Carbohydrate Metabolism

Presented By: Ramesh Kumar
(Assist. Prof., L.S.C.P. Sirsa)

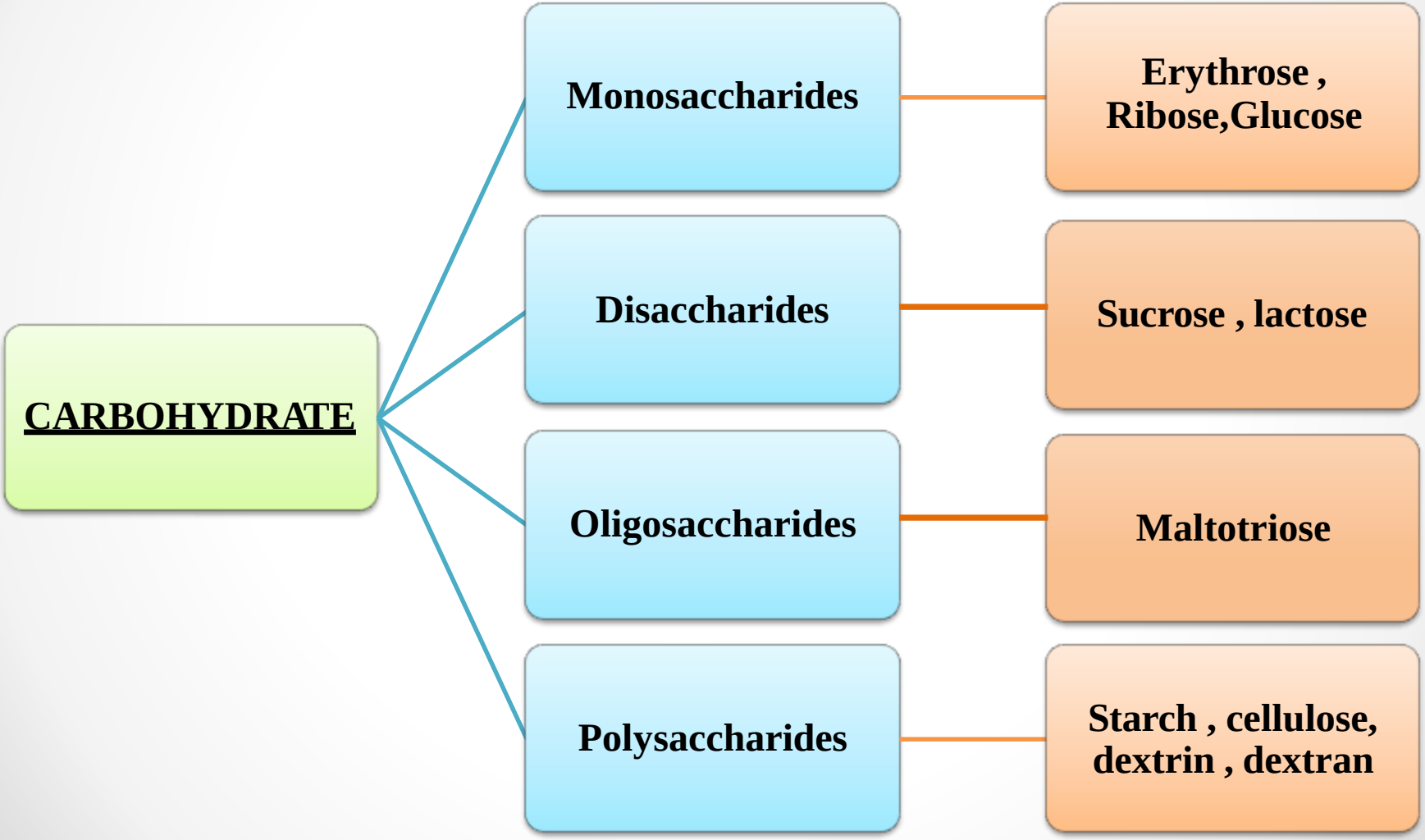
Lord Shiva College of Pharmacy, Sirsa

INTRODUCTION OF CARBOHYDRATES

CARBOHYDRATE

- Most abundant organic molecule on earth.
- *Carbohydrates are defined as aldehyde or keto derivatives of polyhydric alcohols.*
- For example: Glycerol on oxidation is converted to D-glyceraldehyde, which is a carbohydrate derived from the trihydric alcohol (glycerol).
- All carbohydrates have the general formula $C_nH_{2n}O_n$ [or it can be re-written as $C_n(H_2O)_n$] .

CLASSIFICATION OF CARBOHYDRATES



FUNCTIONS OF CARBOHYDRATES

- Main source of energy in the body. Energy production from carbohydrates will be 4 k calories/g (16 k Joules/g).
- Storage form of energy (starch and glycogen).
- Excess carbohydrate is converted to fat.
- Glycoproteins and glycolipids are components of cell membranes and receptors.
- Structural basis of many organisms. For example, cellulose of plants, exoskeleton of insects etc.

Biomedical Importance Of Glucose

- Glucose is a major carbohydrate
- It is a major fuel of tissues
- It is converted into other carbohydrates

✓ Glycogen for storage.
✓ Ribose in nucleic acids.
✓ Galactose in lactose of milk.
✓ They form glycoproteins & proteoglycans
✓ They are present in some lipoproteins (LDL) .
✓ Present in plasma membrane:glycocalyx.
✓ Glycophorin is a major intergral membrane glycoprotein of human erythrocytes.

Metabolism

Thousands of chemical reactions are taking place inside a cell in an organized, well co-ordinated and purposeful manner; all these reactions are called as METABOLISM.

TYPES OF METABOLIC PATHWAY:

- ✓ **Catabolic Pathway**
- ✓ **Anabolic Pathway**
- ✓ **Amphibolic Pathway**

STAGES AND PHASES OF METABOLISM:

- ✓ **Primary**
- ✓ **Secondary**
- ✓ **Tertiary**

Major Pathways of Carbohydrate Metabolism

1) Glycolysis

2) Citric Acid Cycle

3) Gluconeogenesis

4) Glycogenesis

5) Glycogenolysis

6) Hexose monophosphate shunt

7) Uronic Acid Pathway

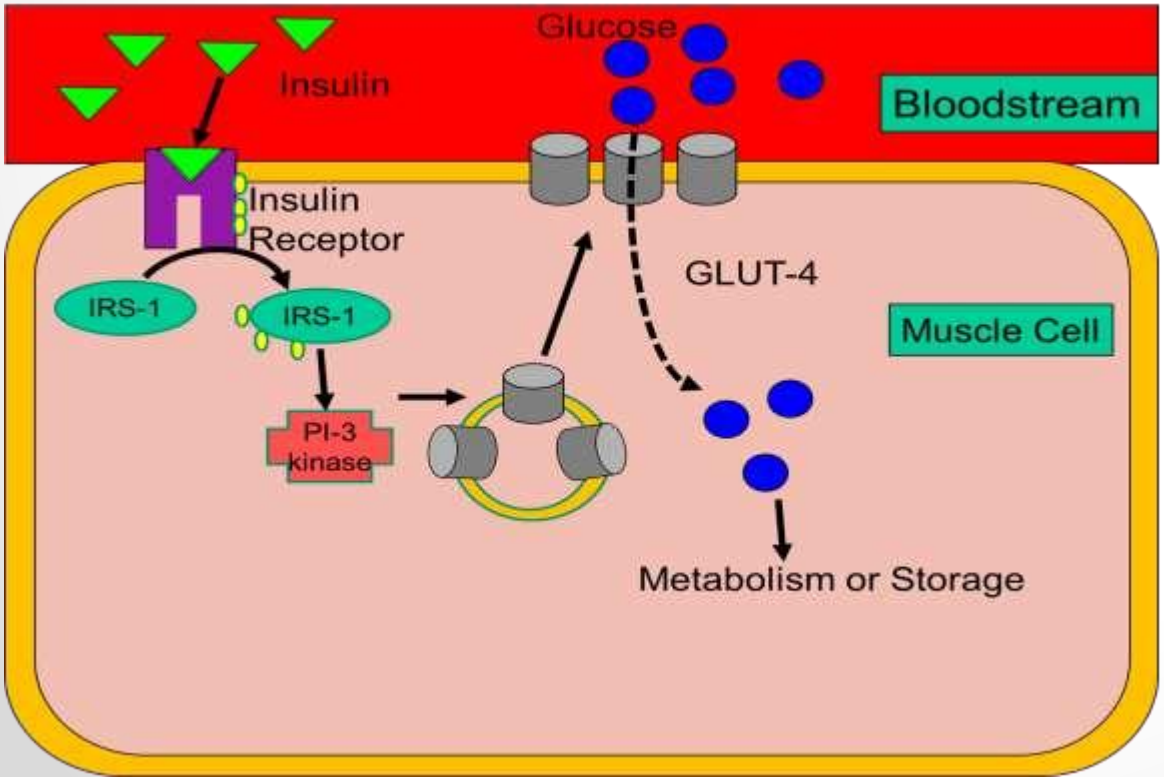
8) Galactose Metabolism

9) Fructose Metabolism

10) Amino sugar metabolism

Entry of Glucose into cells

1) Insulin-independent transport system of glucose: Not dependent on hormone insulin. This is operative in – hepatocytes, erythrocytes (GLUT-1) and brain.
2) Insulin-dependent transport system: Muscles and adipose tissue (GLUT-4).



Type 2 *Diabetes mellitus*:
-Due to reduction in the quantity of GLUT-4 in insulin deficiency.

Glycolysis

Embden-Meyerhof pathway

(or)

E.M.Pathway

Definition:

Glycolysis is defined as the sequence of reactions converting glucose (or glycogen) to pyruvate or lactate, with the production of ATP

Salient features:

1) Takes place in all cells of the body.
2) Enzymes present in “cytosomal fraction” of the cell.
3) Lactate – end product – anaerobic condition.
4) Pyruvate (finally oxidized to CO_2 & H_2O) – end product of aerobic condition.
5) Tissues lacking mitochondria – major pathway – ATP synthesis.
6) Very essential for brain – dependent on glucose for energy.
7) Central metabolic pathway
8) Reversal of glycolysis – results in gluconeogenesis.

Reactions of Glycolysis

1) Energy Investment phase (or) priming phase

2) Splitting phase

3) Energy generation phase

Energy Investment Phase

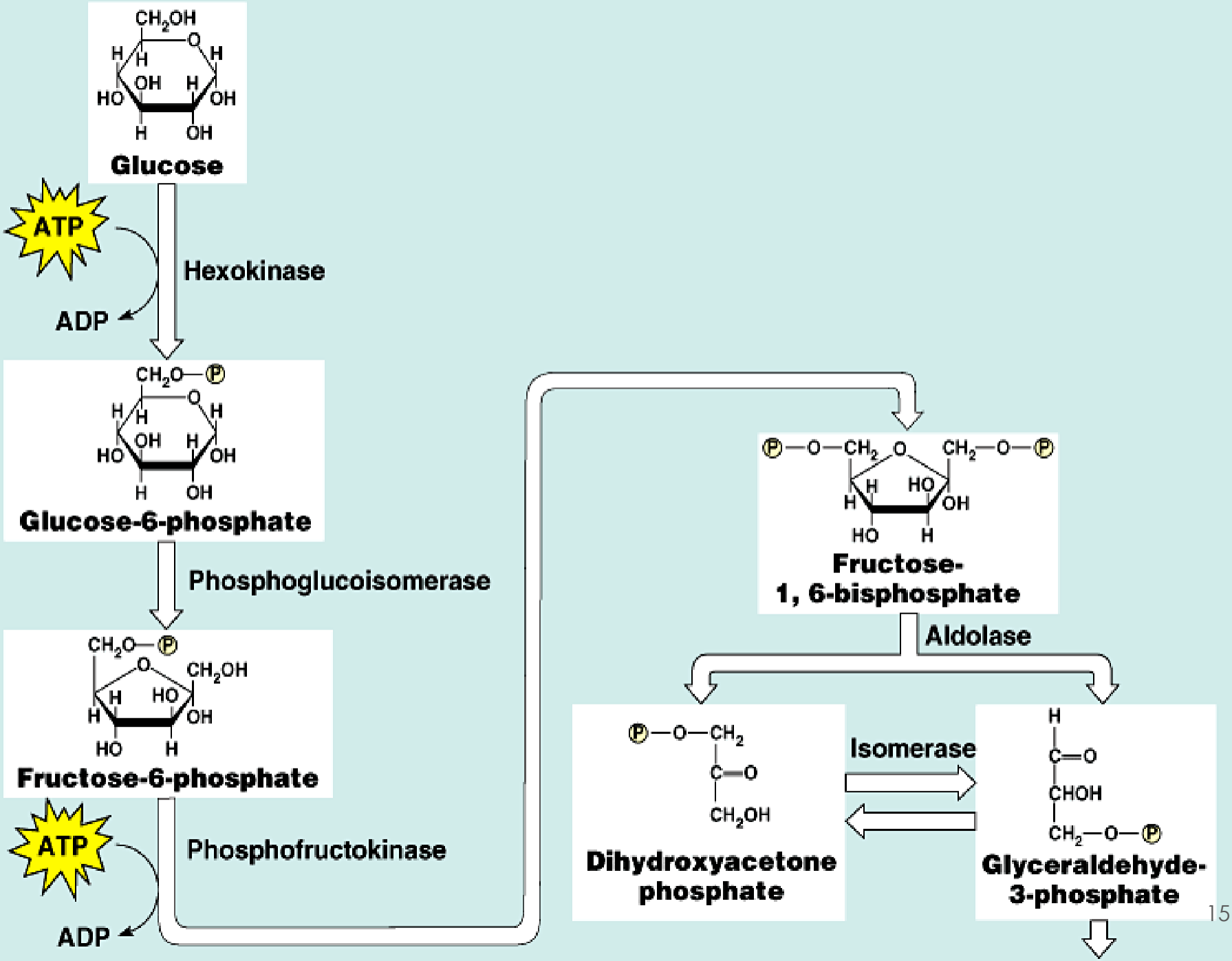
- **Glucose** is phosphorylated to **glucose-6-phosphate** by *hexokinase (or) glucokinase*.
- Glucose-6-phosphate undergoes isomerization to give **fructose -6- phosphate** in the presense of *phospho-hexose isomerase* and Mg^{2+}
- Fructose-6-phosphate is phoshorylated to **fructose 1,6-bisphosphate** by *phosphofructokinase*.

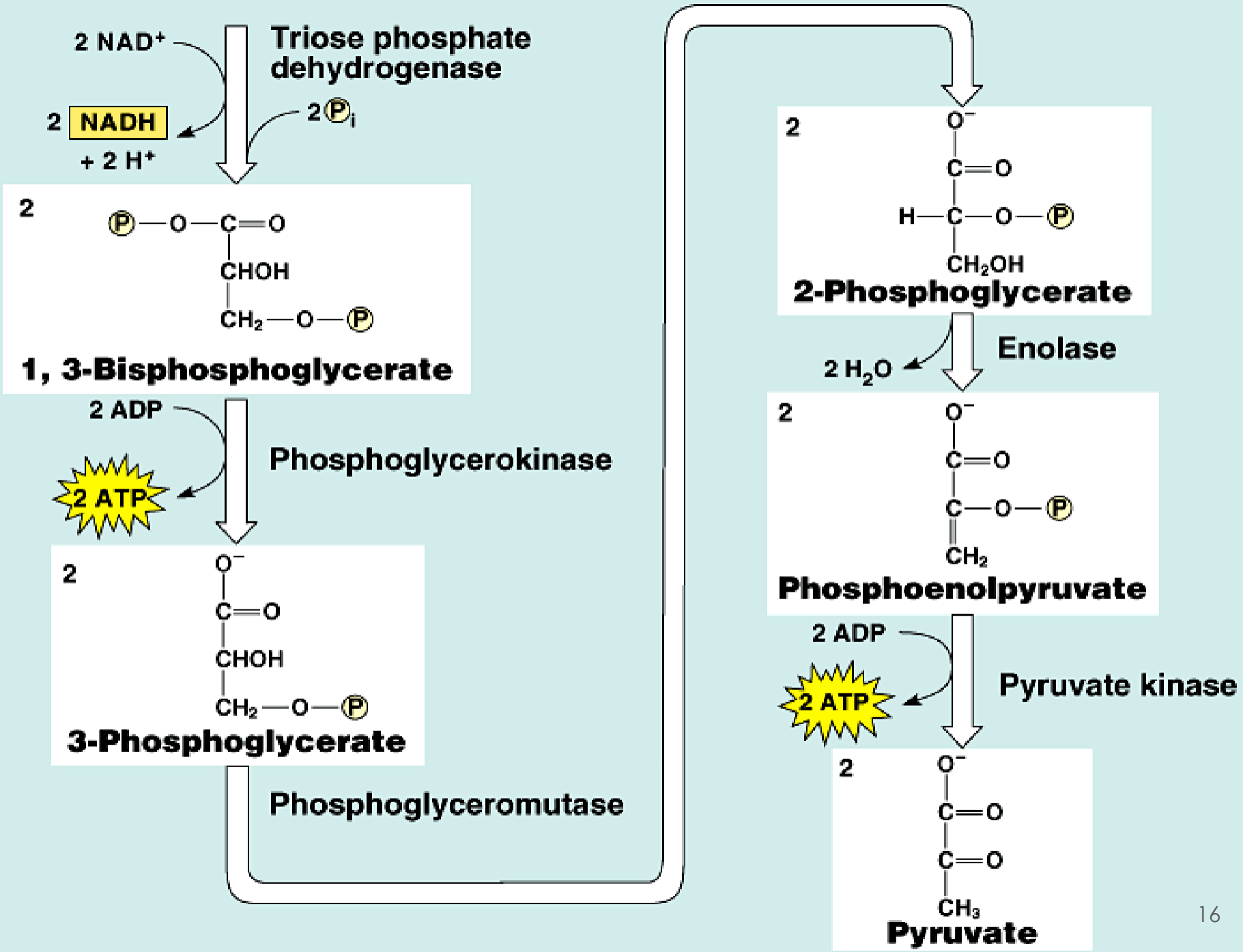
Splitting Phase

- Fructose 1,6-bisphosphate → **glyceraldehyde 3-phosphate** + **dihydroxyacetone phosphate.**(*aldolase enzyme*)
- **2 molecules** of glyceraldehyde 3-phosphate are obtained from 1 molecule of glucose

Energy Generation Phase

- Glyceraldehyde 3-phosphate → **1,3-bisphosphoglycerate**(*glyceraldehyde 3-phosphate hydrogenase)*
- 1,3-bisphosphoglycerate → **3-phosphoglycerate** (*phosphoglycerate kinase*)
- 3-phosphoglycerate → **2-phosphoglycerate** (*phosphoglycerate mutase*)
- 2-phosphoglycerate → **phosphoenol pyruvate** (*enolase* + Mg^{2+} & Mn^{2+})
- Phosphoenol pyruvate → **pyruvate [enol]** (*pyruvate kinase*) → **pyruvate [keto]** → **L-Lactate** *(lactate dehydrogenase)*


Glucose
ATP
Hexokinase
ADP
Glucose-6-phosphate
Phosphoglucoisomerase
Fructose-6-phosphate
ATP
Phosphofructokinase
ADP
Fructose-
1, 6-bisphosphate
Aldolase
Dihydroxyacetone
phosphate
Isomerase
Glyceraldehyde-
3-phosphate


2 NAD+
Triose phosphate dehydrogenase
2 NADH
+ 2 H+
2 Pi
2
1, 3-Bisphosphoglycerate
2 ADP
2 ATP
Phosphoglycerokinase
2
3-Phosphoglycerate
Phosphoglyceromutase
2
2-Phosphoglycerate
2 H2O
Enolase
2
Phosphoenolpyruvate
2 ADP
2 ATP
Pyruvate kinase
2
Pyruvate

Energetics of Glycolysis

ATP production = ATP produced - ATPutilized

	ATP produced	ATP utilized	Net energy
In absence of oxygen (anaerobic glycolysis)	4 ATP (Substrate level phosphorylation) 2ATP from 1,3 DPG. 2ATP from phosphoenol pyruvate	2ATP From glucose to glucose -6-p. From fructose -6-p to fructose 1,6 p.	2 ATP
In presence of oxygen (aerobic glycolysis)	4 ATP (substrate level phosphorylation) 2ATP from 1,3 BPG. 2ATP from phosphoenol pyruvate. + 4ATP or 6ATP (from oxidation of 2 NADH + H in mitochondria).	2ATP -From glucose to glucose -6-p. From fructose -6-p to fructose 1,6 p.	8 ATP/ 6 ATP (Pyruvate dehydrogenase 2NADH,ETC, Oxidative phosphorylation)

CITRIC ACID CYCLE

KREBS CYCLE / TRICARBOXYLIC ACID/ TCA CYCLE

Essentially involves the oxidation of acetyl CoA to CO_2 and H_2O.
This Cycle utilizes about two-third of total oxygen consumed by the body.

Brief History:

- Hans Adolf Krebs
- 1937
- Studies of oxygen consumptiom in pigeon breast muscle.

Location of TCA

- Mitochondrial matrix
- In close proximity to the electronic transport chain.

Overview

- 65-70% of the ATP is synthesized
- Name : TCA used because at the onset of the cycle tricarboxylic acids participate.

Reactions of citric acid cycle

1) **Formation of citrate** : Condensation of acetyl CoA and oxaloacetate → catalysed by citrate synthase.

2) & 3) **Citrate is isomerized to isocitrate** → aconitase (two steps).

4) & 5) **Formation of ά-ketoglutarate** : enzyme isocitrate dehydrogenase.

6) **Conversion of ά-ketoglutarate to succinyl CoA** : through oxidative decarboxylation, catalysed by ά-ketoglutarate dehydrogenase complex.

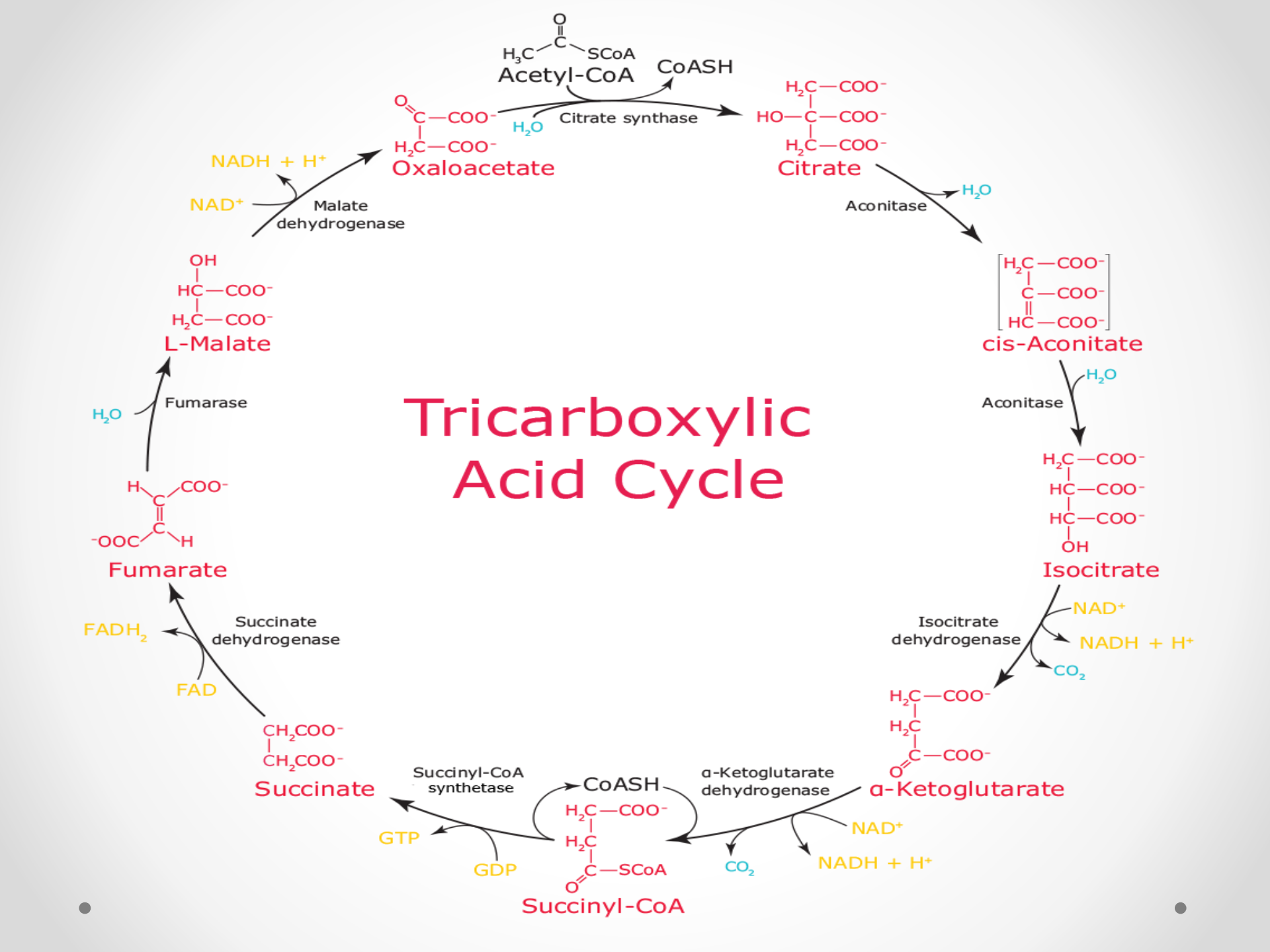
7) **Formation of succinate** : enzyme succinate thiokinase

GTP + ADP ←→ ATP + GDP (nucleoside diphosphate kinase)

8) **Conversion of succinate to fumarase** : enzyme succinate dehydrogenase

9) **Formation of malate** : enzyme fumarase

10) **Conversion of malate to oxaloacetate** : enzyme malate dehydrogenase.


Tricarboxylic Acid Cycle
Acetyl-CoA
CoASH
Citrate synthase
Oxaloacetate
Citrate
Aconitase
cis-Aconitate
Aconitase
Isocitrate
Isocitrate dehydrogenase
α-Ketoglutarate
α-Ketoglutarate dehydrogenase
Succinyl-CoA
Succinyl-CoA synthetase
Succinate
Succinate dehydrogenase
Fumarate
Fumarase
L-Malate
Malate dehydrogenase
NADH + H+
NAD+
FADH2
FAD
GTP
GDP
CO2
H2O

- TCA cycle is strictly **aerobic** in contrast to glycolysis.

- Total of **12 ATP** are produced from one acetyl CoA:-

✓ During the process of oxidation of acetyl CoA via citric acid cycle → 3 NADH & 1 FADH2.

✓ Oxidation of 3 NADH by electron transport chain coupled with oxidative phosphorylation results in 9 ATP, FADH2 → 2 ATP.

✓ One substrate level phosphorylation.

Energetics of TCA Cycle

Steps 4, 6, 10 → 3 NADH

1 NADH = 3 ATP] 3 ATP x 3 = 9 ATP

Step 8 → 1 $FADH_2$

1 $FADH_2$ = 2 ATP] 2 ATP x 1 = 2 ATP

Step 7 → 1 GTP

1 GTP = 1 ATP 1 ATP x 1 = 1 ATP

Therefore 1 acetyl CoA gives 12 ATP

Therefore 1 acetyl CoA gives 12 ATP

Two acetyl CoA in citric acid cycle produces 24 ATP

Energetics of complete oxidation of glucose

Aerobic glycolysis → 8 ATP

Oxidation of 2 pyruvate = **6 ATP**

Oxidation of 2 Acetyl CoA by TCA cycle → 24 ATP

Net Gain = 38 ATP

Significance of TCA Cycle

- **Acts as the final common pathway for the oxidation of carbohydrates, lipids, and proteins.**
- **Serves as the crossroad for the interconversion among carbohydrates, lipids, and non-essential amino acids, and as a source of biosynthetic intermediates.**

HEXOSE MONOPHOSPHATE SHUNT

HMP Shunt/ Pentose Phosphate Pathway/ Phosphogluconate Pathway

* This is an alternative pathway to glycolysis and TCA cycle for the oxidation of glucose.

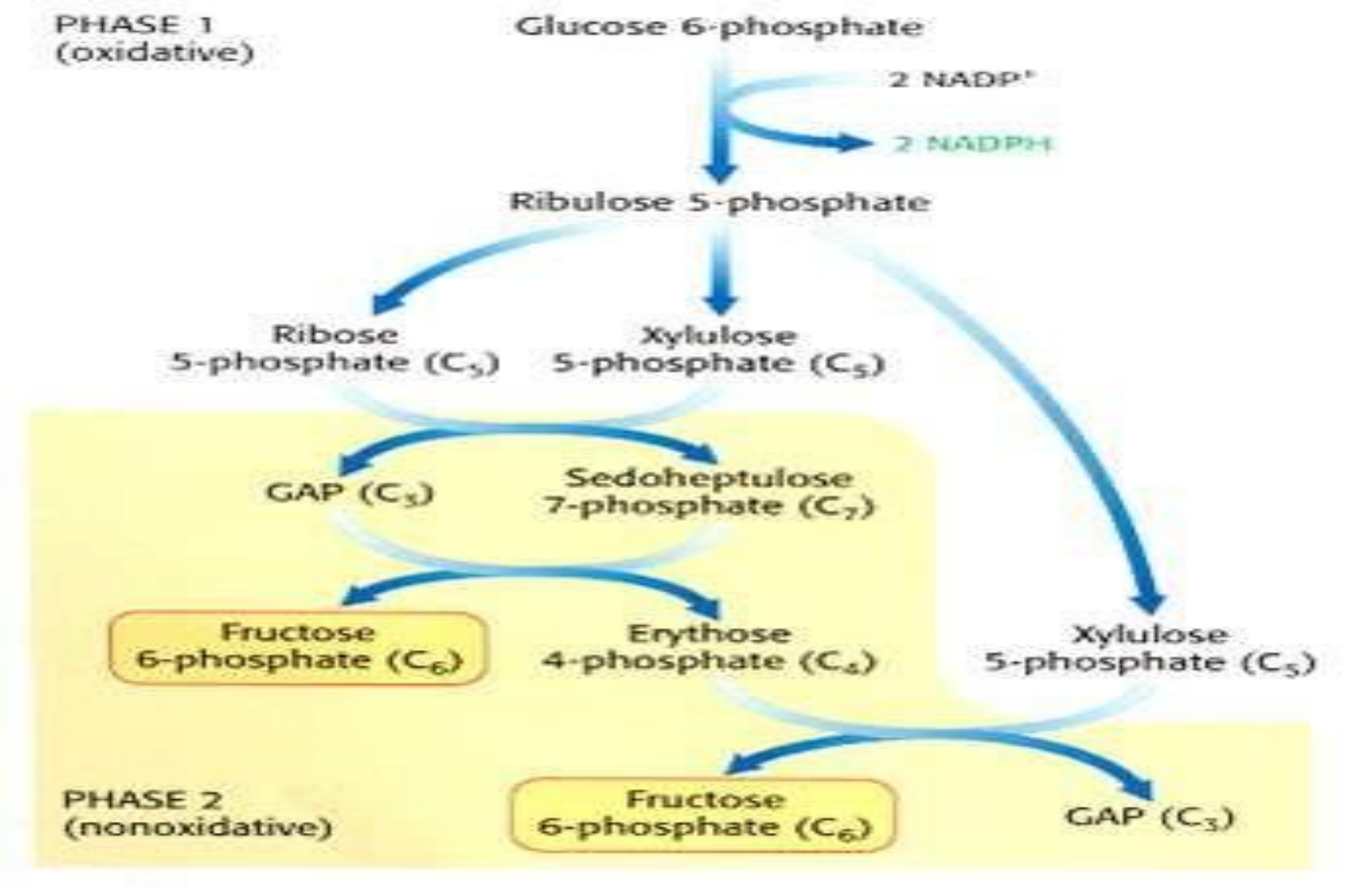
* Anabolic in nature, since it is concerned with the biosynthesis of NADPH and pentoses.

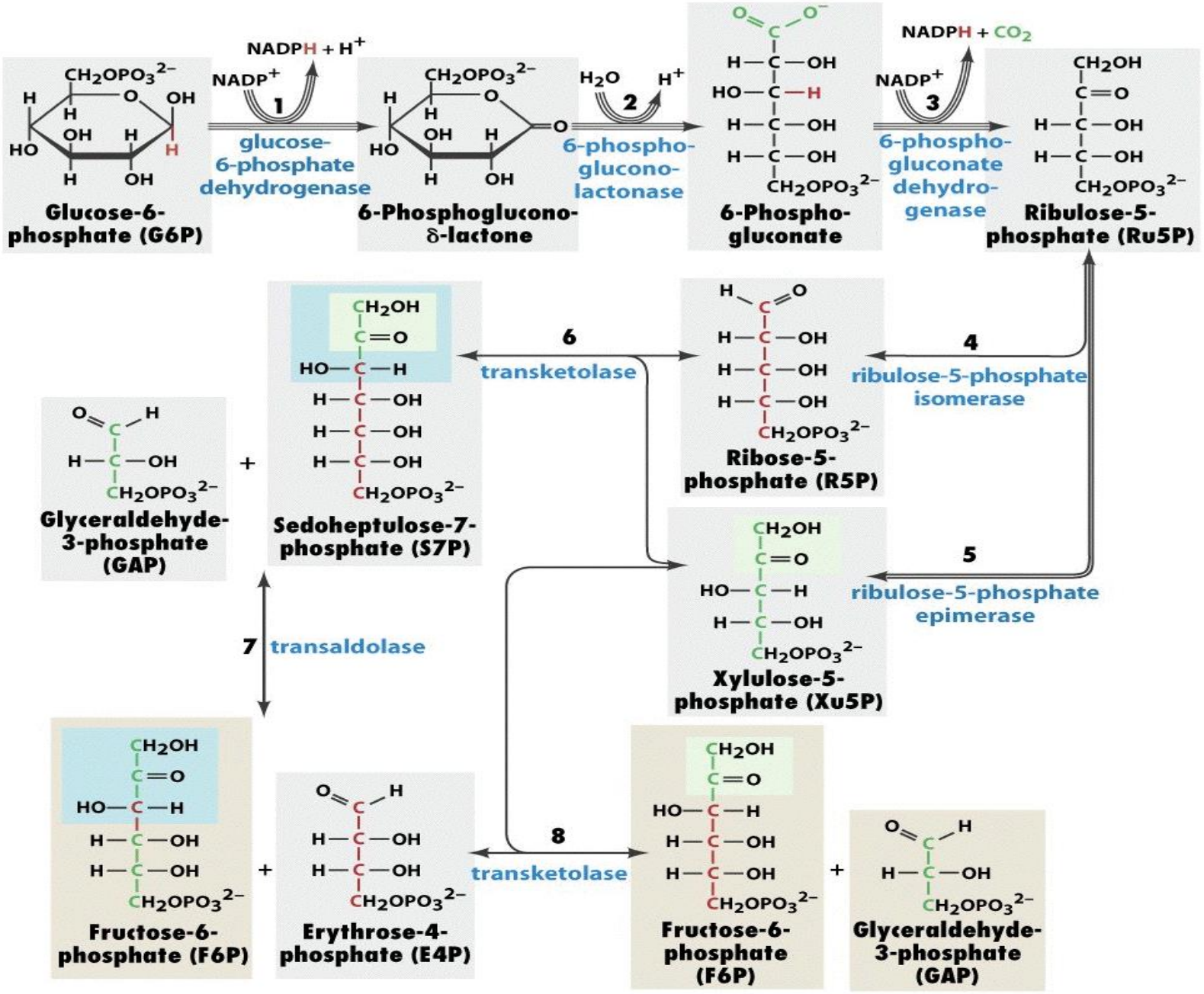
* Unique multifunctional pathway

* Enzymes located – cytosol

*Tissues active – liver, adipose tissue, adrenal gland, erythrocytes, testes and lactating mammary gland.

Reactions of the HMP Shunt Pathway




Glucose-6-phosphate (G6P)
NADP+
NADPH + H+
1
glucose-6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone
H2O
H+
2
6-phospho-gluconolactonase
6-Phospho-gluconate
NADP+
NADPH + CO2
3
6-phospho-gluconate dehydro-genase
Ribulose-5-phosphate (Ru5P)
4
ribulose-5-phosphate isomerase
Ribose-5-phosphate (R5P)
6
transketolase
Sedoheptulose-7-phosphate (S7P)
Glyceraldehyde-3-phosphate (GAP)
5
ribulose-5-phosphate epimerase
Xylulose-5-phosphate (Xu5P)
7
transaldolase
Fructose-6-phosphate (F6P)
Erythrose-4-phosphate (E4P)
8
transketolase
Fructose-6-phosphate (F6P)
Glyceraldehyde-3-phosphate (GAP)

Significance of HMP Shunt

- Pentose or its derivatives are useful for the synthesis of nucleic acids and nucleotides.

- NADPH is required :

  -For reductive biosynthesis of fatty acids and steroids.

  - For the synthesis of certain amino acids.

  - Anti-oxidant reaction

  - Hydroxylation reaction– detoxification of drugs.

  - Phagocytosis

  - Preserve the integrity of RBC membrane.

G6PD Deficiency

Introduction

- **Glucose-6-phosphate dehydrogenase deficiency** (**G6PD deficiency**) also known as **favism** (after the fava bean) is an X-linked recessive genetic condition that predisposes to hemolysis and resultant jaundice in response to a number of triggers.
- Mediterranean and African origin.
- The condition is characterized by abnormally low levels of glucose-6- phosphate dehydrogenase, an enzyme involved in the **pentose phosphate pathway** that is especially important in the red blood cell. G6PD deficiency is the most common human enzyme defect.
- All mutations that cause G6PD deficiency are found on the long arm of the X chromosome, on band Xq28.

- **Favism** is defined as a hemolytic response to the consumption of broad beans.
- Not all individuals with G6PD deficiency show favism.
- More prevalent in infants and children, and G6PD genetic variant can influence chemical sensitivity
- 6-phosphogluconate dehydrogenase (6PGD) deficiency has similar symptoms and is often mistaken for G6PD deficiency, as the affected enzyme is within the same pathway, however these diseases are not linked and can be found within the same patient.
- A side effect of this disease is that it confers protection against malaria, in particular the form of malaria caused by *Plasmodium falciparum*, the most deadly form of malaria.

Signs & Symptoms

- Prolonged neonatal jaundice, possibly leading to kernicterus.
- Hemolytic crises in response to:
  - ✓ Illness (especially infections)
  - ✓ Certain drugs
  - ✓ Certain foods, most notably broad beans
  - ✓ Certain chemicals
- Diabetic ketoacidosis
- Very severe crises can cause acute kidney failure

Pathology

- Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in the pentose phosphate.
- G6PD converts glucose-6-phosphate into 6-phosphoglucono-δ-lactone and is the rate-limiting enzyme of this metabolic pathway that supplies reducing energy to cells by maintaining the level of the reduced form of the co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH). The NADPH in turn maintains the supply of reduced glutathione in the cells that is used to mop up free radicals that cause oxidative damage.
- The G6PD / NADPH pathway is the *only* source of reduced glutathione in red blood cells (erythrocytes).

- People with G6PD deficiency are therefore at risk of hemolytic anemia in states of oxidative stress.
- Broad beans, e.g., fava beans, contain high levels of vicine, divicine, convicine and isouramil, all of which create oxidants. The molecules are reducing agents but reduce oxygen to hydrogen peroxide, itself a strong oxidising agent.
- When all remaining reduced glutathione is consumed, enzymes and other proteins (including hemoglobin) are subsequently damaged by the oxidants, leading to cross-bonding and protein deposition in the red cell membranes.
- Damaged red cells are phagocytosed and sequestered in the spleen.
- The hemoglobin is metabolized to bilirubin (causing jaundice at high concentrations).
- The red cells rarely disintegrate in the circulation, so hemoglobin is rarely excreted directly by the kidney, but this can occur in severe cases, causing acute renal failure.

Drugs

Many substances are potentially harmful to people with G6PD deficiency. Variation in response to these substances makes individual predictions difficult.

- Antimalarial drugs that can cause acute hemolysis in people with G6PD deficiency include primaquine, pamaquine, and chloroquine.
- Sulfonamides (such as sulfanilamide, sulfamethoxazole, and mafenide), thiazolesulfone, methylene blue, and naphthalene should also be avoided by people with G6PD deficiency as they **antagonize folate synthesis**
- Certain analgesics (such as aspirin, phenazopyridine, and acetanilide).
- Henna has been known to cause hemolytic crisis in G6PD-deficient infants.

Classification

The World Health Organization classifies G6PD genetic variants into five classes, the first three of which are deficiency states.

- Class I: Severe deficiency (<10% activity) with chronic (nonspherocytic) hemolytic anemia
- Class II: Severe deficiency (<10% activity), with intermittent hemolysis
- Class III: Mild deficiency (10-60% activity), hemolysis with stressors only
- Class IV: Non-deficient variant, no clinical sequelae
- Class V: Increased enzyme activity, no clinical sequelae

GLYCOGEN METABOLISM

- ✓Glycogen is a storage form of glucose in animals.
- ✓Stored mostly in liver (6-8%) and muscle (1-2%)
- ✓Due to muscle mass the quantity of glycogen in muscle = 250g and liver =75g
- ✓Stored as granules in the cytosol.
- ✓Functions : Liver glycogen – maintain the blood glucose level
  Muscle glycogen – serves as fuel reserve

GLYCOGENESIS

- Synthesis of glycogen from glucose.
- Takes place in cytosol.
- Requires UTP and ATP besides glucose.
- Steps in synthesis :

1) Synthesis of UDP- glucose
2) Requirement of primer to initiate glycogenesis
3) Glycogen synthesis by glycogen synthase
4) Formation of branches in glycogen

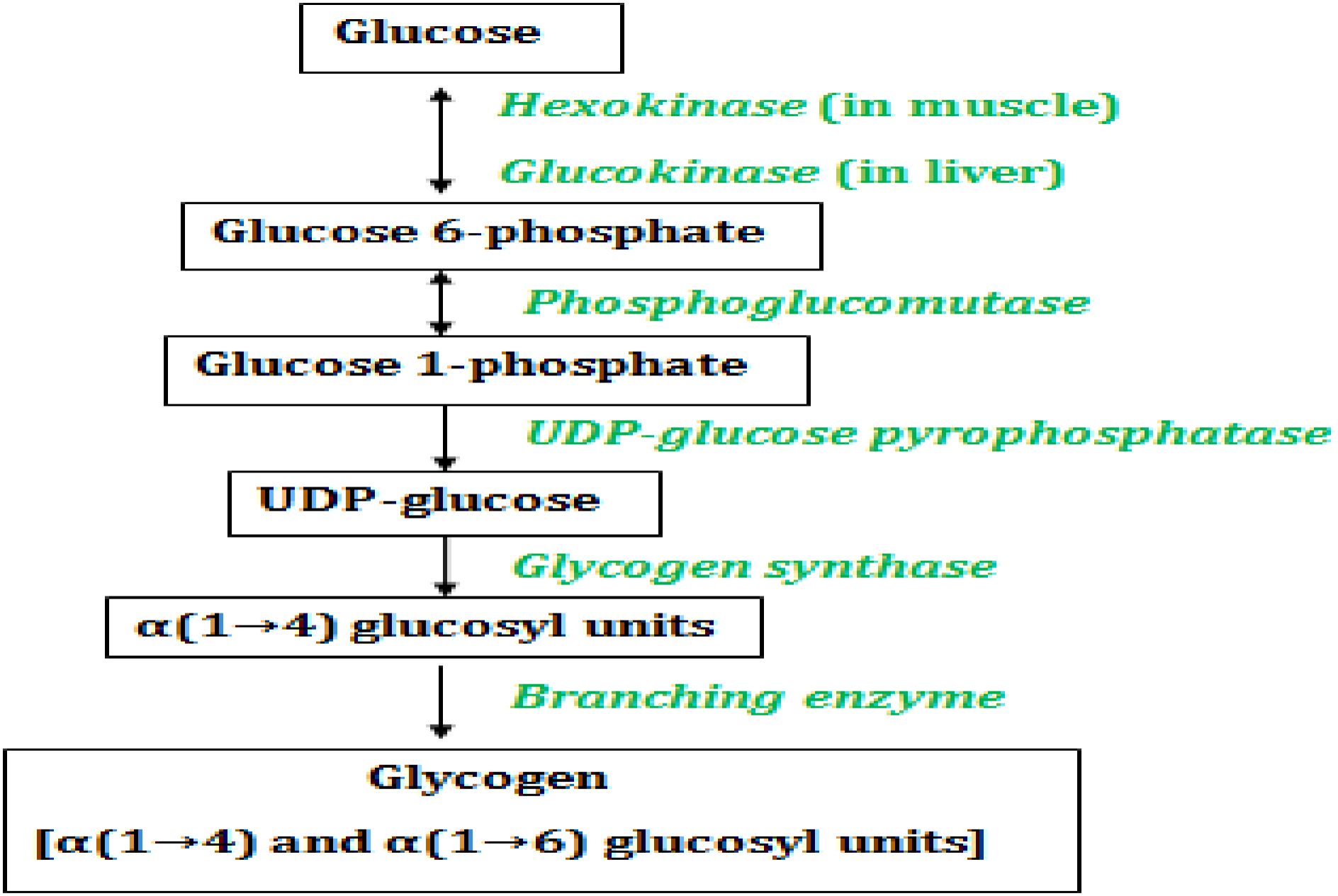


Diagram: Steps of glycogenesis

GLYCOGENOLYSIS

- Degradation of stored glycogen in liver and muscle constitutes glycogenolysis.

- Irreversible pathway takes place in cytosol.

- Hormonal effect on glycogen metabolism :
1) Elevated glucagon – increases glycogen degradation
2) Elevated insulin – increases glycogen synthesis

- Degraded by breaking majorly α-1,4- and α-1,6-glycosidic bonds.

- Steps in glycogenolysis:
1) Action of glycogen phosphorylase
2) Action of debranching enzyme
3) Formation of glucose-6-phosphate and glucose

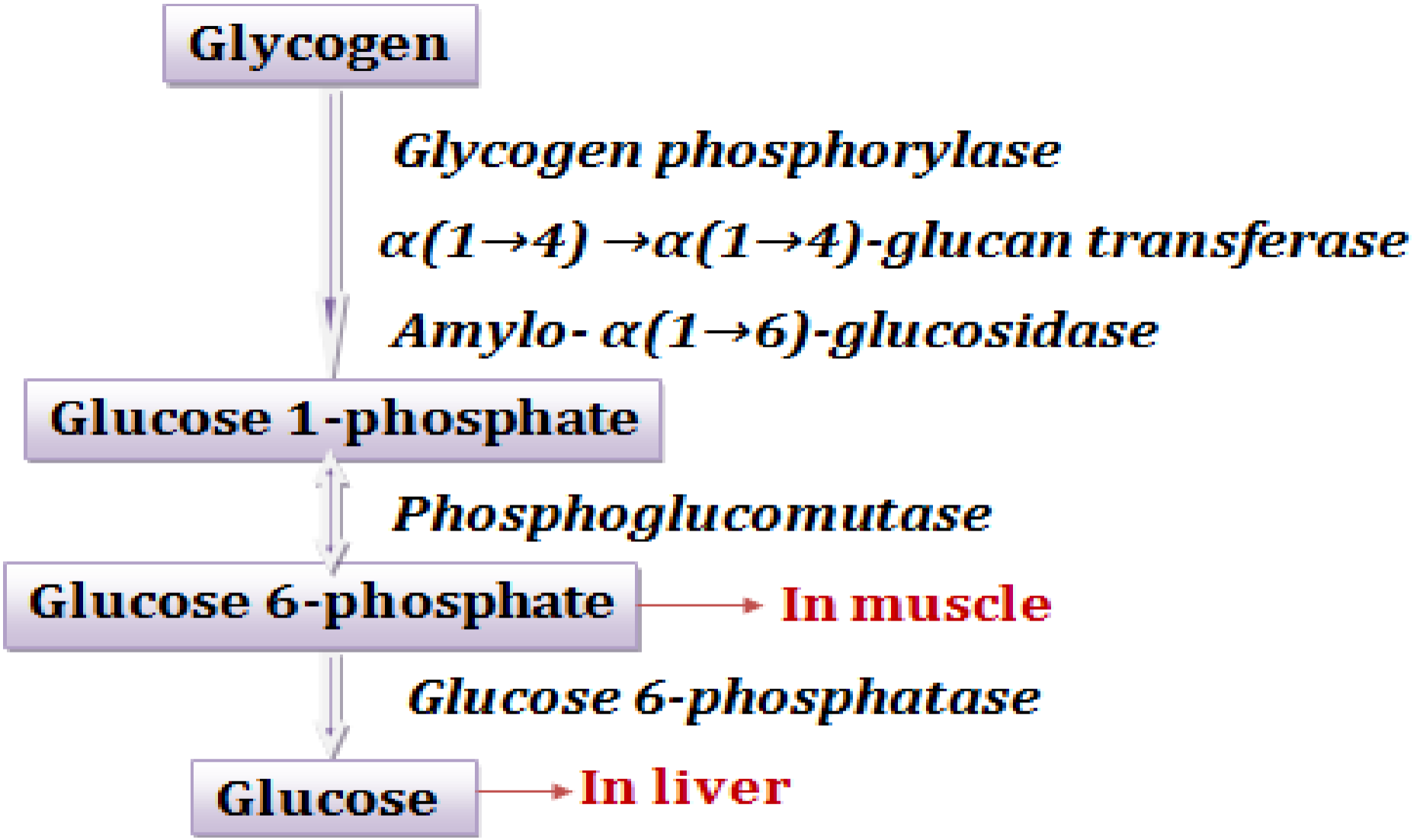


Diagram: Steps of glycogenolysis

Glycogen storage diseases

TYPE	ENZYME DEFECT	CLINICAL FEATURES
Type I (Von Gierke's disease)	Glucose-6-phosphatase deficiency.	Hypoglycemia, enlarged liver and kidneys, gastro-intestinal symptoms, Nose bleed, short stature, gout
Type II (Pompe's disease)	Acid maltase deficiency	Diminished muscle tone, heart failure, enlarged tongue
Type III (Cori's disease,Forbe disease)	Debranching enzyme deficiency	Hypoglycemia, enlarged liver, cirrhosis, muscle weakness, cardiac involvement
Type IV (Andersen's disease)	Branching enzyme deficiency	Enlarged liver & spleen, cirrhosis, diminished muscle tone, possible nervous system involvement
Type V (Mcardle's disease)	Muscle phosphorylase deficiency	Muscle weakness, fatigue and muscle cramps

TYPE	ENZYME DEFECT	CLINICAL FEATURES
Type VI (Her's disease)	Liver phosphorylase deficiency	Mild hypoglycemia, enlarged liver, short stature in childhood
Type VII (Tarui's disease)	Phosphofructokinase deficiency	Muscle pain, weakness and decreased endurance
Type VIII	Liver phosphorylase kinase	Mild hypoglycemia, enlarged liver, short stature in childhood, possible muscle weakness and cramps
Type 0	Liver glycogen synthetase	Hypoglycemia, possible liver enlargement

GLUCONEOGENESIS

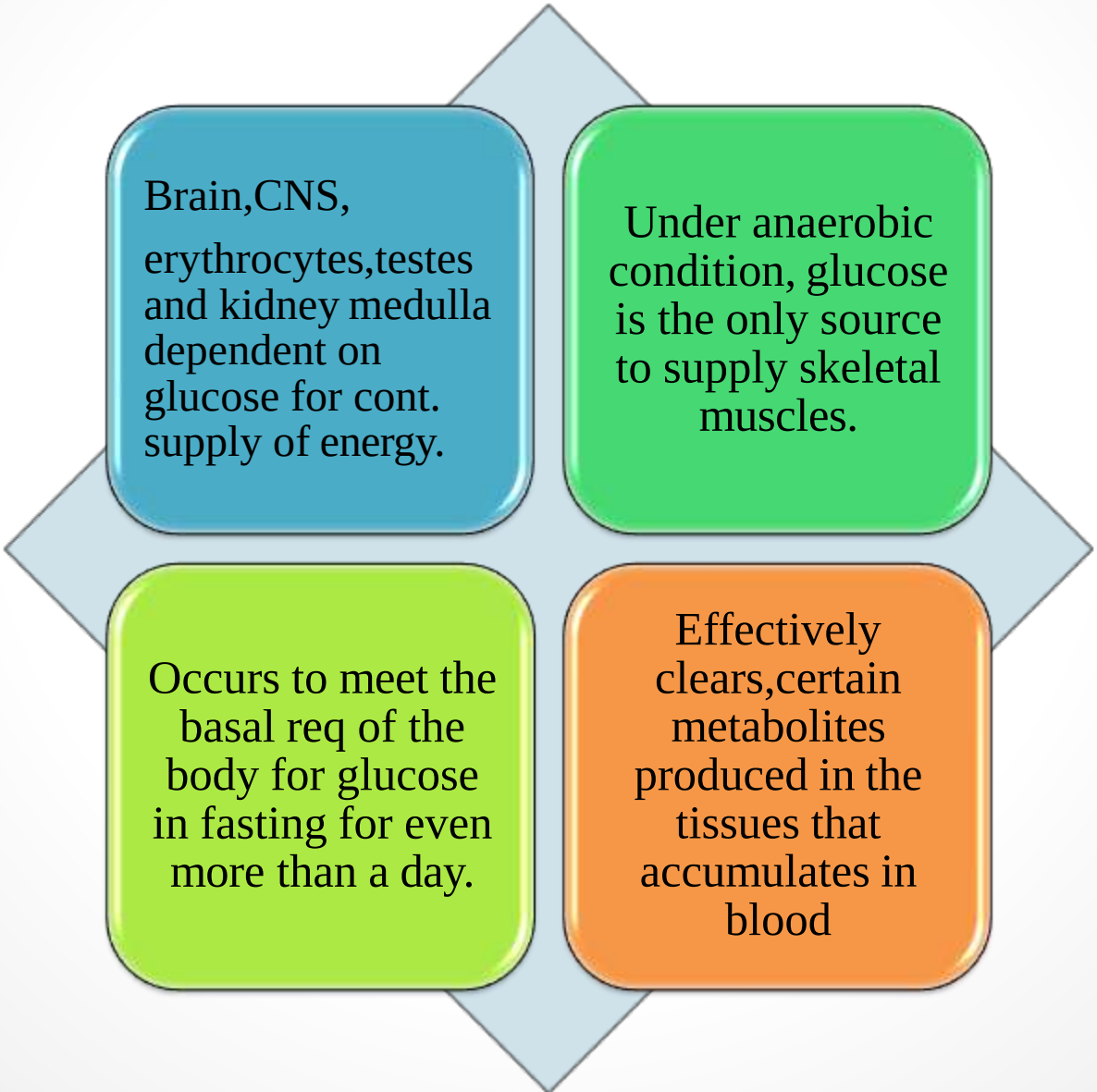
The synthesis of glucose from non-carbohydrate compounds is known as gluconeogenesis.

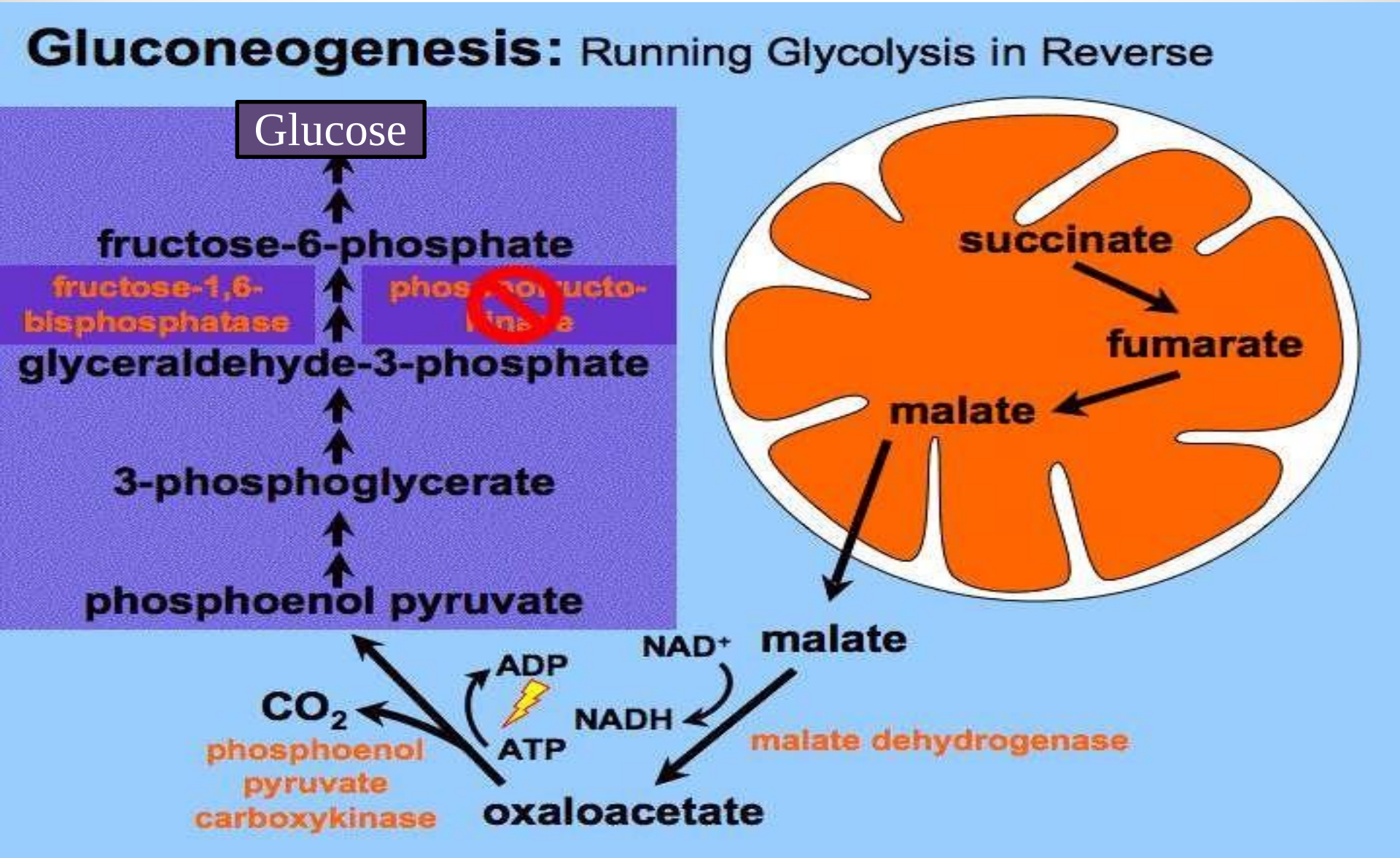
Major substrate/precursors : lactate, pyruvate, glycogenic amino acids, propionate & glycerol.

-Takes place in liver (1kg glucose) ; kidney matrix($1/3^{rd}$).

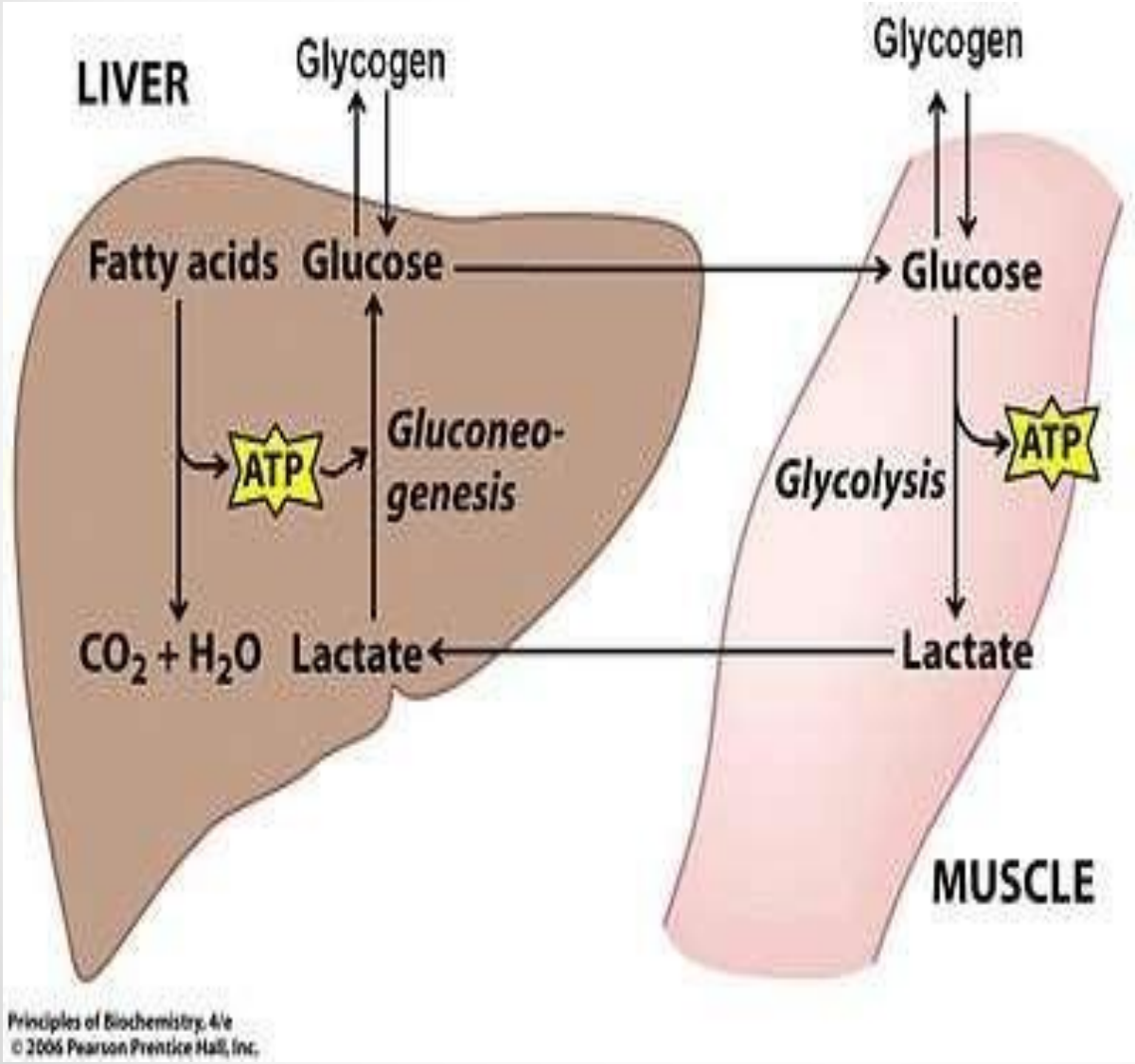
- Occurs in cytosol and some produced in mitochondria.

Importance of Gluconeogenesis



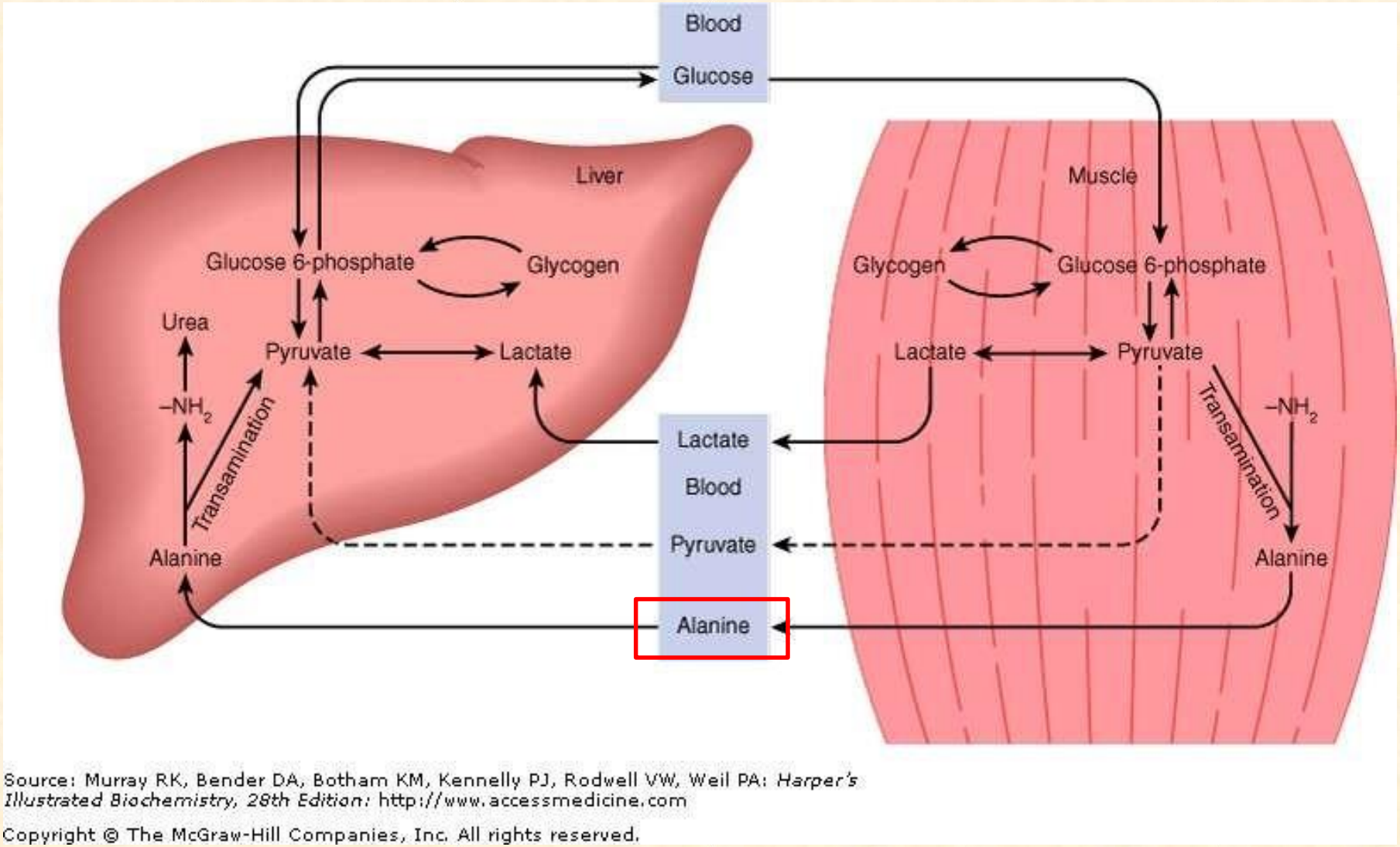

Gluconeogenesis: Running Glycolysis in Reverse
Glucose
fructose-6-phosphate
fructose-1,6-bisphosphatase
glyceraldehyde-3-phosphate
3-phosphoglycerate
phosphoenol pyruvate
succinate
fumarate
malate
malate
NAD+
NADH
malate dehydrogenase
ADP
ATP
CO2
phosphoenol pyruvate carboxykinase
oxaloacetate

Cori Cycle



The cycle involves the **synthesis of glucose in liver from the skeletal muscle lactate** and the reuse of glucose thus synthesized by the muscle for energy purpose is known as Cori cycle.

Glucose-Alanine Cycle



Source: Murray RK, Bender DA, Botham KM, Kennelly PJ, Rodwell VW, Weil PA: *Harper's Illustrated Biochemistry, 28th Edition:* http://www.accessmedicine.com

Significance of Gluconeogenesis

- Glucose occupies a key position in the metabolism and its continuous supply is absolutely essential to the body.
- Brain and CNS, erythrocytes, testes and kidney medulla are dependant on glucose for continuous supply.
- Glucose is the only source that supplies energy to the skeletal muscle, under anaerobic conditions.
- In fasting, gluconeogenesis must occur to meet the basal requirements of the body for glucose.

HORMONAL REGULATION OF CARBOHYDRATE METABOLISM

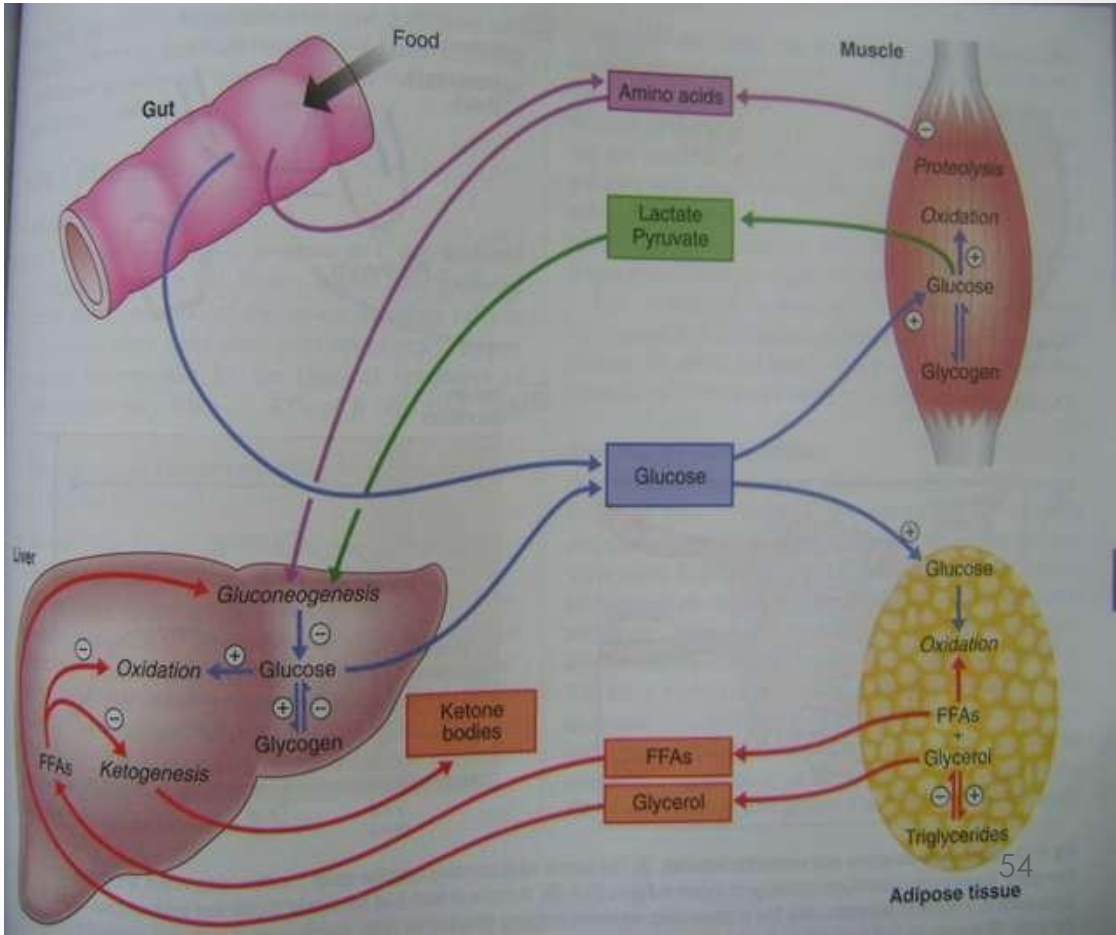
Regulation of Blood glucose

- Postabsorptive state: Blood glucose is 4.5-5.5mmol/L.
- After carbohydrate meal: 6.5-7.2mmol/L
- During fasting : 3.3-3.9mmol/L

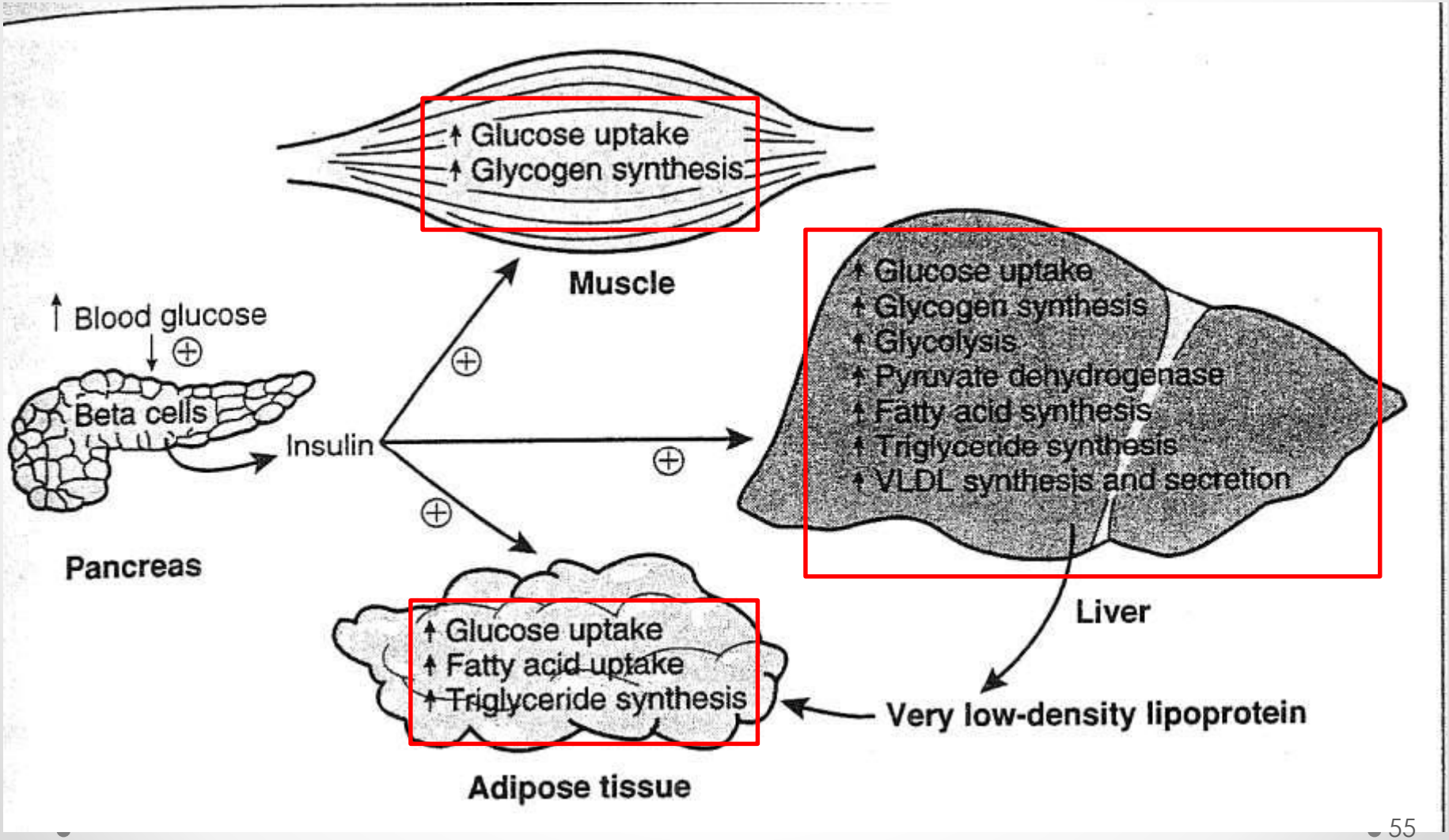
Metabolic & hormonal mechanisms regulate blood glucose level

Maintenance of stable levels of glucose in blood is by

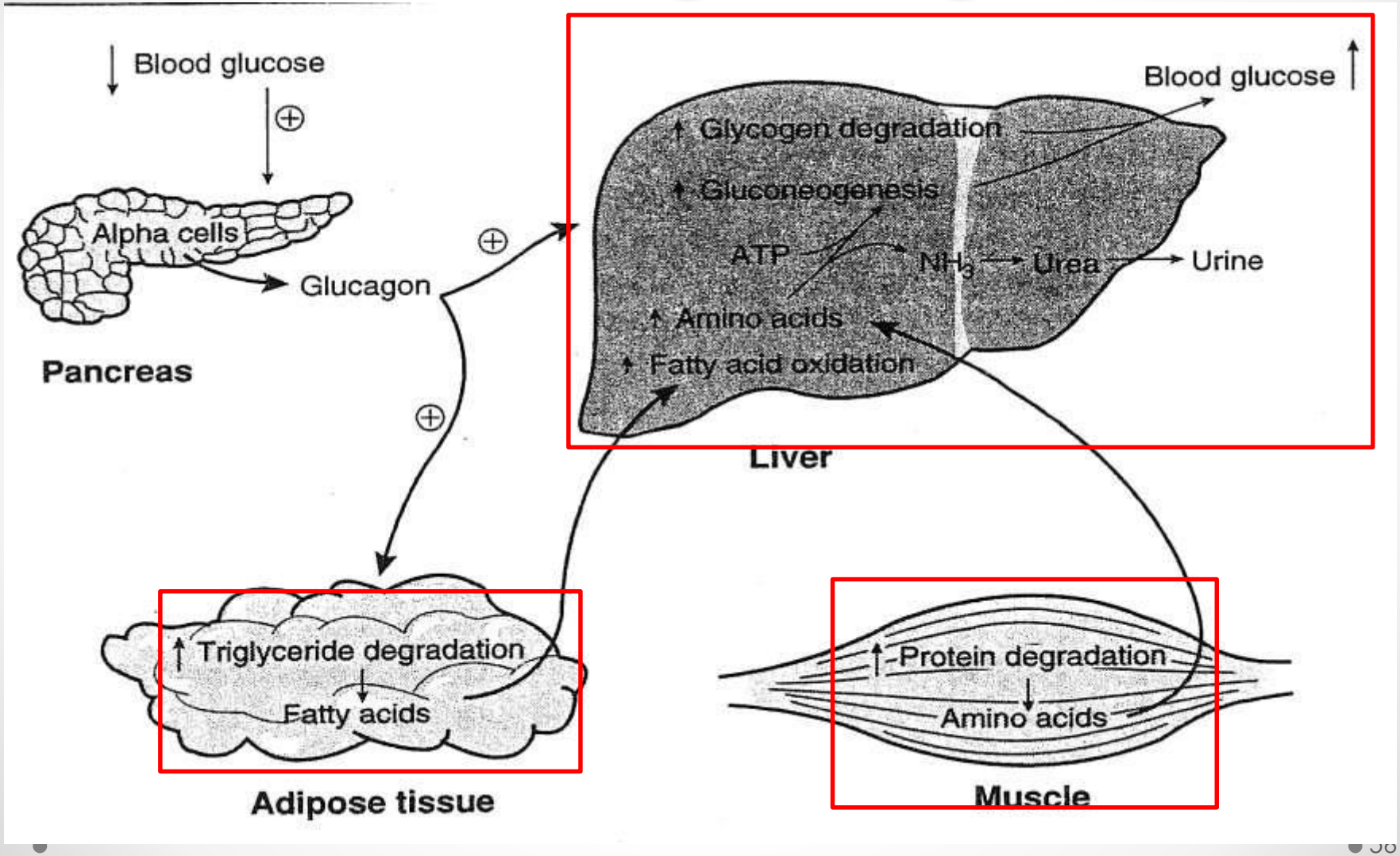
- ✓ Liver.
- ✓ Extrahepatic tissues.
- ✓ Hormones .



Regulation of blood glucose levels
Insulin



Role of glucagon



Role of thyroid hormone

- ✓ It stimulates glycogenolysis & gluconeogenesis.

Hypothyroidism

- Fasting blood glucose is lowered.
- Patients have decreased ability to utilise glucose.
- Patients are less sensitive to insulin than normal or hyperthyroid patients.

Hyperthyroid

- Fasting blood glucose is elevated
- Patients utilise glucose at normal or increased rate

Glucocorticoids

- ✓ Glucocorticoids are antagonistic to insulin.
- ✓ Inhibit the utilisation of glucose in extrahepatic tissues.
- ✓ Increased gluconeogenesis .

Epinephrine

- ✓ Secreted by adrenal medulla.
- ✓ It stimulates glycogenolysis in liver & muscle.
- ✓ It diminishes the release of insulin from pancreas.

Other Hormones

- Anterior pituitary hormones

Growth hormone:

- ✓ Elevates blood glucose level & antagonizes action of insulin.
- ✓ Growth hormone is stimulated by hypoglycemia (decreases glucose uptake in tissues)
- ✓ Chronic administration of growth hormone leads to diabetes due to B cell exhaustion.

SEX HORMONES

- ✓Estrogens cause increased liberation of insulin.

- ✓Testosterone decrease blood sugar level.

Hyperglycemia

- Thirst, dry mouth
- Polyuria
- Tiredness, fatigue
- Blurring of vision.
- Nausea, headache,
- Hyperphagia
- Mood change

Hypoglycemia

- Sweating
- Trembling,pounding heart
- Anxiety, hunger
- Confusion, drowsiness
- Speech difficulty
- Incoordination.
- Inability to concentrate

Clinical aspects

- ✓ Glycosuria: occurs when venous blood glucose concentration exceeds

  9.5-10.0mmol/L

- ✓ Fructose-1,6-Biphosphatase deficiency causes lactic acidosis & hypoglycemia..

Diabetes Mellitus

A multi-organ catabolic response caused by insulin insufficiency

Muscles

- Protein catabolism for gluconeogenesis

Adipose tissue

- Lipolysis for fatty acid release

Liver

- Ketogenesis from fatty acid oxidation
- Gluconeogenesis from amino acids and glycerol

Kidney

- Ketonuria and cation excretion
- Renal ammonia genesis