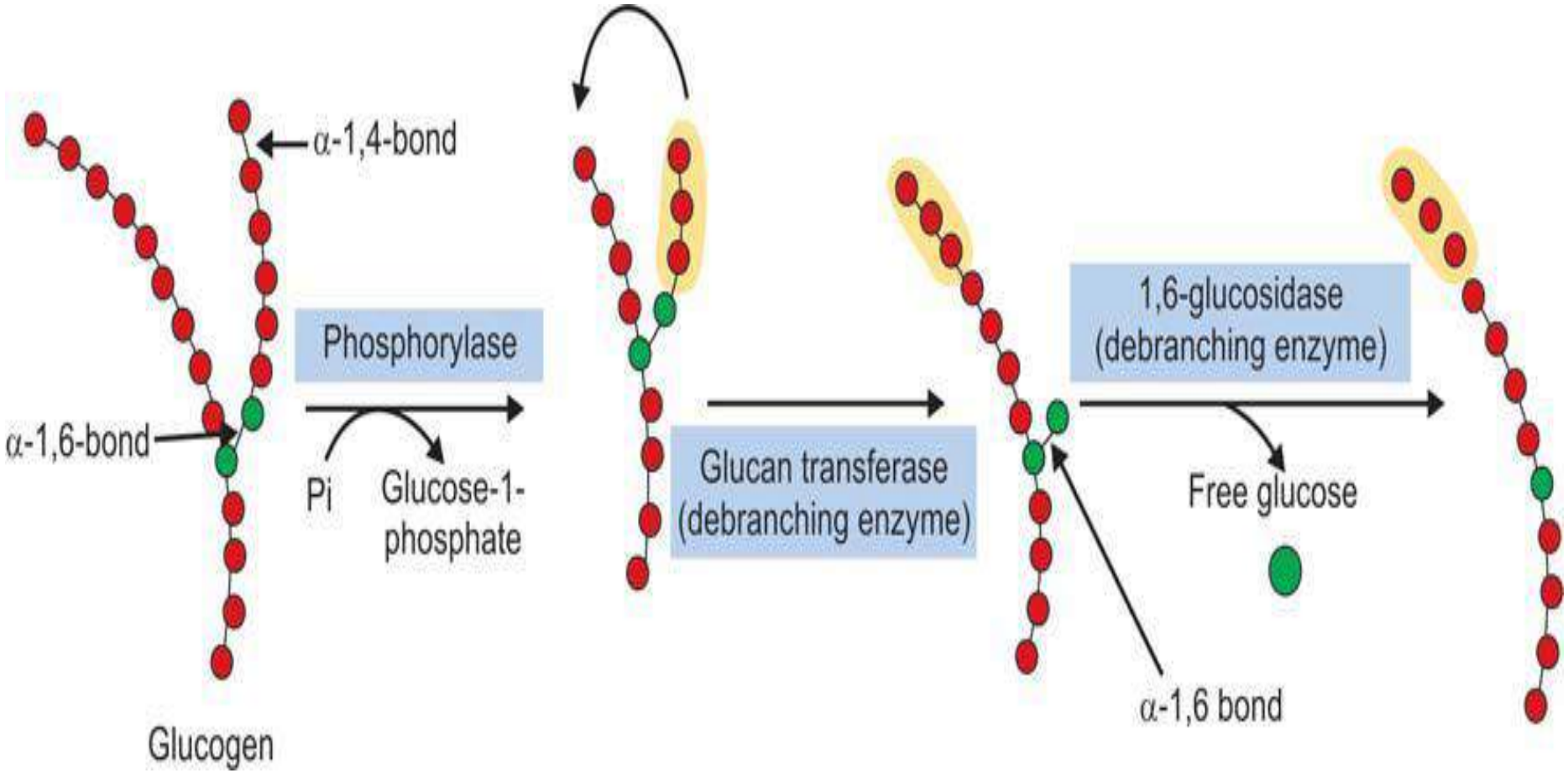

Glycogen
Branching enzyme
1, 4 Glucosyl units
Pi
UDP
Glycogen synthase
Glycogen Phosphorylase
Glucan transferase
Debranching enzyme
Glycogen primer
UDPGlc
UDPGlc pyrophosphorylase
PPi
Glucose-1-phosphate
Free glucose from debranching enzy
UTP
Mg2+
Phosphoglucomutase
Glucose-6-phosphate
ADP
H2O
Glucokinase
Mg2+
Glucose-6-phosphatase
ATP
Pi
Glucose



Schematic representation of glycogenesis (mechanism of branching)

Glycogenolysis

Degradation of glycogen to glucose-6-phosphate in muscle and to glucose in liver



Schematic representation of glycogenolysis (mechanism of debranching)

Significance of Glycogenolysis and Glycogenesis

In liver

- Following a meal, excess glucose is removed from the portal circulation and stored as glycogen by glycogenesis.
- Conversely, between meals, blood glucose levels are maintained within the normal range by release of glucose from liver glycogen by glycogenolysis.

In muscle

- The function of muscle glycogen is to act as a readily available source of glucose within the muscle itself during muscle contraction.
- *The muscle cannot release glucose into the blood, because of the absence of glucose-6-phosphatase*
- Muscle glycogen stores are used exclusively by muscle

Regulation of Glycogenesis and Glycogenolysis

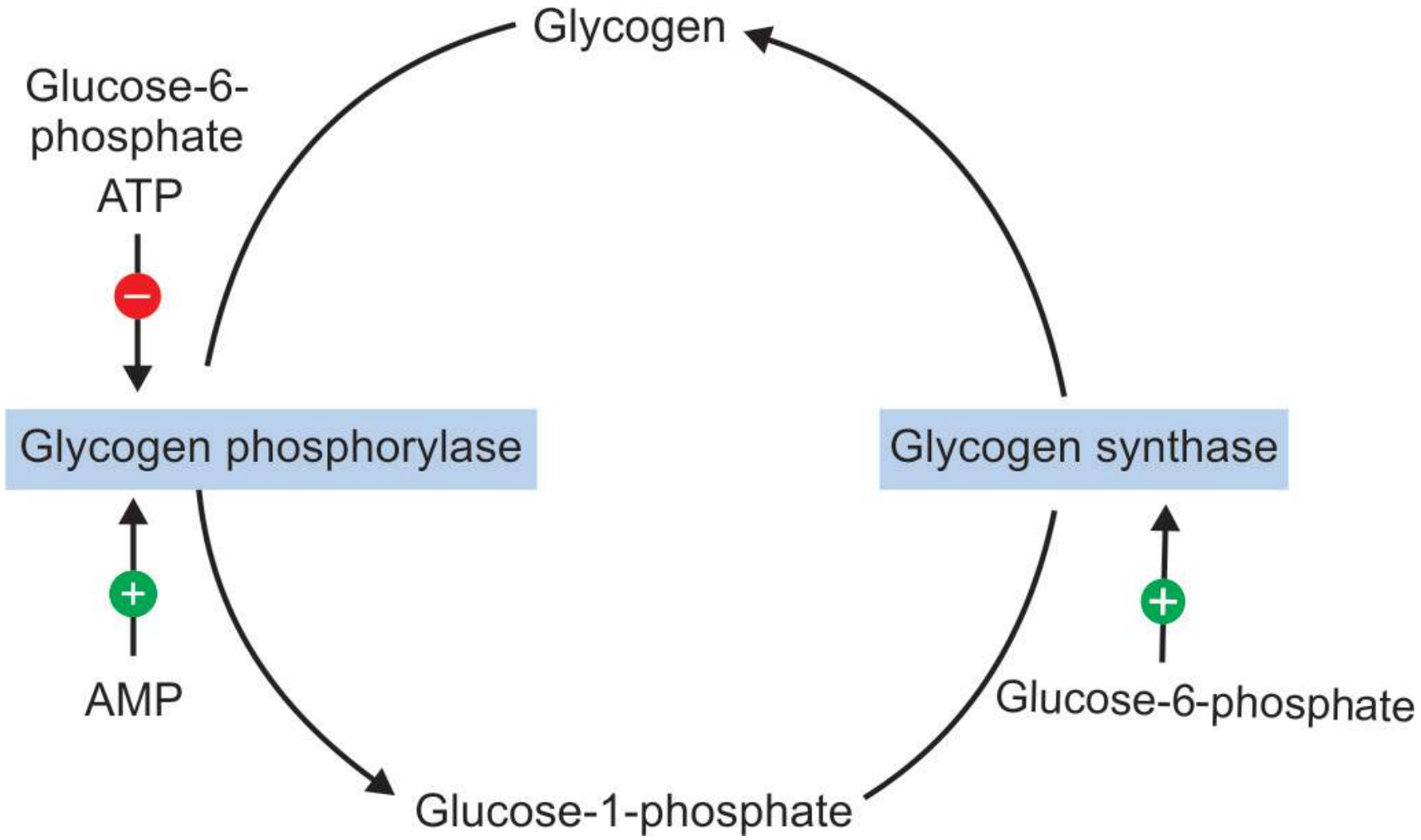
- The principal enzymes controlling glycogen metabolism are:
  - *Glycogen phosphorylase*
  - *Glycogen synthase*

Principal enzymes are regulated reciprocally:

- Hormonal regulation

- Allosteric regulation.

Allosteric regulation of glycogenesis and glycogenolysis



Hormonal regulation

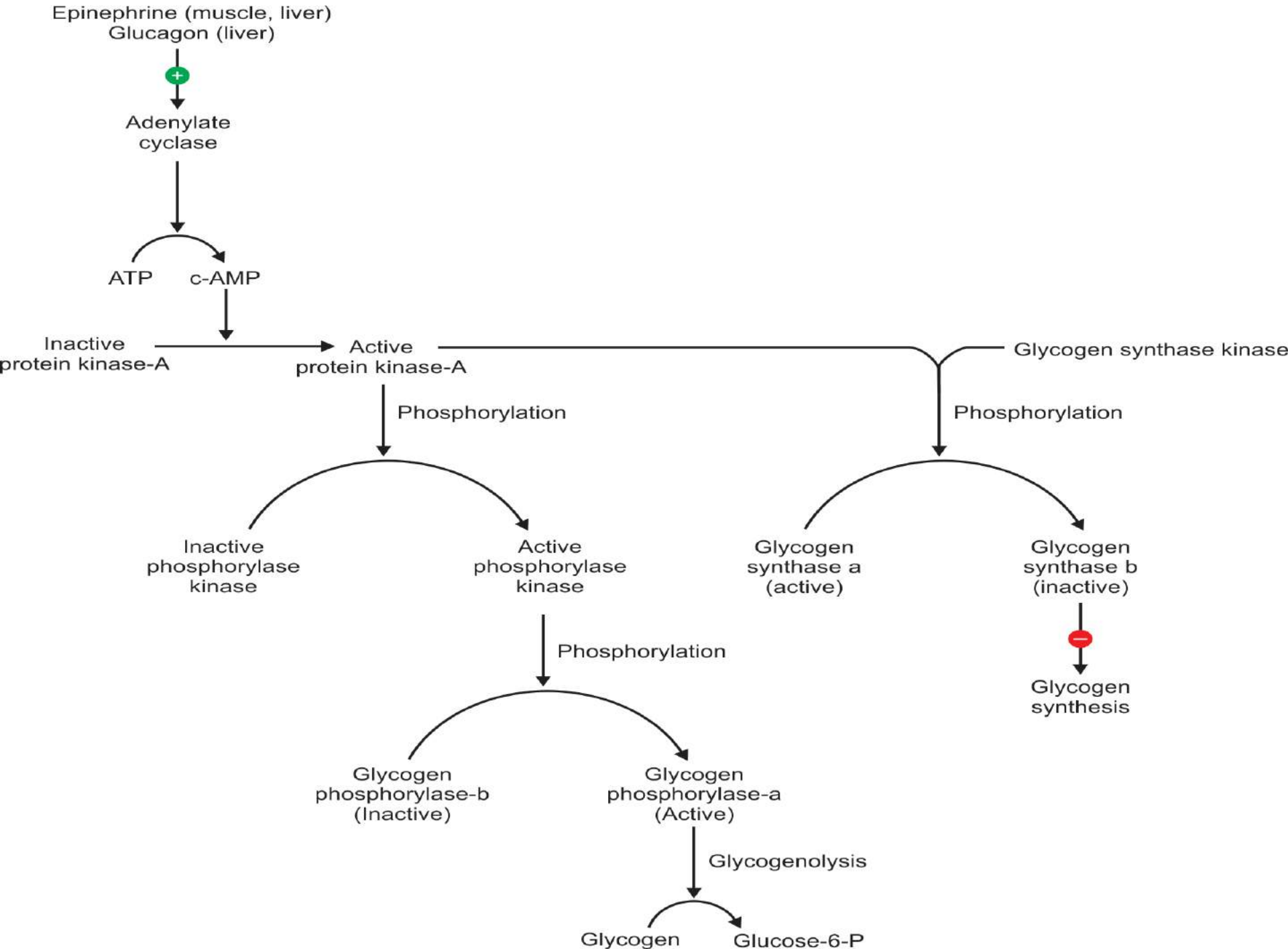
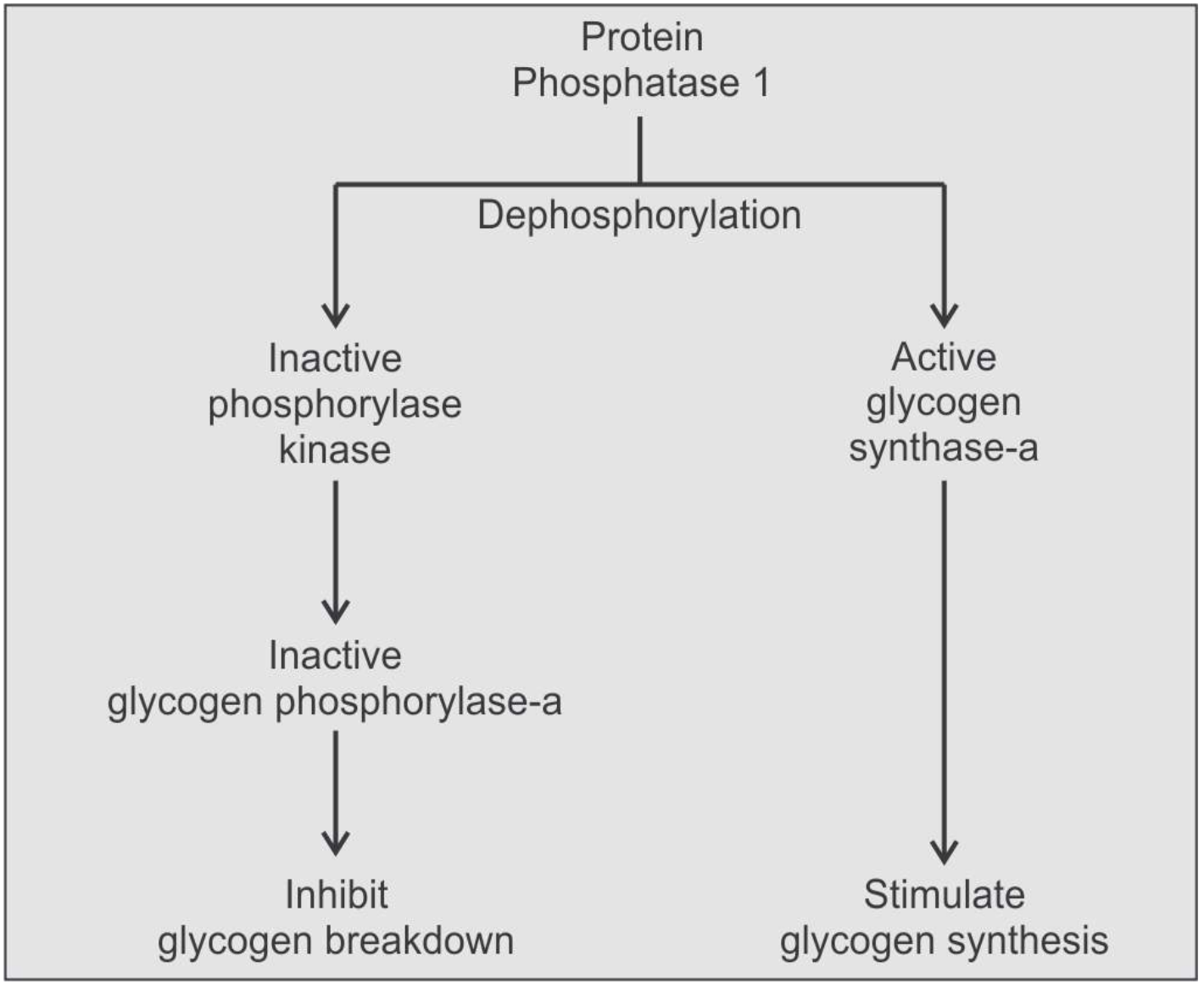

Epinephrine (muscle, liver)
Glucagon (liver)
+
Adenylate cyclase
ATP
c-AMP
Inactive protein kinase-A
Active protein kinase-A
Glycogen synthase kinase
Phosphorylation
Phosphorylation
Inactive phosphorylase kinase
Active phosphorylase kinase
Glycogen synthase a (active)
Glycogen synthase b (inactive)
−
Glycogen synthesis
Phosphorylation
Glycogen phosphorylase-b (Inactive)
Glycogen phosphorylase-a (Active)
Glycogenolysis
Glycogen
Glucose-6-P

Figure 10.37: Regulation of glycogen synthesis by action of protein phosphatase-1.



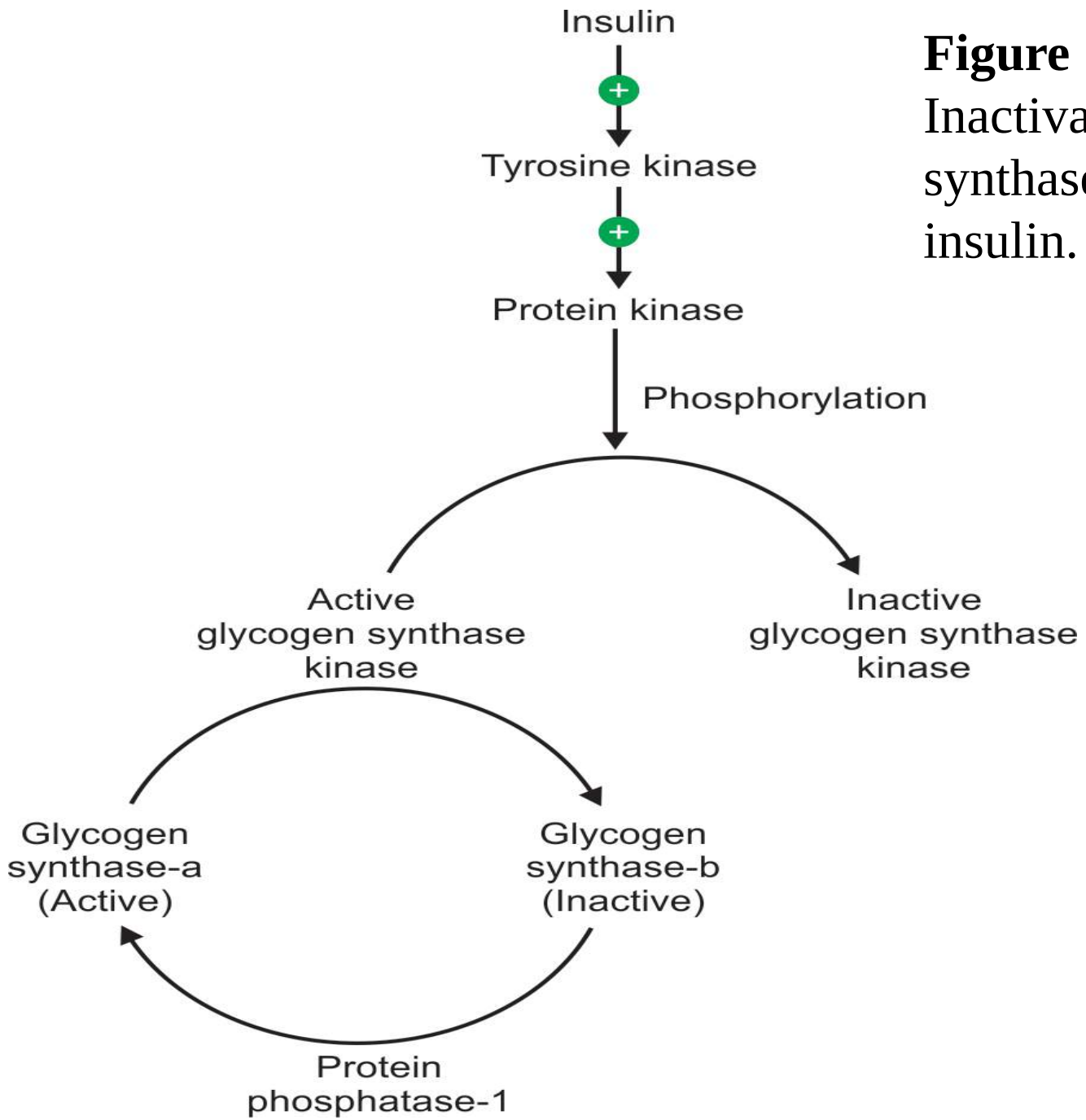


Figure 10.38:
Inactivation of glycogen synthase kinase by insulin.

Glycogen Storage Disease

- Glycogen storage disease is a group of genetic diseases, that result from a defect in enzyme required for either glycogen synthesis or degradation.
- Characterized by deposition of either normal or abnormal glycogen in the specific tissues

TABLE 10.6: Glycogen storage diseases (glycogenosis).

Type (name)	*Enzyme affected*
Type 0	Glycogen synthase
Type Ia (Von Gierke's disease)	Glucose-6-phosphatase
Type Ib	Endoplasmic reticulum, glucose-6-phosphate transporter (GLUT-7)
Type Ic	Microsomal P_i transporter
Type II (Pompe disease)	Lysosomal α-1,4-glucosidase (acid maltase)
Type IIIa (Limit dextrinosis, Forbes or Cori disease)	Liver and muscle debranching enzyme
Type IIIb	Liver debranching enzyme (muscle enzyme normal)
Type IV (Andersen disease)	Branching enzyme
Type V (Mc-Ardle syndrome)	Muscle glycogen phosphorylase
Type VI (Hers disease)	Liver phosphorylase
Type VII (Tarui disease)	Muscle phosphofructokinase-1
Type VIb, VIII, or IX	Phosphorylase kinase
Type XI (Fanconi-Bickel disease)	Glucose transporter (GLUT-2)

Pentose Phosphate Pathway

- The pentose phosphate pathway is an alternative route for the oxidation of glucose.

- It is the pathway for formation of pentose phosphate.

- It is also called *hexose monophosphate shunt*.

Characteristics of Pentose Phosphate pathway

- A multicyclic process
- It does not generate ATP.
- Three molecules of glucose-6-phosphate give rise to three molecules of CO_2 and three molecules of 5-carbon sugars

Location

The enzymes of pentose phosphate pathway are present in cytosol of all cells.

TABLE 10.7: Tissues most enriched in pentose phosphate pathway enzymes and their functions.

Tissues	*Functions*
Adrenal gland	Steroid synthesis
Testes	Steroid hormone synthesis
Ovaries	Steroid hormone synthesis
Liver	Fatty acid, cholesterol, and bile acid synthesis
	P450-dependent detoxification reactions
Adipose tissue	Fatty acid synthesis
Mammary gland	Fatty acid synthesis
Red blood cell	Maintenance of reduced glutathione
Neutrophils	Generation of superoxide

Pathway divided in to two phases:

1. Phase I : Oxidative irreversible phase

2. Phase II : Non-oxidative reversible phase.

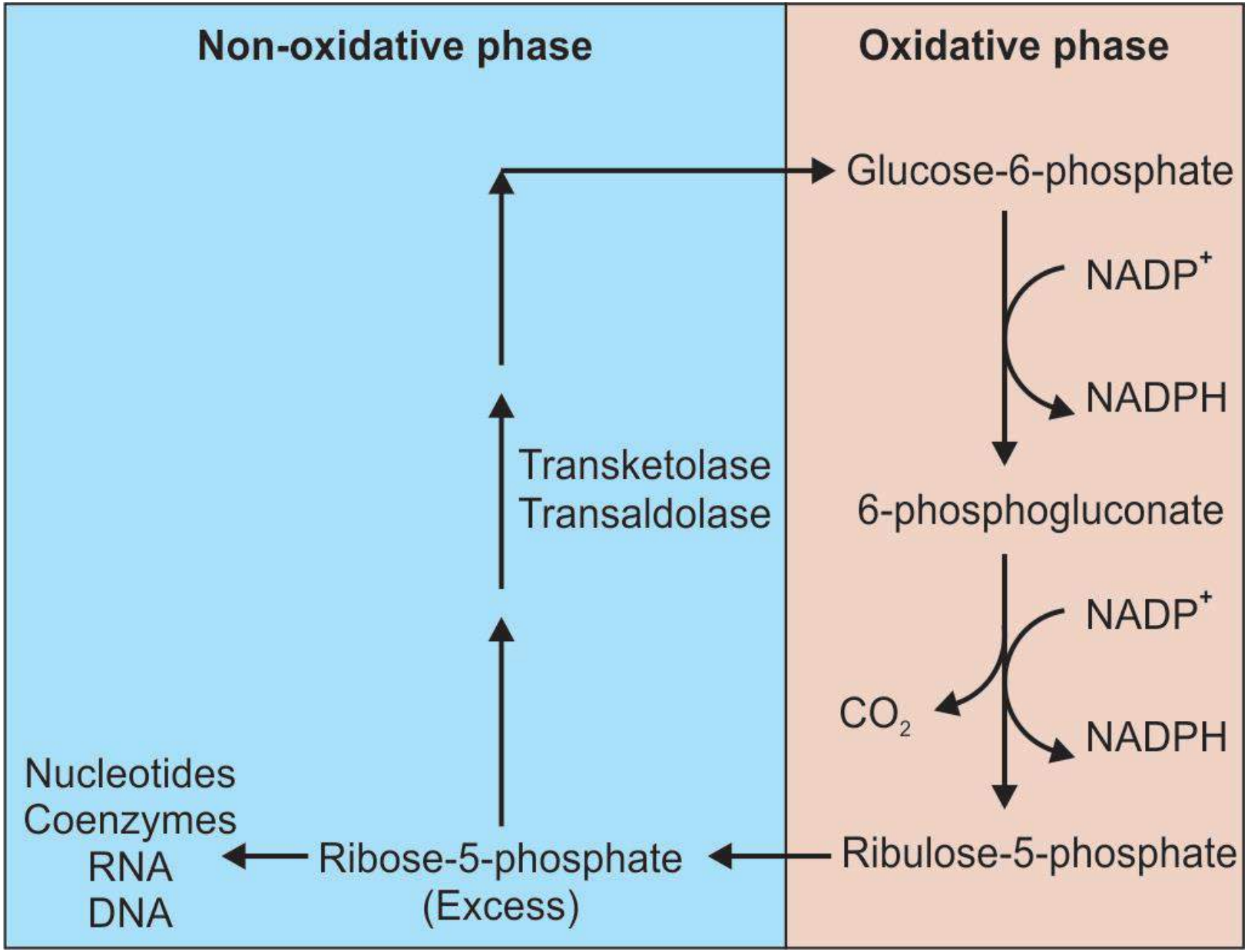
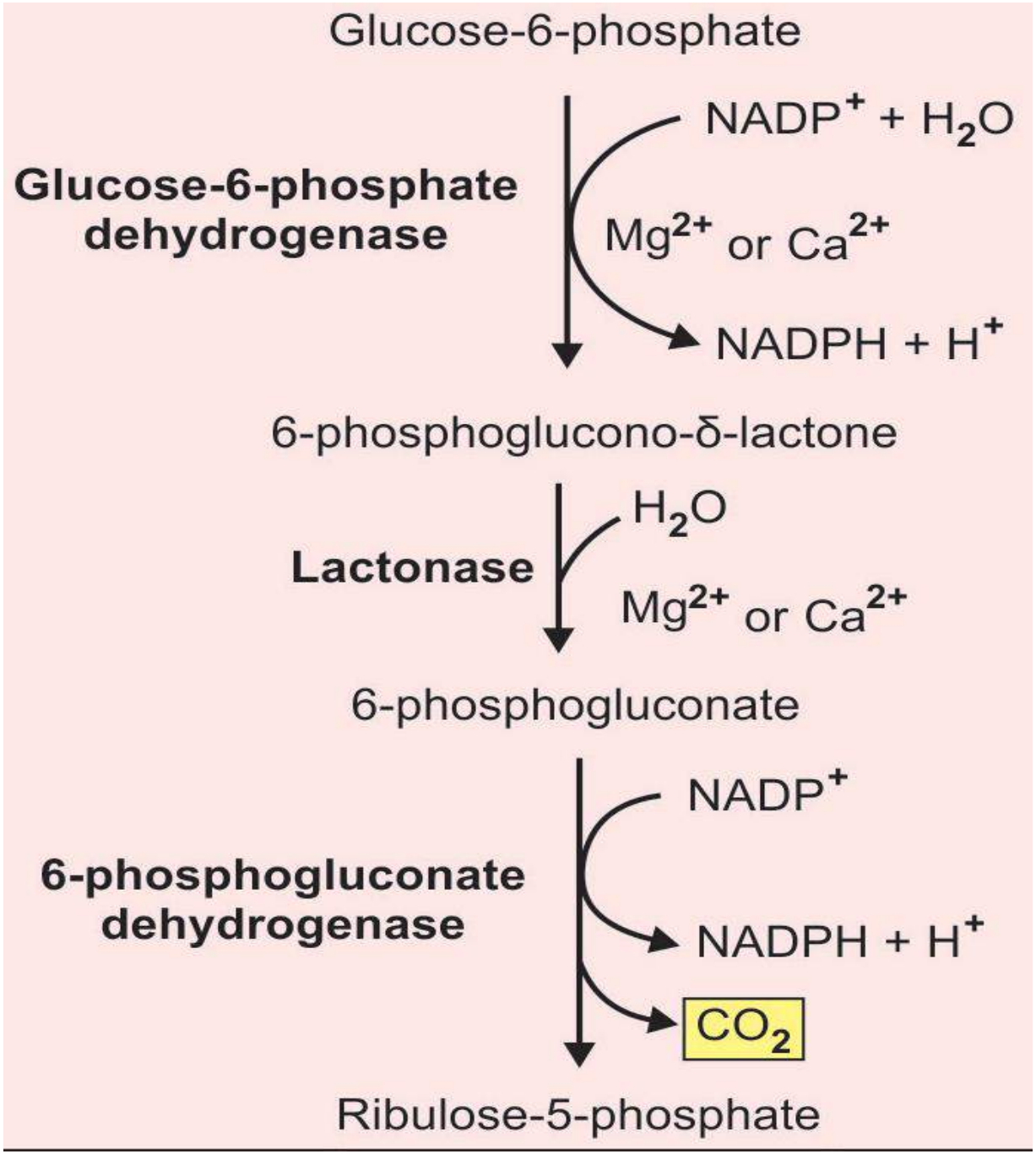
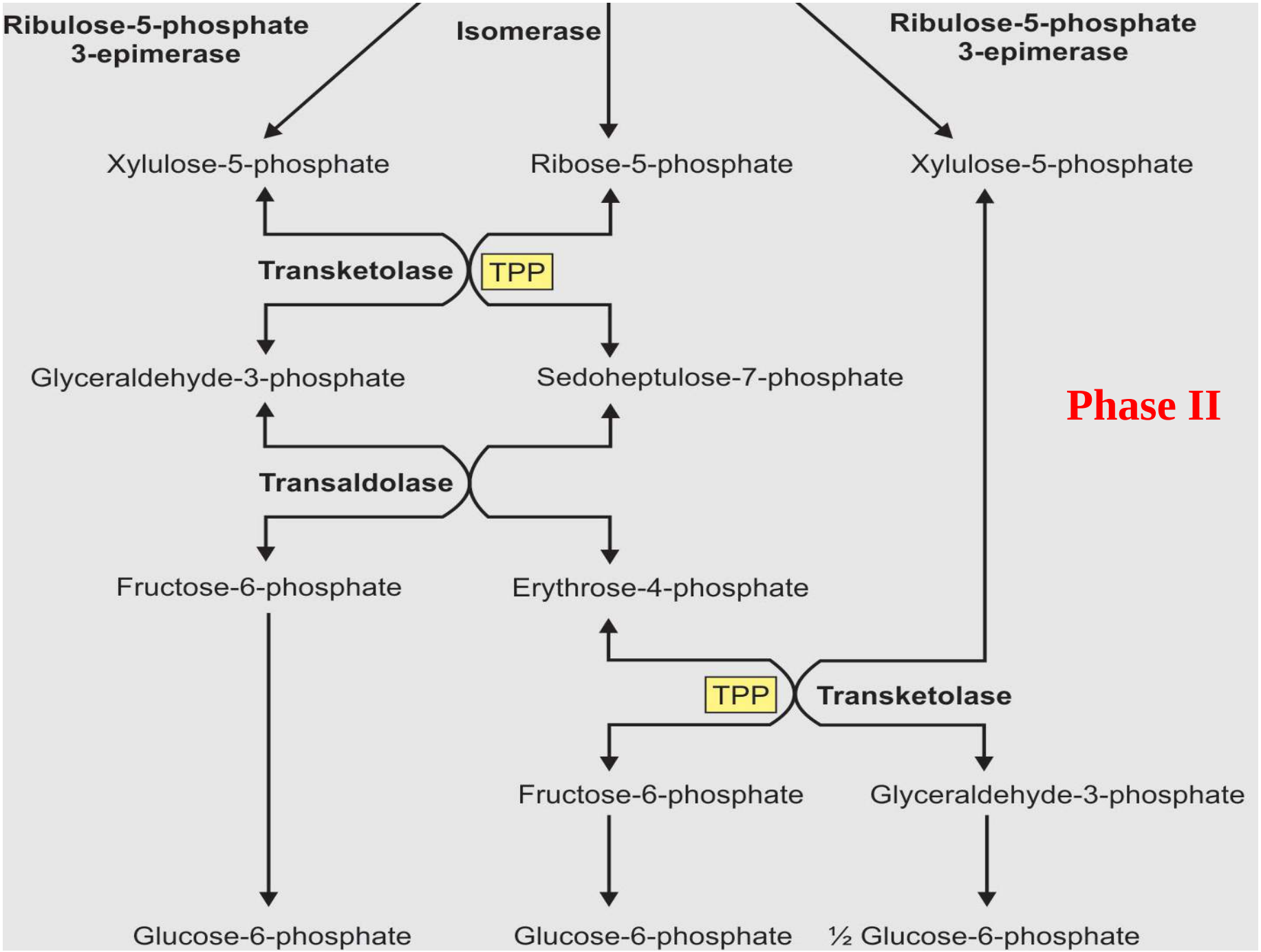


Figure 10.39: Outline of pentose phosphate pathway.

Phase I: Oxidative




Ribulose-5-phosphate 3-epimerase
Isomerase
Ribulose-5-phosphate 3-epimerase
Xylulose-5-phosphate
Ribose-5-phosphate
Xylulose-5-phosphate
Transketolase
TPP
Glyceraldehyde-3-phosphate
Sedoheptulose-7-phosphate
Phase II
Transaldolase
Fructose-6-phosphate
Erythrose-4-phosphate
TPP
Transketolase
Fructose-6-phosphate
Glyceraldehyde-3-phosphate
Glucose-6-phosphate
Glucose-6-phosphate
½ Glucose-6-phosphate

Significance of Pentose Phosphate Pathway

- The pentoses (ribose-5-phosphate) required for the biosynthesis of nucteotide and nucleic acids RNA and DNA are provided by pentose phosphate pathway.

- It provides a route for the interconversion of pentoses and hexoses

- It generates NADPH which are required in

1. Biosynthesis of

   Fatty acids

   Cholesterol

   Steroid hormones

   Neurotransmitters.

2. Detoxification reactions

- In RBC, NADPH is required to maintain the level of reduced glutathione. The reduced glutathione protects the RBC membrane from toxic effect of H_2O_2 by reducing $H_2O_2$to H_2O
- NADPH also keeps iron of hemoglobin in reduced ferrous (Fe^{2+}) state and prevents the formation of methemoglobin.

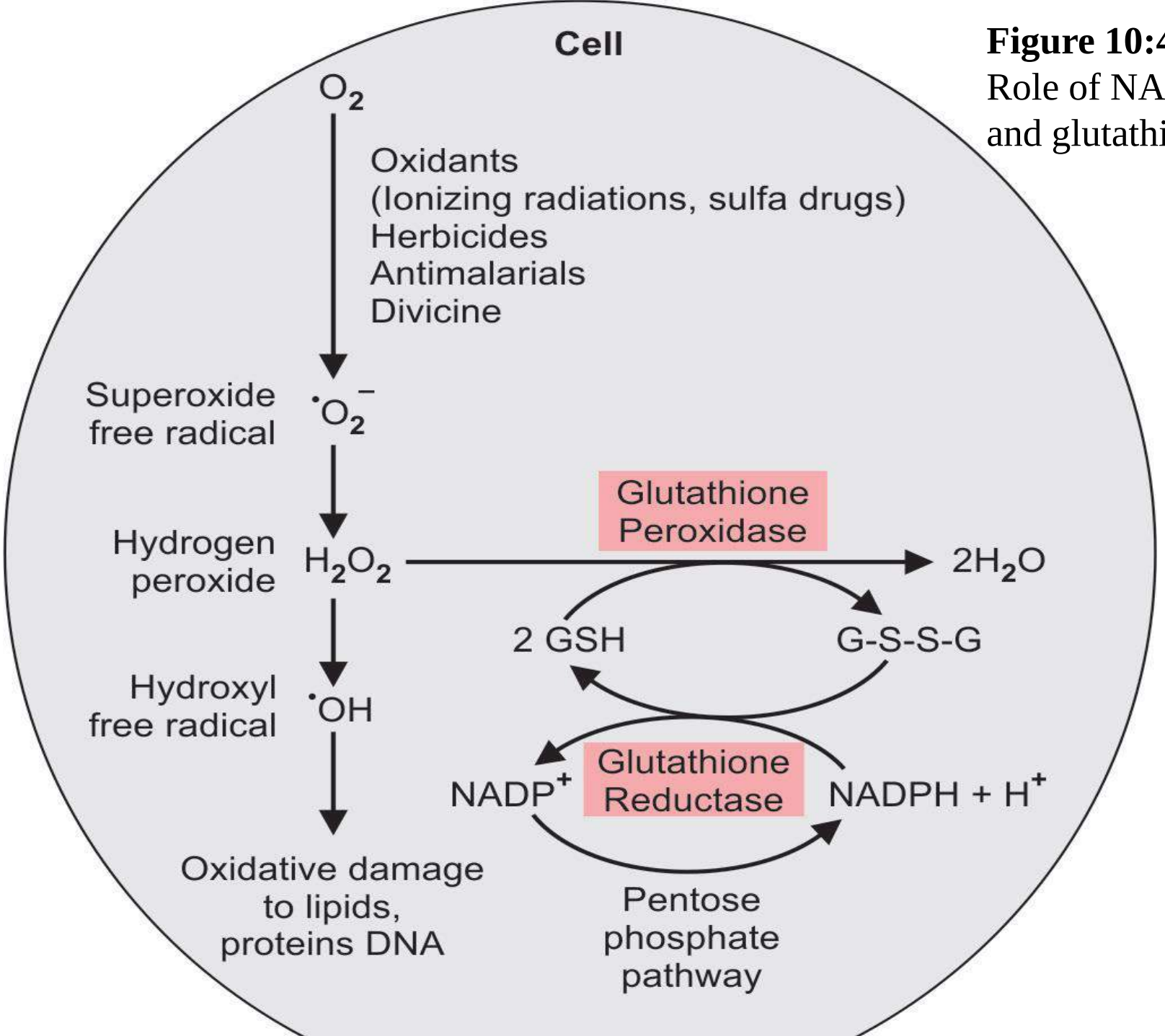


Figure 10:41: Role of NADPH and glutathione

Regulation of Pentose Phosphate Pathway

- *Glucose-6-phosphate dehydrogenase (G-6-PD)* is the rate limiting enzyme.
- The activity of this enzyme is regulated by cellular concentration of NADPH. NADPH is competitive inhibitor of G-6-PD.

An increased concentration of NADPH decreases activity of G-6-PD, for example:

- Under well-fed condition, the level of NADPH decreases and pentose phosphate pathway is stimulated.
- In starvation and diabetes, the level of NADPH is high and inhibits the pathway.

- Insulin enhances the pathway by inducing the enzyme G-6-PD and 6-phosphogluconolactone dehydrogenase.

Disorders of Pentose Phosphate Pathway

Deficiency of Glucose-6-phosphate dehydrogenase (G-6-PD)

Glucose 6-phosphate dehydrogenase deficiency is X linked inherited disorder, characterized by hemolytic anemia, due to excessive hemolysis.

Most individuals are asymptomatic. However, some individuals with G-6-PD deficiency develop hemolytic anemia if they are exposed to drugs like antibiotic, antipyretic or Antimalarial, e.g. primaquine ,chloroquine

A 20-year-old male suffering from malaria was treated with chloroquine and manifested as hemolytic anemia. Provisional diagnosis of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency was made.

Questions

a. Which reaction is catalyzed by the enzyme G-6-PD?

b. How does deficiency of G-6-PD produce hemolytic anemia?

c. Name the pathway in which this reaction occurs.

G-6-PD deficiency and resistance to malaria

Persons with G-6-PD deficiency cannot support growth of the malarial parasite, *Plasmodium falciparum* and thus are less susceptible to malaria than the normal person.

Wernicke-Korsakoff Syndrome

- A genetic disorder due to reduced activity of the TPP-dependent transketolase enzyme.

- The reduced activity of transketolase is due to reduced affinity for TPP

- In the chronic thiamine deficiency the transketolase enzyme has a much reduced activity leading to the Wernicke- Korsakoff syndrome.
- The symptoms of Wernicke-Korsakoff syndrome include weakness, mental disorder, loss of memory, partial paralysis, etc.

Uronic Acid Pathway (Glucuronic Acid Cycle)

Definition

- A pathway in liver for the conversion of glucose to glucuronic acid, ascorbic acid (except in humans) and pentoses
- An alternative oxidative pathway for glucose but does not generate ATP

Significance of Uronic Acid Pathway

- Uronic acid pathway is a source of UDP -glucuronate.
- UDP-glucuronate is a precursor in synthesis of proteoglycans (glycosaminoglycans) and glycoproteins.
- UDP-glucuronate is involved in detoxification reactions that occur in liver e.g.bilirubin,steroid hormones

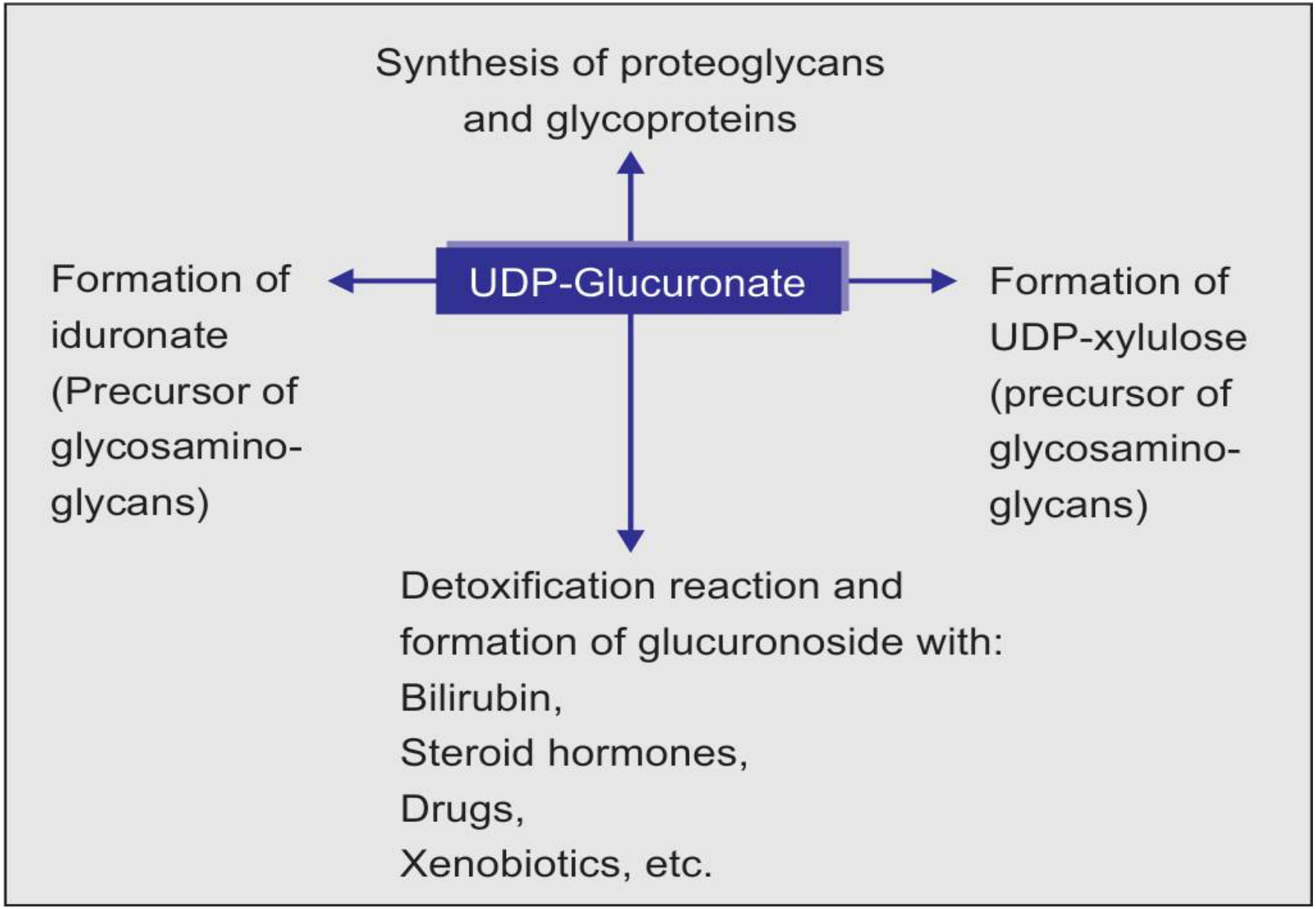


Figure 10.43: Metabolic role of UDP-glucuronate.

- The uronic acid pathway is a source of UDP-glucose, which is used for glycogen formation.

- The uronic acid pathway provides a mechanism by which dietary D-xylulose can enter the central metabolic pathway

Galactose Metabolism And Galactosemia

Galactose is derived from disaccharide, lactose (the milk sugar) of the diet.

- It is important for the formation of:

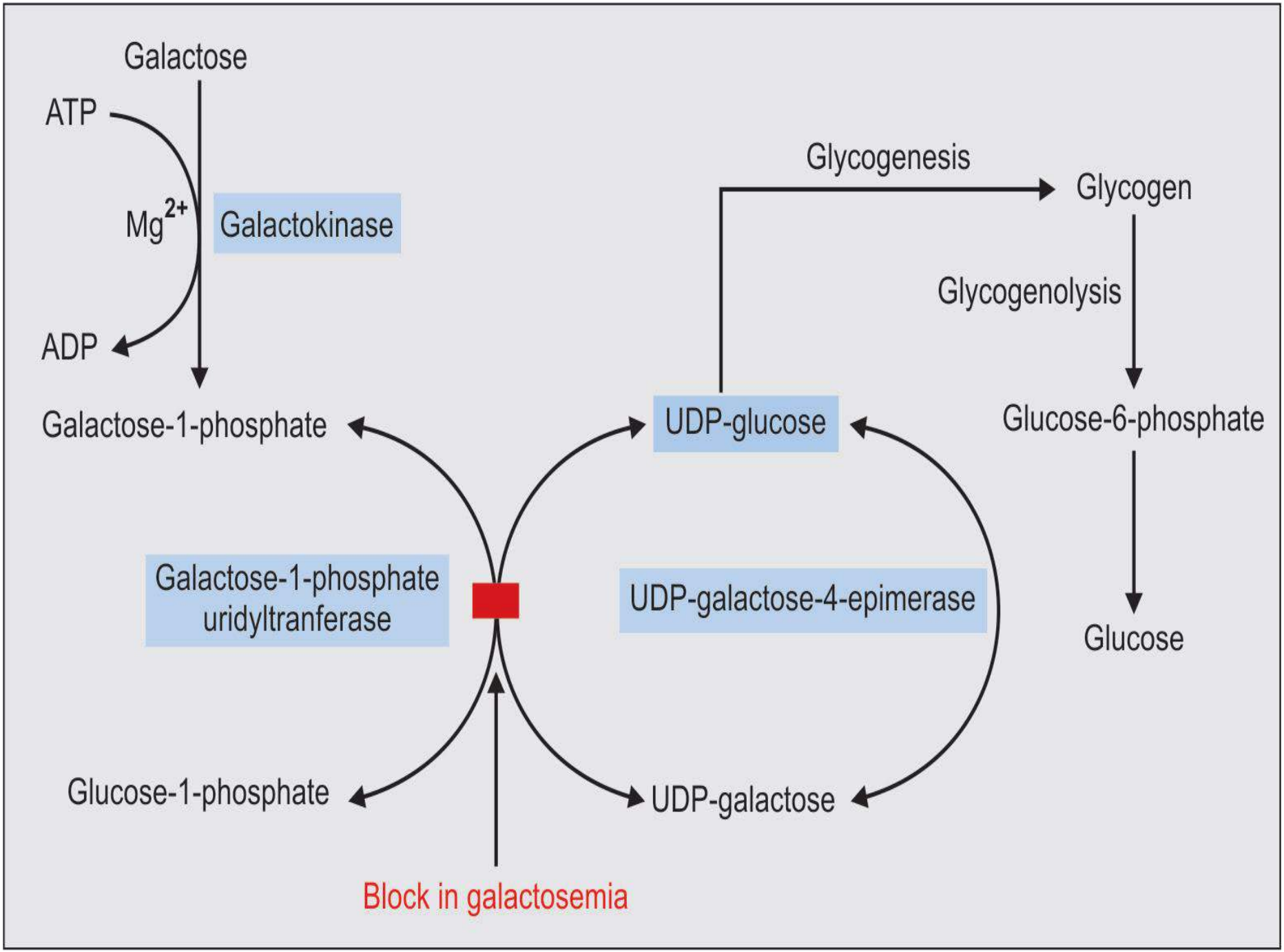
  Glycolipids

  Glycoproteins

  Proteoglycans

  Lactose during lactation.

Galactose is readily converted in the liver to glucose.


Galactose
ATP
Mg^{2+}
Galactokinase
ADP
Galactose-1-phosphate
Glycogenesis
Glycogen
Glycogenolysis
Glucose-6-phosphate
Glucose
UDP-glucose
Galactose-1-phosphate uridyltranferase
UDP-galactose-4-epimerase
Glucose-1-phosphate
UDP-galactose
Block in galactosemia

Galactosemia

- It is an inborn error of galactose metabolism.
- Caused by deficiency of enzyme galactose-1-phosphate uridyl transferase
- The inherited deficiencies of galactokinase and UDPgalactose-4-epimerase also lead to minor types of galactosemia.

- It causes a rise in galactose in blood and urine and leads to accumulation of galactose and galactose-1-phosphate in blood, liver, brain , kidney and eye lenses.
- In these organs, the galactose is reduced to galactitol by the enzyme aldose reductase.

Clinical findings

The accumulation of galactitol and galactose-1-phosphate in liver, brain and eye lenses causes:

- Liver failure (hepatomegaly followed by cirrhosis)
- Mental retardation and
- Cataract formation

Treatment:

- Galactose in milk and milk products should be eliminated from the diet.

- Sufficient galactose for the body's need can be synthesized endogenously as UDP-galactose.

A 6-month-old infant was presented with elevated blood and urine galactose.

Questions

a. Name the disease.

b. Give the biochemical steps related to the disease and point out the metabolic defect.

c. What are the clinical manifestation of the disease

BLOOD GLUCOSE LEVEL AND ITS REGULATION

- Blood glucose level maintained within 70-100 *mg/dl.*

- Levels above normal range : *Hyperglycemia*,

  Levels below normal range : *Hypoglycemia.*

- After the intake of a carbohydrate meal, blood glucose level rises to 120-140 mg/dl.

Factors involved in the *regulation* of blood glucose are:

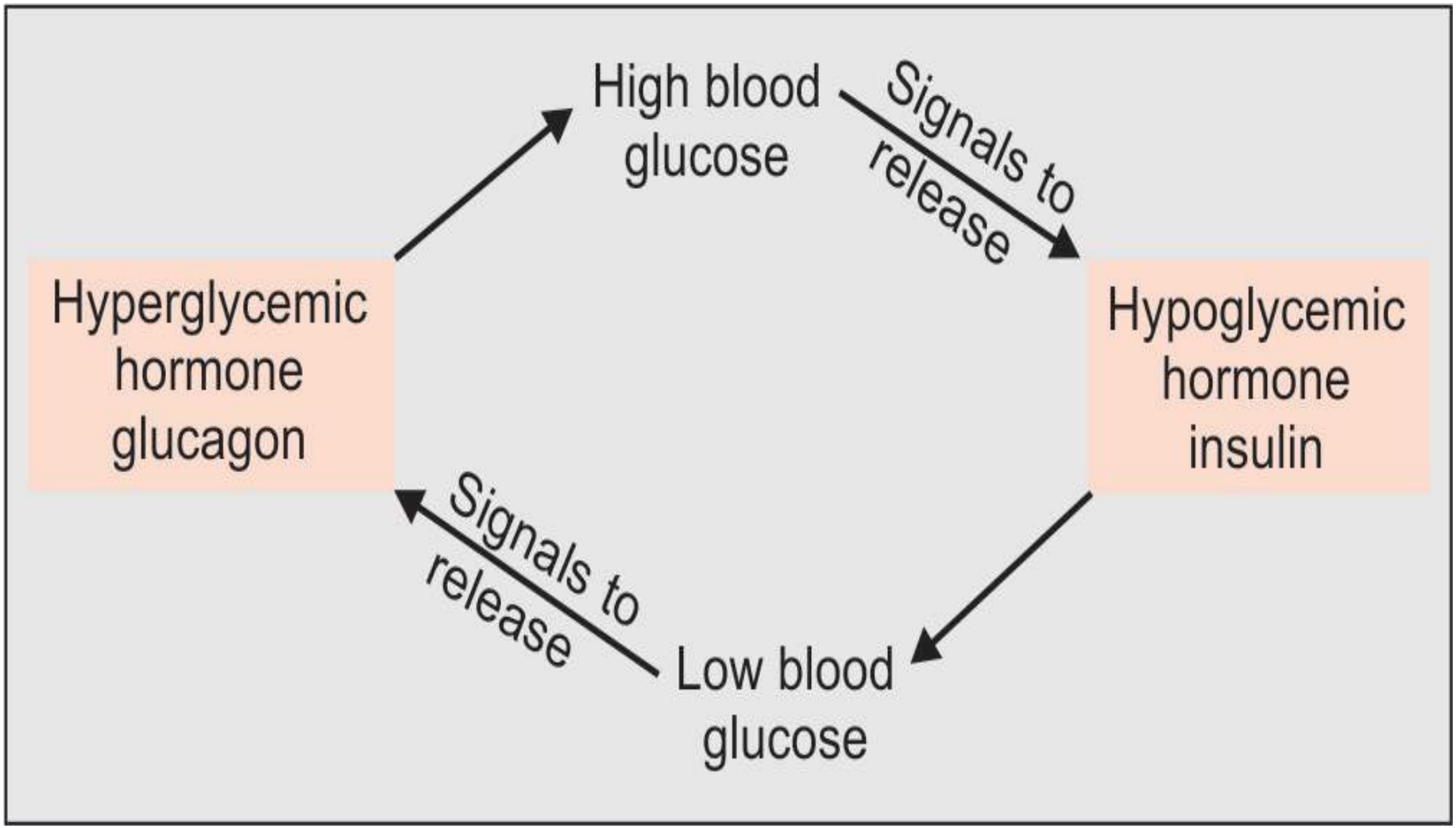
1. Hormones
2. Metabolic processes
3. Renal mechanism

Two major hormones controlling blood glucose levels are:

1. Insulin (hypoglycemic hormone)

2. Glucagon (hyperglycemic hormone).

Figure 10.48: Reciprocal control of insulin and glucagon on the homeostasis.



Maintenance of Glucose in Fed State (Hyperglycemic condition)

- Increased blood glucose level ,*hyperglycemia occur* after each meal
- Increased level of blood glucose releases *insulin*
- Insulin reduces the blood glucose level in a number of ways

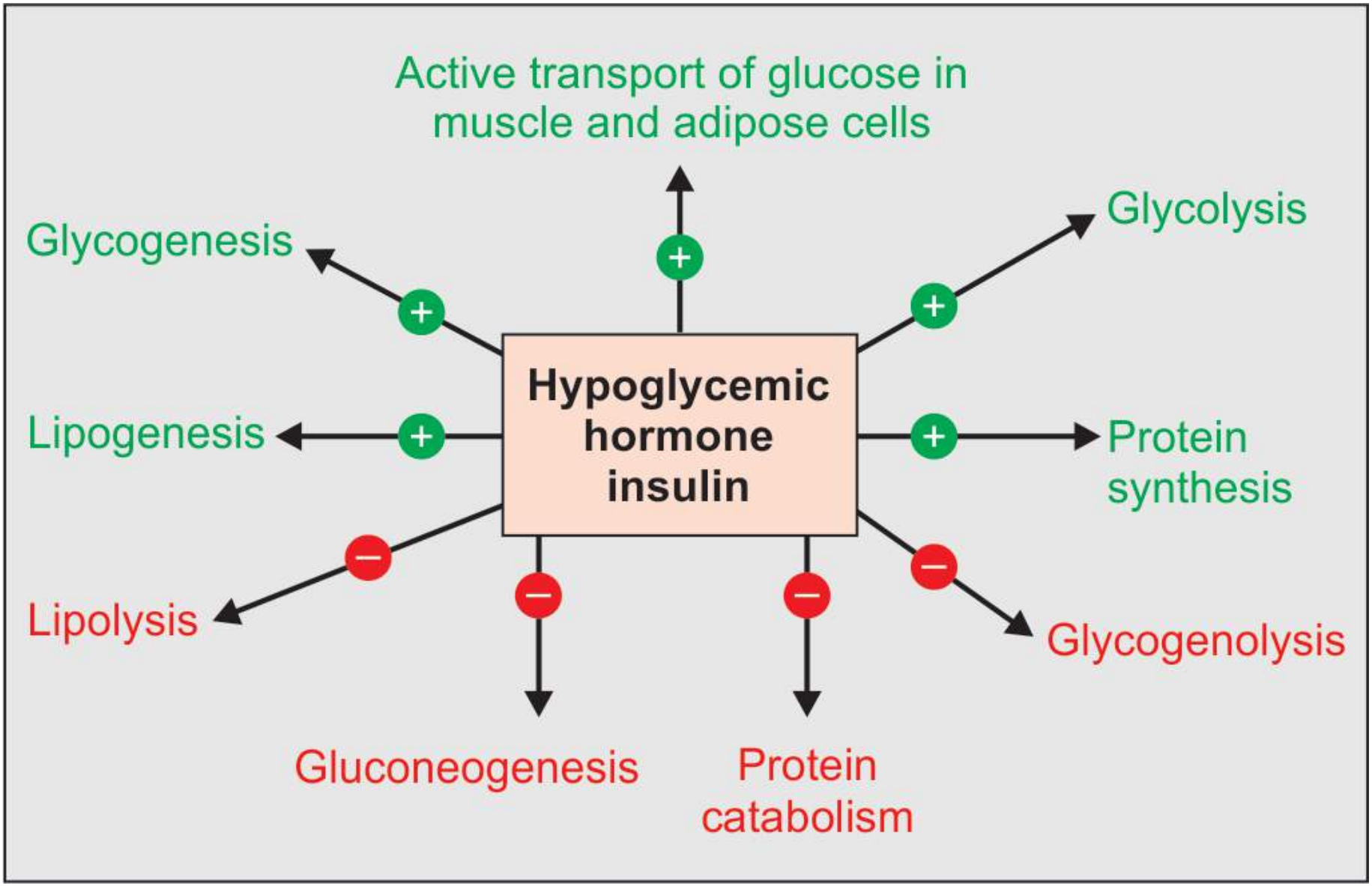


Figure 10.49: Various metabolic systems affected by insulin.

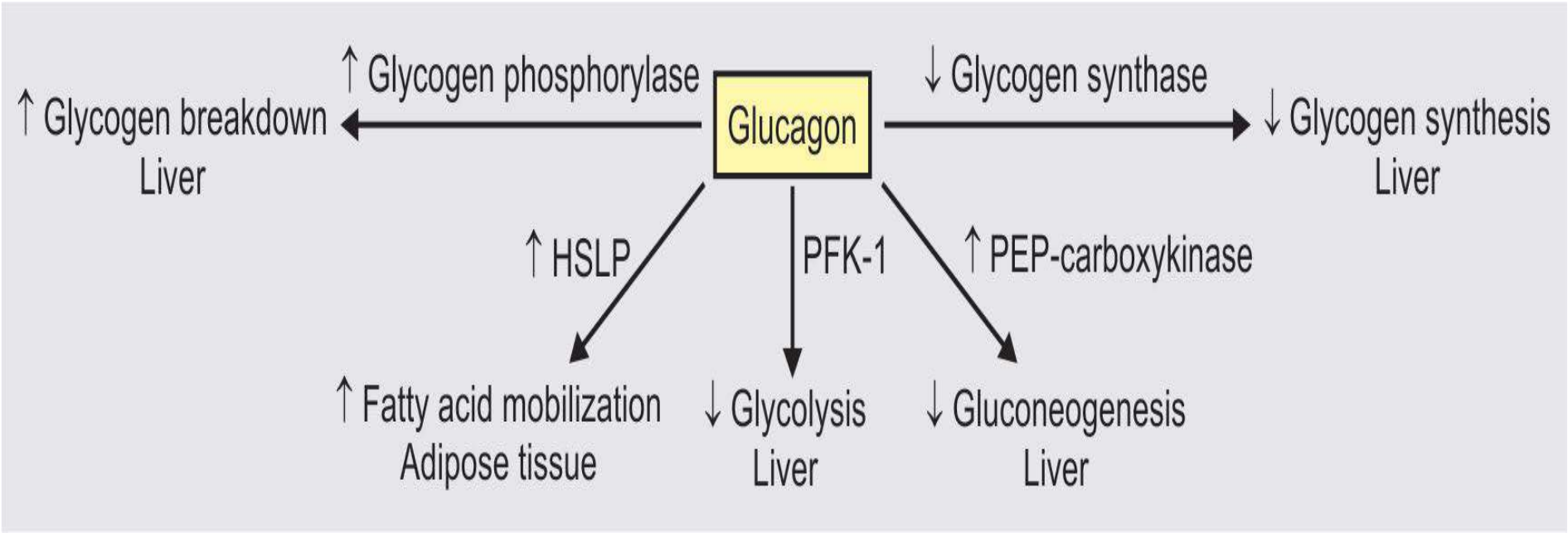


Figure 10.50: Effect of glucagon on blood glucose.

Maintenance of Blood Glucose in Fasting State (Hypoglycemic Condition)

•

Decreased level of blood glucose (hypoglycemia) causes release of hyperglycemic hormones, e.g.

- Glucagon
- Epinephrine or adrenaline
- Glucocorticoids
- Growth hormone
- ACTH
- Thyroxin.

Glucagon

Glucagon opposes the action of insulin. It acts primarily in the liver as follows:

- In the liver, it stimulates glycogenolysis & inhibits glycogen synthesis
- Enhances gluconeogenesis from amino acids and lactic acids

Epinephrine or Adrenaline

- Stimulates glycogenolysis in the liver and the muscle by stimulating glycogen phosphorylase
- In muscle due to absence of glucose-6-phosphatase, glycogenolysis results with the formation of lactate, whereas in the liver, glucose is the main product, leading to increase in blood

Glucocorticoids

- Increases Gluconeogenesis by increasing the:
  - activity of enzymes of gluconeogenesis.
  - protein catabolism to provide glucogenic amino acid
  - hepatic uptake of amino acids.
- Inhibit utilization of glucose in extra-hepatic tissues.

Growth hormone and anterior pituitary hormones

- Growth hormone and ACTH antagonise the action of insulin.
- Growth hormone decreases glucose uptake in the muscle and ACTH decreases glucose utilization by the tissue.

Thyroxine

- Accelerates hepatic glycogenolysis with consequent rise in blood glucose.

- It may also increase the rate of absorption of hexoses from the intestine

Renal Control Mechanism

If the blood glucose level is raised above *180 mg/100 ml,* complete tubular reabsorption of glucose does not occur and the extra amount appears in the urine causing *glycosuria.*

GLYCOSURIA

- Excretion of detectable amount of sugar in urine is known as *glycosuria.*
- Glycosuria results from the rise of blood glucose above its renal threshold level (180 mg%)

Glycosuria may be due to various reasons on the basis of which is classified into following groups:

1. Alimentary glycosuria
2. Renal glycosuria
3. Diabetic glycosuria.

DIABETES MELLITUS

Definition

Syndrome of impaired carbohydrate,fat and protein metabolism, caused by either:

- Lack of insulin secretion

or

- Decreased sensitivity of tissues to insulin.

Classification of Diabetes Mellitus

1. Type I diabetes mellitus or insulin dependent diabetes mellitus (IDDM) or juvenile diabetes.
2. Type II diabètes mellites or non insulin dépendent diabetes mellitus (NIDDM) or adult diabetes mellitus.

Type l diabetes mellitus

Cause

Lack of insulin secretion due to destruction of pancreatic beta cells. The destructions of beta cells may be due to:

1. Viral infection
2. Autoimmune disorder
3. Hereditary tendency of beta cell degeneration.

Onset

- At about 14 years of age and for this reason it is called juvenile diabetes mellitus.
- Juvenile’ means teenage in Latin.

Symptoms

- It develops symptoms very abruptly with:
  - Polyuria (frequent urination)
  - Polydypsia (excessive thirst)
  - Polyphagia (excessive hunger).

- Loss of body weight, weakness, and tiredness.
- Hyperglycemia with glycosuria and ketoacidosis
- The patients of type-I diabetes mellitus are not obese.

Treatment

Since patients of IDDM (type-I) fail to secrete insulin, administration of exogenous insulin is required.

Type II diabetes mellitus

Cause

- Decreased sensitivity of target tissues to insulin.

  (*insulin resistance).*

- *Inadequate insulin receptors* on cell surfaces of target tissues.

- This syndrome is often found in an obese person.

Onset

- After age 40 and the disorder develops gradually.

- Therefore, this syndrome is referred to as adult onset diabetes.

Symptoms

- The symptoms are developed gradually
- Similar to that of type-I
- Except Ketoacidosis is usually not present in type II diabetes mellitus

Treatment

- NIDDM (type-II) can be treated in early stages by diet control, exercise and weight reduction

- No exogenous insulin administration is required..

- Drugs that increase insulin sensitivity or drugs that cause additional release of insulin by the pancreas may be used.

- In the later stages insulin administration is required.

Metabolic changes occur in diabetes mellitus

Changes in levels of insulin and glucagon affect metabolism in three tissues; liver, muscle and adipose tissue.

- The lack of insulin activity results in failure of transfer of glucose from the blood into cells and leads to hyperglycemia.
- Elevated levels of blood glucose and ketone bodies are the characteristic feature of untreated diabetes mellitus.

- The body responds as it were in the fasting state with stimulation of:
  - Glycogenolysis
  - Gluconeogenesis
  - Lipolysis
  - Proteolysis.

- Increased lipolysis leads to increased formation of ketone bodies causing ketoacidosis.
- Due to lack of insulin decreased synthesis of lipoprotein lipase leads to elevated levels of plasma VLDL, resulting in hypertriglyceridemia

- Due to increased rate of proteolysis the amino acids released from muscle are converted to glucose by gluconeogenesis.

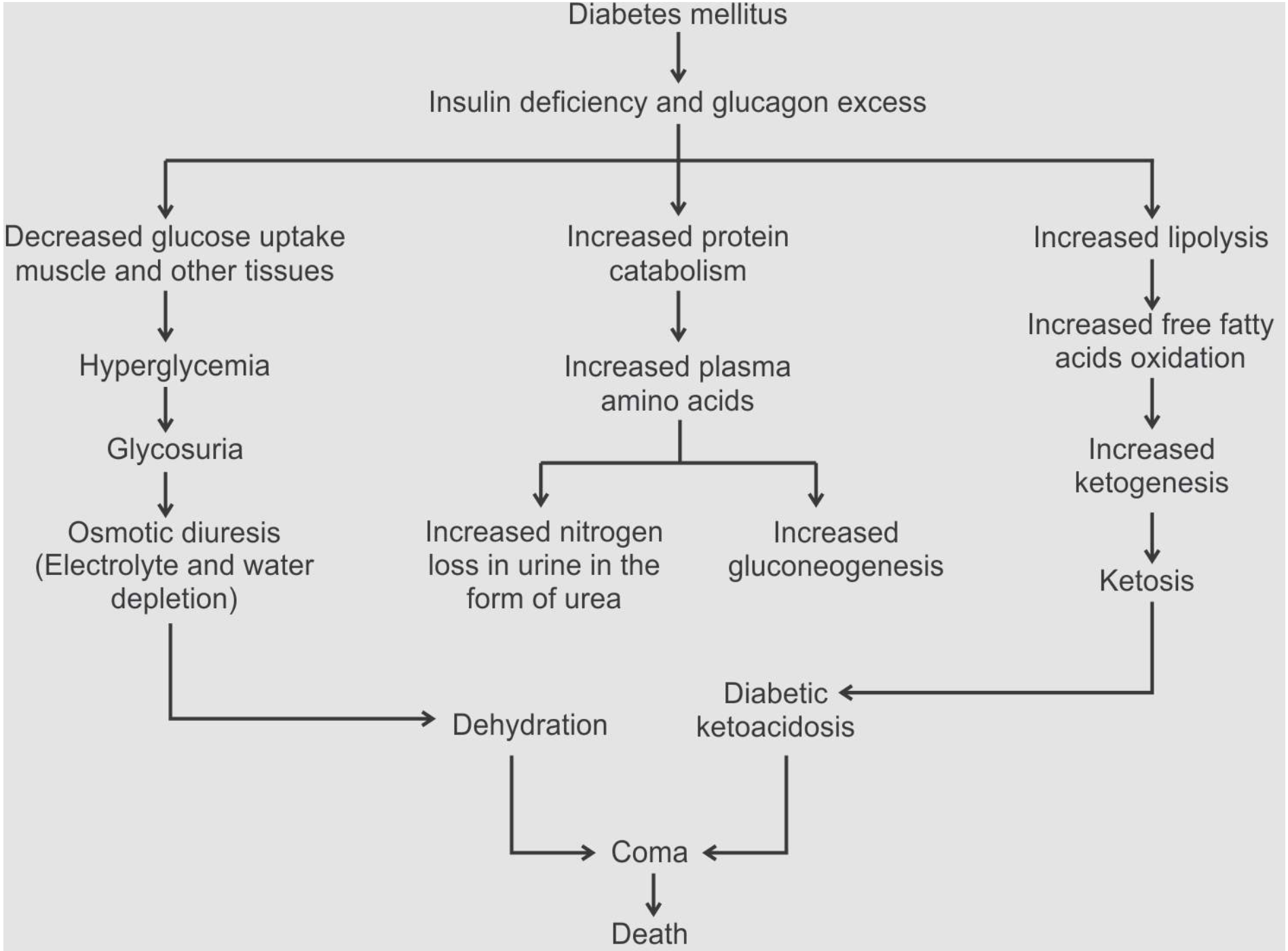

Diabetes mellitus
Insulin deficiency and glucagon excess
Decreased glucose uptake muscle and other tissues
Increased protein catabolism
Increased lipolysis
Hyperglycemia
Glycosuria
Osmotic diuresis (Electrolyte and water depletion)
Increased plasma amino acids
Increased nitrogen loss in urine in the form of urea
Increased gluconeogenesis
Increased free fatty acids oxidation
Increased ketogenesis
Ketosis
Dehydration
Diabetic ketoacidosis
Coma
Death

TABLE 10.8: Comparison of two types of diabetes mellitus

Features	*Type I insulin-dependent diabetes mellitus*	*Type II non-insulin-dependent diabetes mellitus*
Frequency	5 to 10%	90 to 95%
Age of onset	Early during childhood or puberty usually <20 years	Later after age of 40 years
Onset of symptoms	Abrupt and severe	Gradual, insidious
Plasma insulin	Low or absent	Normal to high
Body weight	Low to normal	Obese
Blood glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Ketosis	Common	Rare
Acute complications	Ketoacidosis	Hyperosmolar coma
Treatment with insulin	Necessary	Usually not required

GLUCOSE TOLERANCE TEST (GTT)

- Glucose tolerance test (GTT) is a test to assess the ability of the body to utilize glucose.

- GTT can be performed by two ways:

    1. Oral GTT

    2. Intravenous GTT

Types of Glucose Tolerance Curves

1. Normal glucose tolerance curve
2. Decreased glucose tolerance
3. Increased glucose tolerance.

Decreased glucose tolerance occurs in:

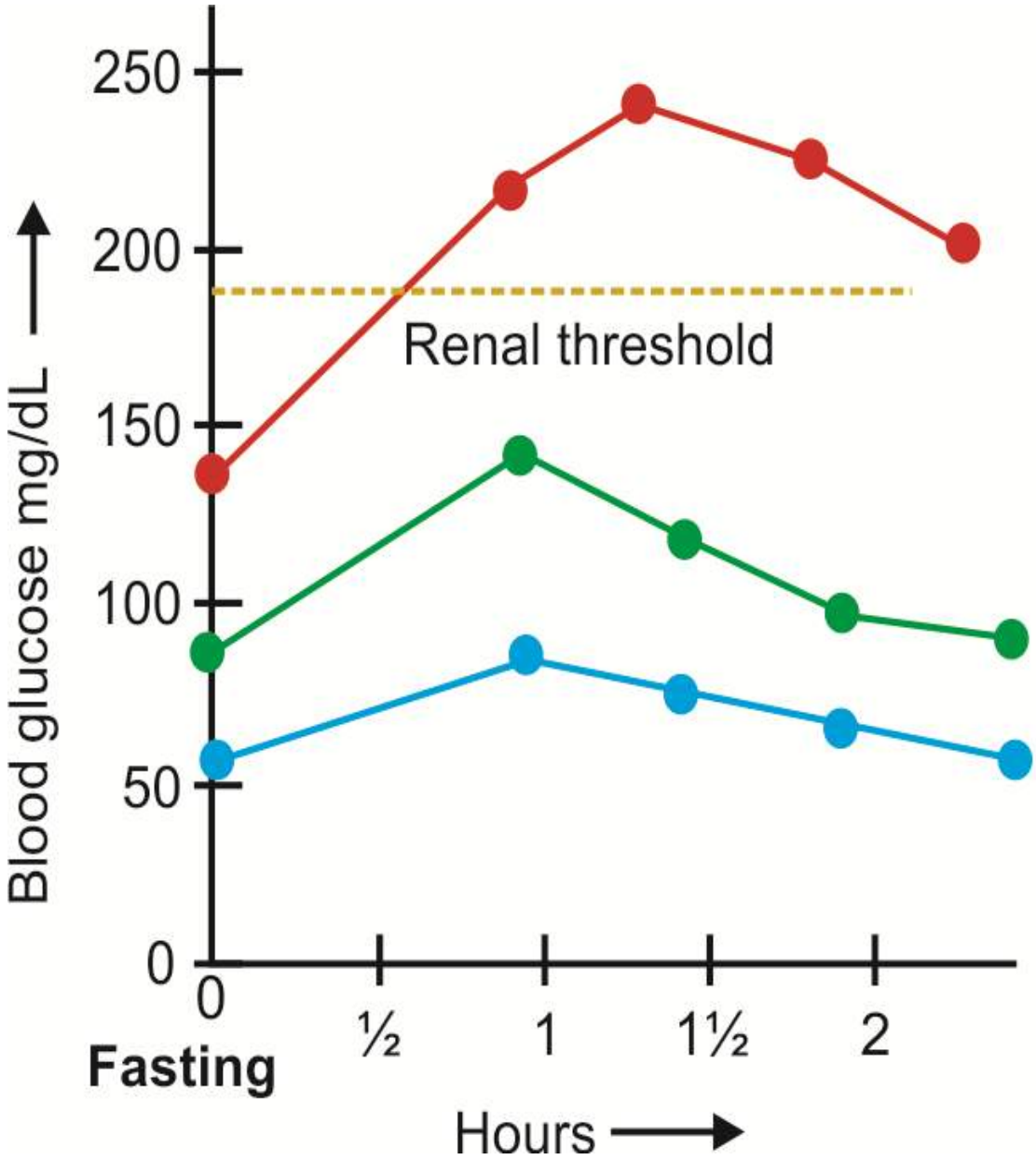
- Diabetes mellitus
- Certain endocrine disorders like:
  - Hyperthyroidism
  - Hyperpituitarism
  - Hyperadrenalism (Cushing's syndrome).

Increased glucose tolerance occurs in :

– Hypothyroidism (myxedema, cretinism)

– Hypoadrenalism (Addison’s disease)

– Hypopituitarism.

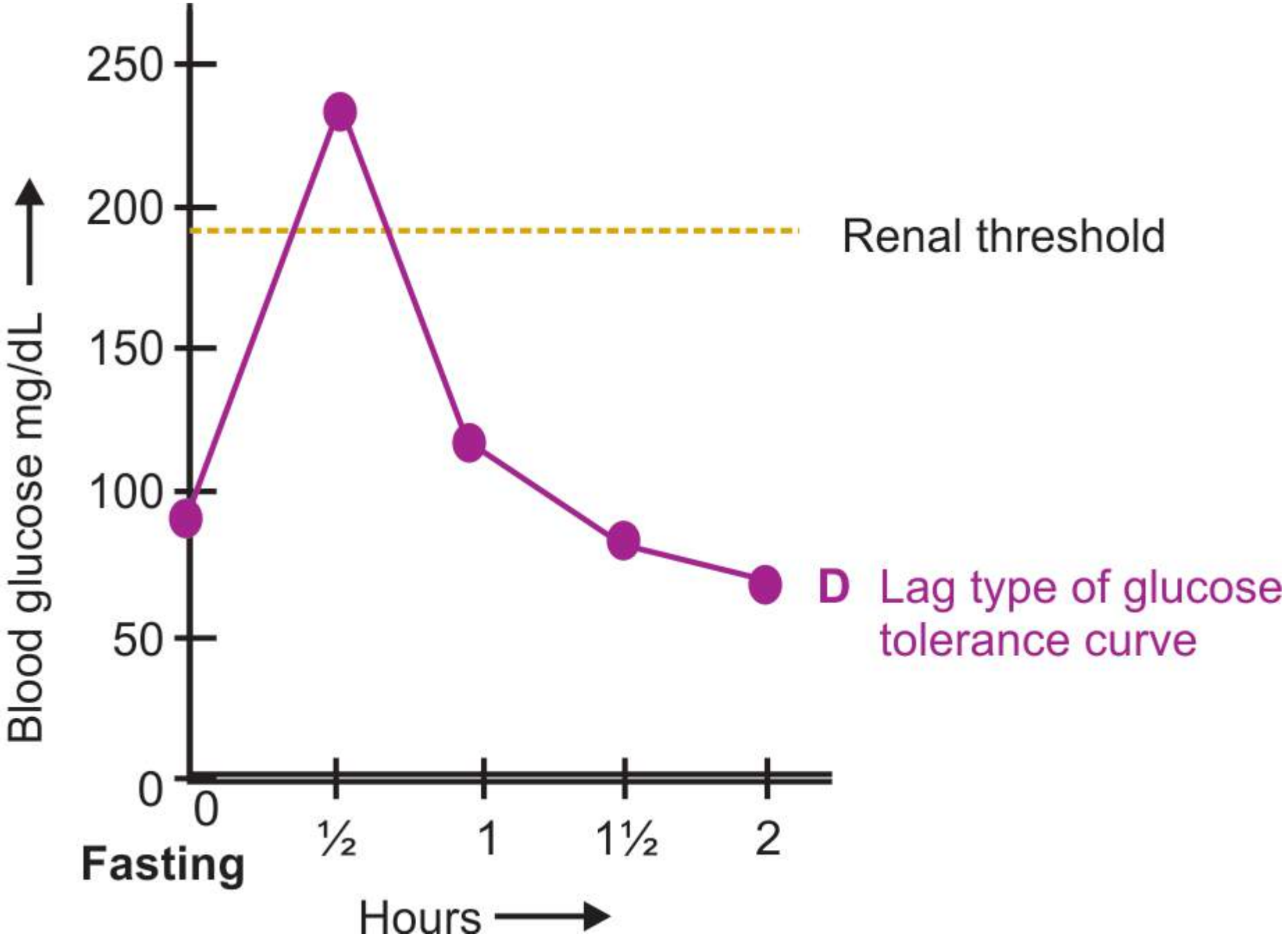


A Diminished glucose tolerance occur in diabetes mellitus and endocrine hyperactivity

B Normal

C Increased glucose tolerance, e.g. in endocrine hypoactivity

The glucose tolerance curves


250
200
150
100
50
0
Blood glucose mg/dL
Renal threshold
D Lag type of glucose tolerance curve
0
Fasting
½
1
1½
2
Hours

Significance of GTT

- GTT is not necessary in symptomatic or in known cases of diabetic patients
- GTT is most important in the investigation of asymptomatic hyperglycemia or glycosuria such as renal glycosuria & alimentary glycosuria.
- Give useful information of endocrine dysfunctions.
- It is also helpful in recognizing milder cases of diabetes.

TABLE 10.9: WHO diabetes diagnostic criteria.

Condition	*2-hour glucose*	*Fasting glucose*	*HbA1c*
Normal	<140 mg/dL (<7.8 mmol/L)	<110 mg/dL (<6.1)	<6.0%
Impaired fasting glycemia	<140 mg/dL (<7.8 mmol/L)	≥110 mg/dL (≥6.1 mmol/L) and <126 mg/dL (<7.0 mmol/L)	6.0–6.4%
Impaired glucose tolerance	≥140 mg/dL (≥7.8 mmol/L)	<126 mg/dL (<7.0 mmol/L)	6.0–6.4%
Diabetes mellitus	≥200 mg/dL (≥11.1 mmol/L)	≥126 mg/dL (≥7.0 mmol/L)	≥ 6.5