Faculty of Pharmacy
Biochemistry-2

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Lecturer of Biochemestry

Lecture 4

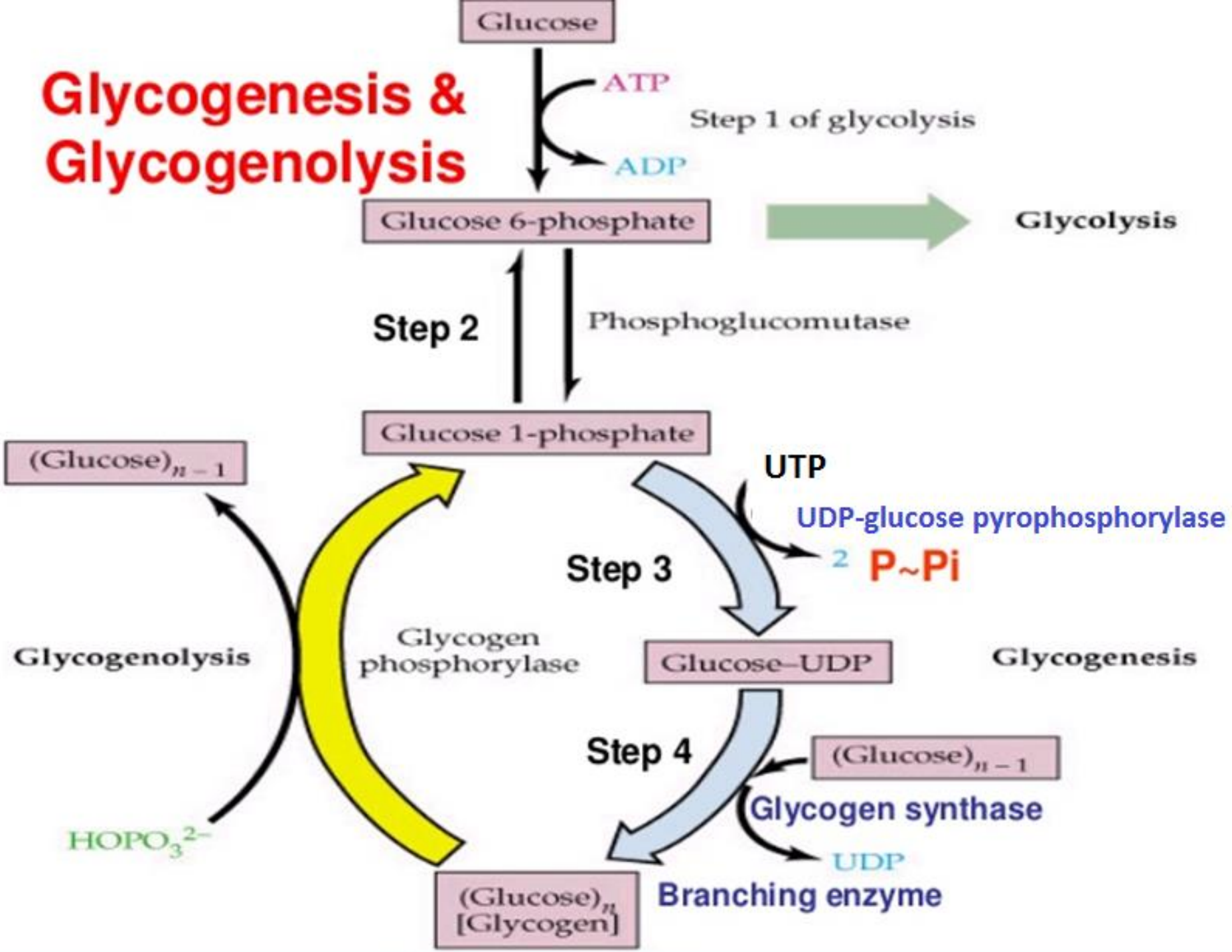
Glycogen Metabolism

- Glycogen is a polysaccharide present mainly in liver and muscles of human, acting as a reserve or storage form of glucose. Its metabolism involves two processes, namely glycogenesis and glycogenolysis

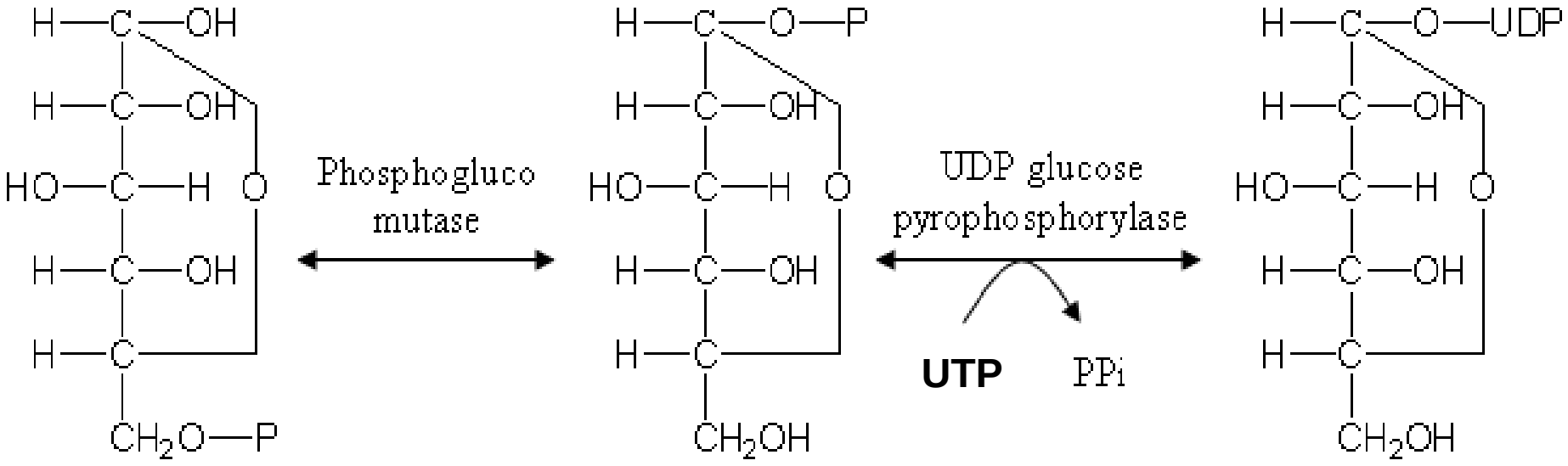
1- Glycogenesis

- **Definition:** Synthesis of glycogen from glucose. It occurs in all tissues of the body, but chiefly in liver and muscles.

Site: Cytosol of muscle and liver cells


Glycogenesis &
Glycogenolysis
Glucose
ATP
Step 1 of glycolysis
ADP
Glucose 6-phosphate
Glycolysis
Step 2
Phosphoglucomutase
Glucose 1-phosphate
(Glucose)n – 1
UTP
UDP-glucose pyrophosphorylase
2 P~Pi
Step 3
Glycogenolysis
Glycogen phosphorylase
Glucose–UDP
Glycogenesis
Step 4
(Glucose)n – 1
Glycogen synthase
UDP
HOPO3 2–
(Glucose)n
[Glycogen]
Branching enzyme

Activation of Glucose



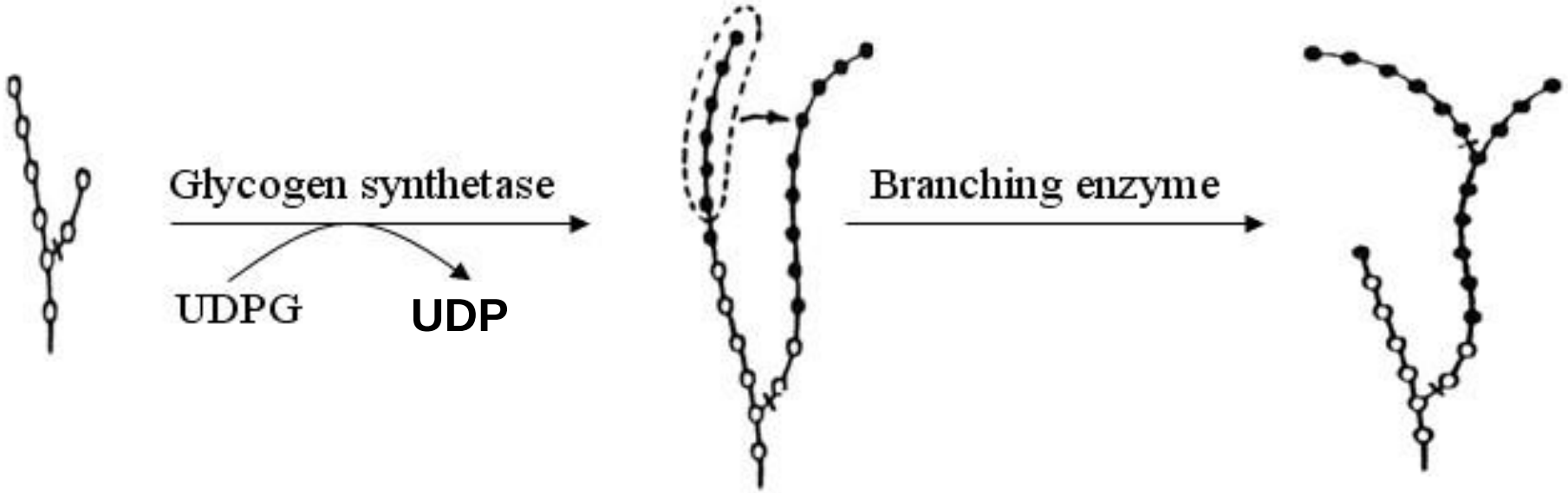
Glucose 6-phosphate

Glucose 1-phosphate

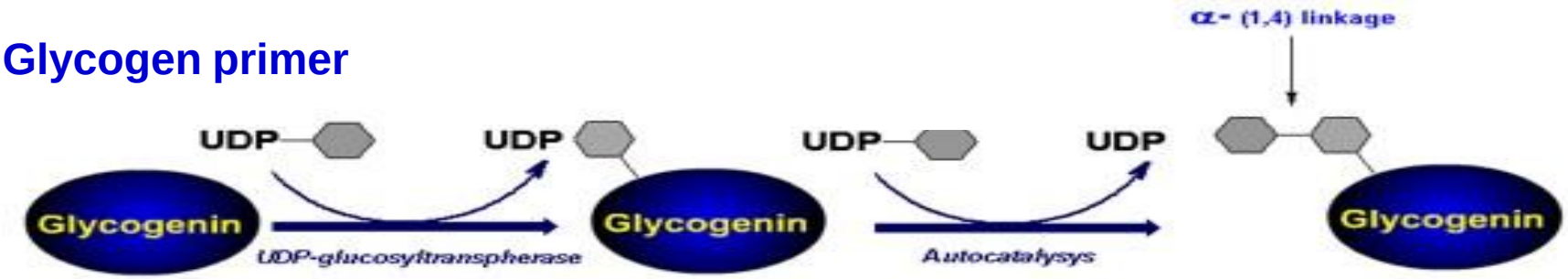
Uridine diphosphate glucose

- **Glycogen synthase** enzyme catalyses the transfer of glucose units of UDP–Glucose to a pre– existing glycogen molecule or glycogen primer.
- C_1 of UDP–Glucose forms a glycosidic bond with C_4 of a terminal glucose residue of glycogen, liberating free UDP.
- When the chain has been lengthened to between 8 and 12 glucose residues, the **branching enzyme** transfers a part of the 1,4–chain to a neighboring chain to form 1,6–linkage, thus establishing a branching point in the molecule.

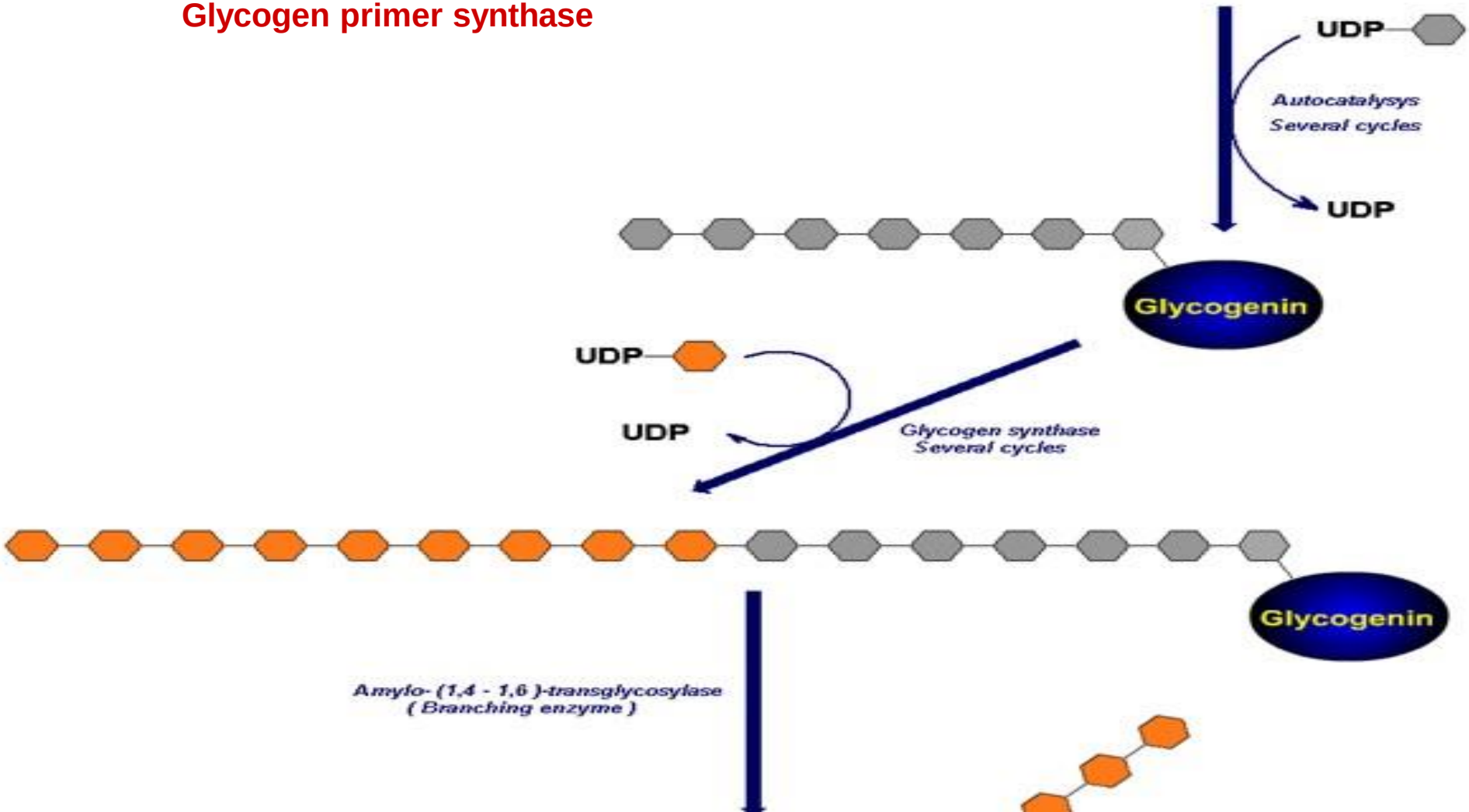
Glycogen Synthase & Branching Enzymes

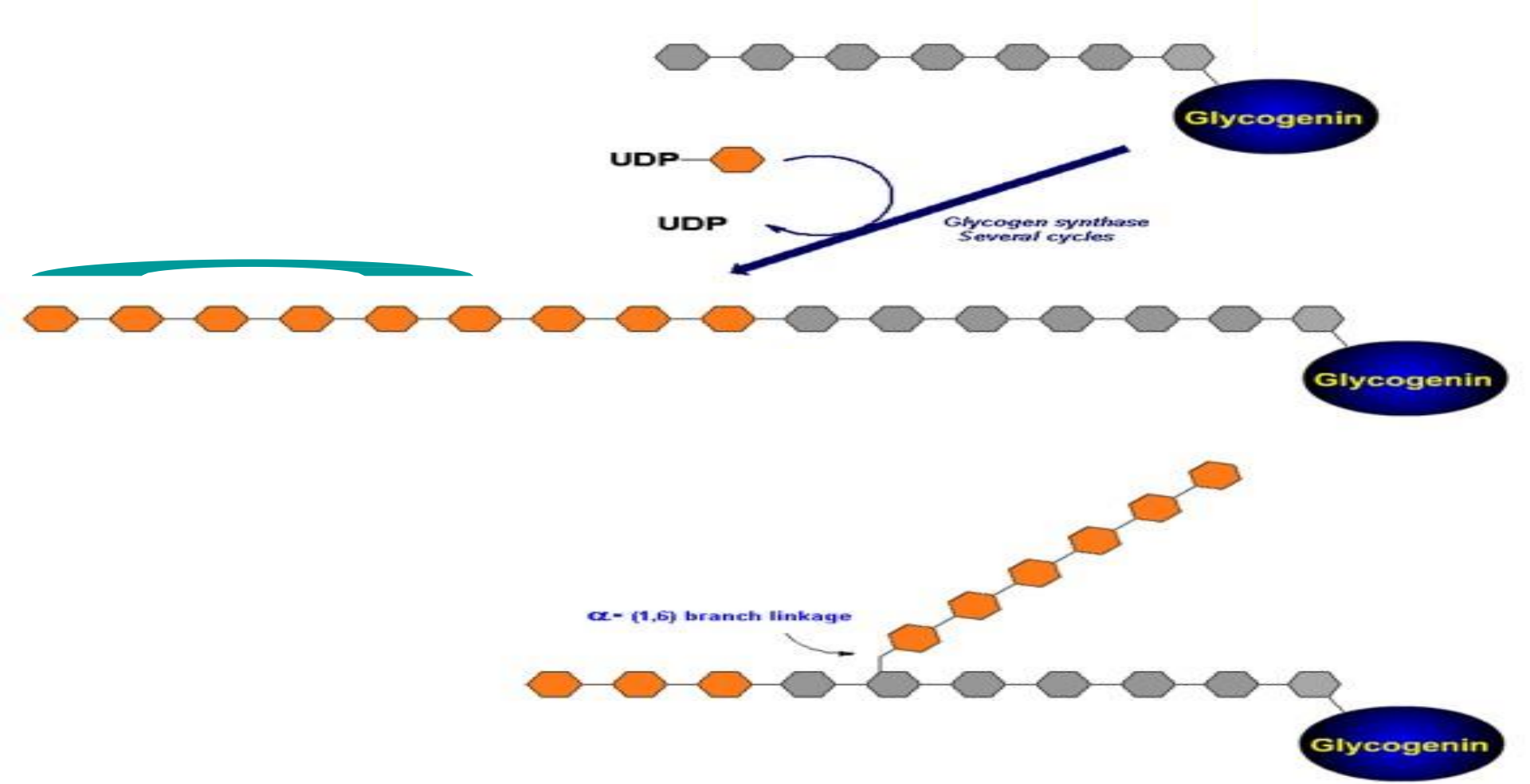


Glycogen primer



Glycogen primer synthase




Glycogenin
UDP
UDP
Glycogen synthase
Several cycles
Glycogenin
α- (1,6) branch linkage
Glycogenin

Glycogenesis

- **Glycogenesis is Stimulated by:**

1	Carbohydrate diet	Releases insulin
2	Insulin	Direct effect
3	G6P	Allosteric effect
4	ATP	Allosteric effect

Glycogenesis

- **Glycogenesis is Inhibited by:**

1	Fasting	Releases adrenaline & glucagon
2	Adrenaline	Direct effect
3	Glucagon	Direct effect
4	Thyroxin	Direct effect

2- Glycogenolysis

- **Definition** It is the breakdown of glycogen into glucose in liver or into lactic acid in muscles.

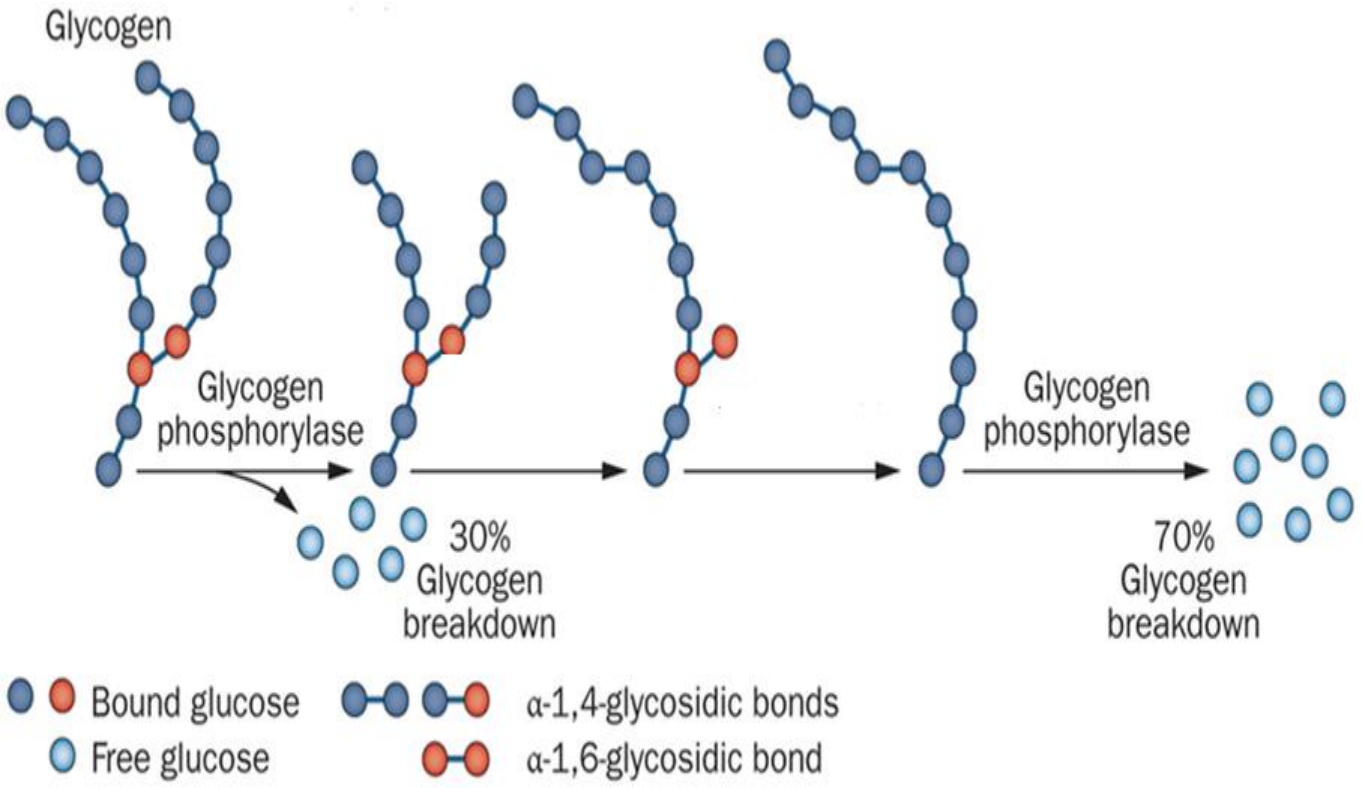
In liver, glycogenolysis maintains the blood glucose level during fasting for less then 18 hours. **In muscles**, glycogenolysis is followed by glycolysis supply the contracting muscle with energy during muscular exercise.

- **Site** Cytoplasm of cells.
- **Steps** Glycogen breakdown is catalyzed by 3 enzymes:

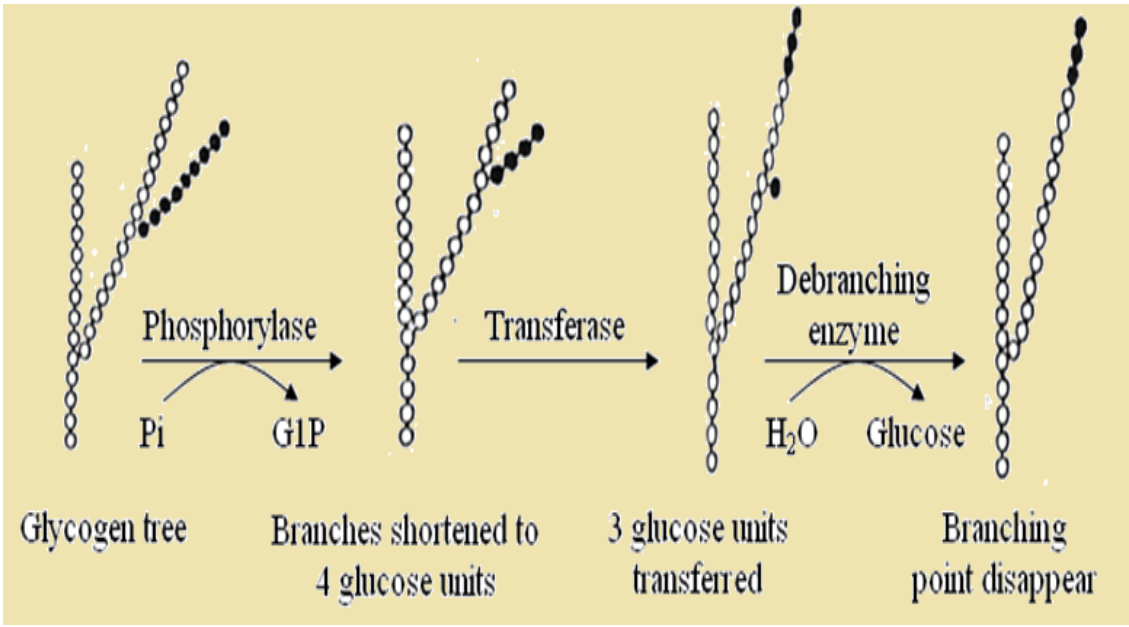
A. **The cleavage of α-1,4 bonds catalyzed by Glycogen phosphorylase:** It acts at the 1,4- glucosidic linkages yielding glucose-1-P. It acts on the ends of glycogen chains & stops when there are four glucose units away from a branch point.

B. **The removal of α-1,6 bonds catalyzed by Transferase:** transfers a trisaccharide unit from one side to the other, thus exposing the 1,6-linkage (branching point).

C. **Degradation of Glycogen Chains catalyzed by: Debranching enzyme:** acts on the 1,6-linkage to liberate a free glucose residue.



Glycogen Metabolism



- Then by the action of **phosphoglucomutase** (Reversible), glucose-1-phosphate can be converted to glucose -6- phosphate.
- In liver and kidney, there is a specific enzyme **glucose-6-phosphatase**, (absent in muscle), that removes phosphate from G6P enabling free glucose to diffuse from the liver cell into the extracellular spaces, including blood, providing nutrient to tissues.
- **Regulation**
- **Phosphorylase** is the key enzyme of glycogenolysis.

Regulation of Glycogenolysis

- G6P inhibits glycogen phosphorylase
- Activation of glycogenolysis during muscle contraction by Calcium.

Differences between liver and muscle glycogen

	Liver glycogen	Muscle glycogen
Sources	Dietary hexoses, gluconeogenesis	Blood glucose
Amount	6 % (about l00gm)	1 % (about 300gm)
Function	Maintenance of blood glucose- Source of energy to liver	Source of energy to muscle
Hydrolysis	Blood glucose	Lactic acid (not give glucose)
E Produced	Used by all tissues	Used by muscles only

Factors Affecting

Diet	Rich in carbohydrates and proteins ↑	Less marked increase
Fasting	Depletion	Little effect
Muscular exercice	Little effect	Depletion

Effect of hormones

Insulin	↑	↑
Glucocorticoids & Growth hormone	↑↑ due to gluconeogenesis	Little ↑ due to hyperglycemia

Glycogen Storage Diseases

- These are inborn errors of metabolism in which one of the enzymes of glycogen metabolism is inactive e.g.

1. **Type I (Von Gierke's Disease):** It results from congenital deficiency of **glucose 6-phosphatase** in liver and kidneys. There is **accumulation of glycogen**. In this disease there is fasting hypoglycemia, hypercholesterolemia and hyperlipemia.

2. **Type III (Cori's disease):** It is characterized by deficiency of **glycogen debranching enzyme**. These patients tend to be hypoglycemic

3. **Type V (McArdle's syndrome):** It is an inherited disease which results from absence of muscle **phosphorylase**. There will be diminished tolerance to exercise, so muscle cramps and reduced blood lactate will occur during exercise

Gluconeogenesis

Gluconeogenesis

- **Definition: It is the formation of glucose from non-carbohydrate sources**
- **Site: Only in the Liver & Kidney**
- **It occurs partly in cytoplasm & partly in mitochondria**

• Importance of Gluconeogenesis:

1. **It is the chief source of blood glucose after the first 18 hours-fasting**
2. **It removes blood lactate produced by RBCs & muscles and blood glycerol produced by adipose tissue or absorbed by intestine**

Sources of Gluconeogenesis

1. Blood Lactate:

- From RBCs and exercising muscles

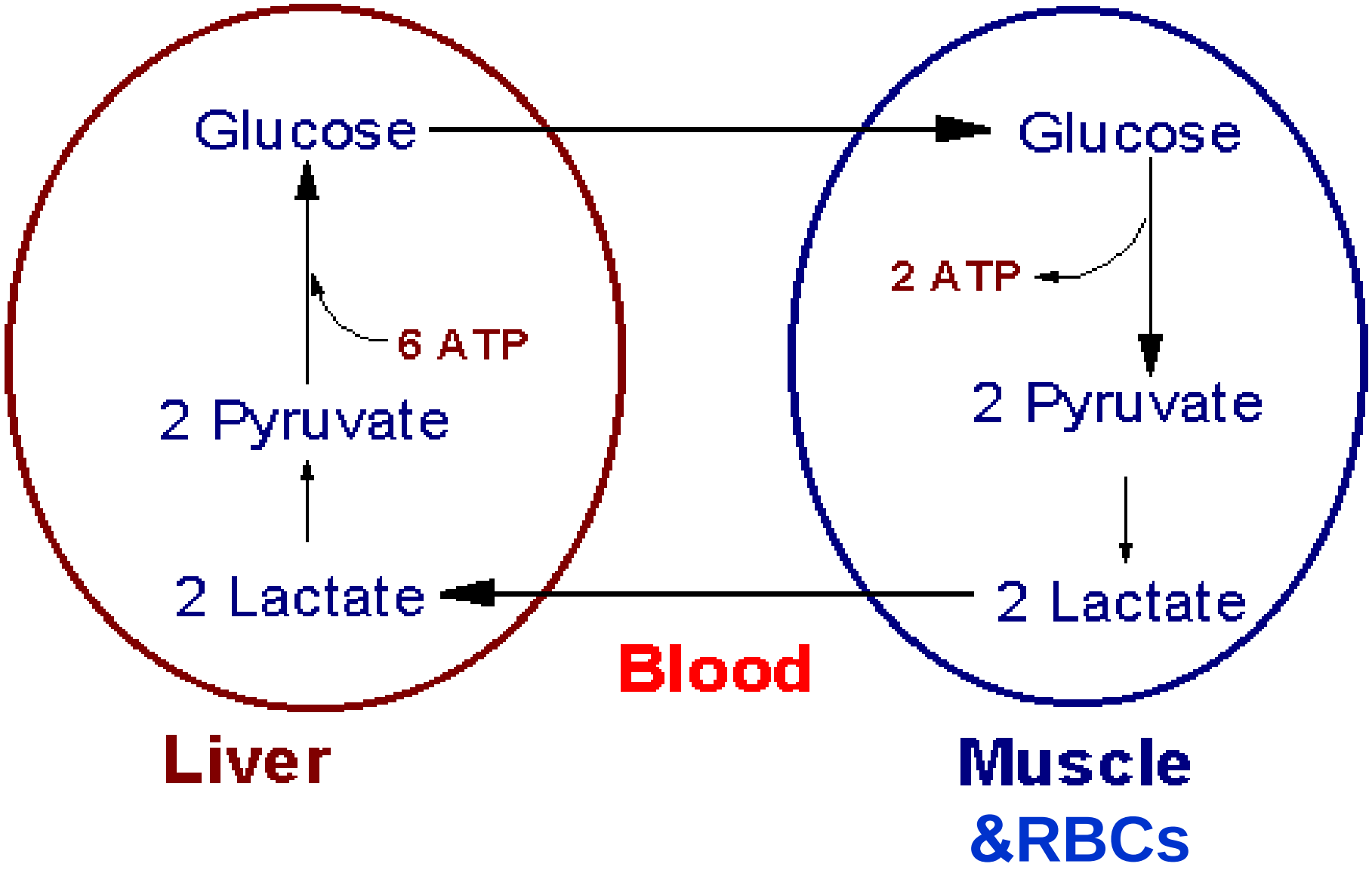
2. Glycerol:

- From adipose or absorbed from intestine

3. Odd chain fatty acids:

4. Glucogenic Amino acids

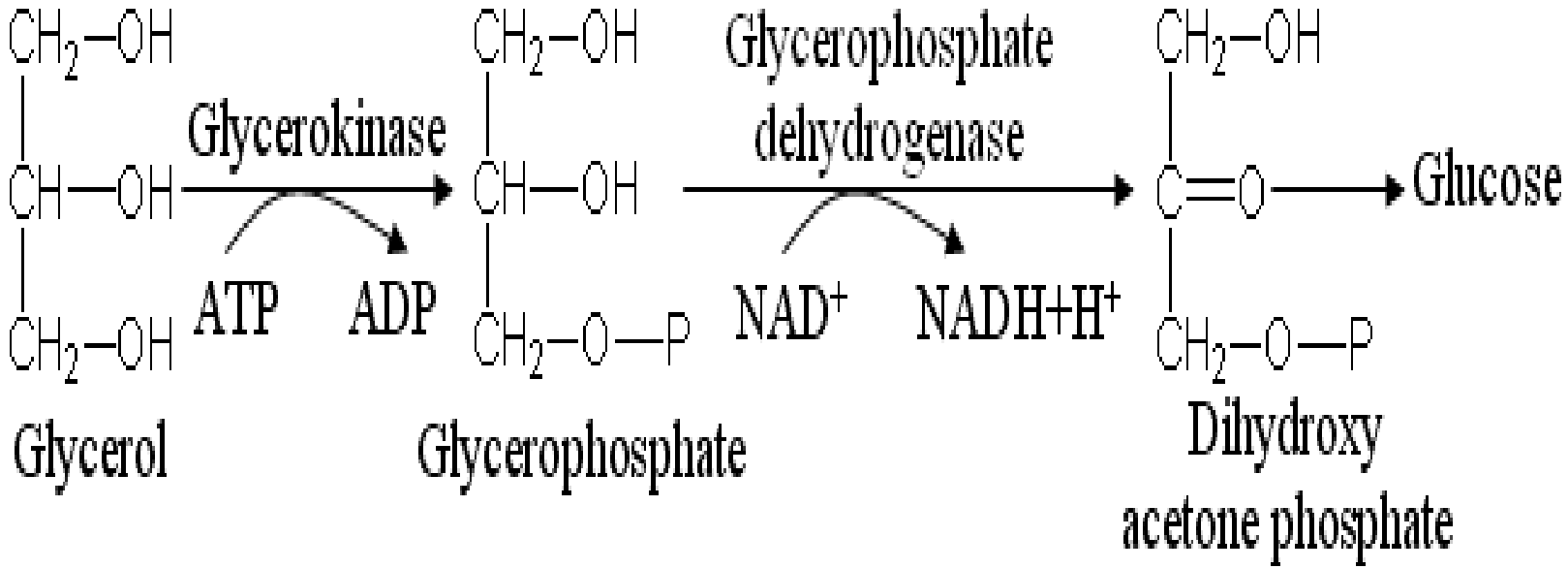
1 The Cori Cycle



2

(Fat)

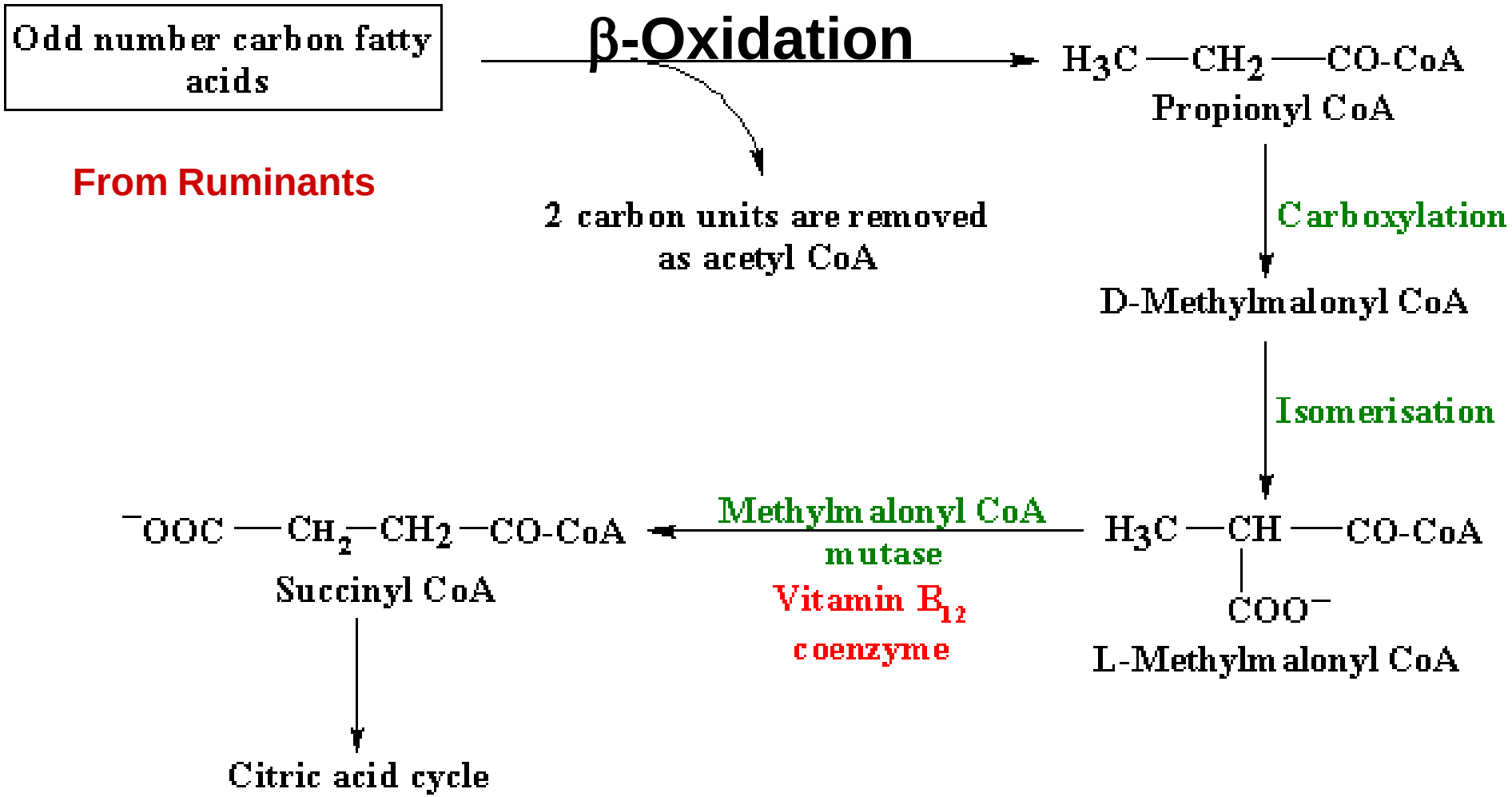
Glycerol: (10% of fats) results from hydrolysis of triglycerides in adipose tissue and diffuses to blood. Also, from digestion of fats in intestine. Glycerol is converted to glucose as follows:



3

Odd chain fatty acids

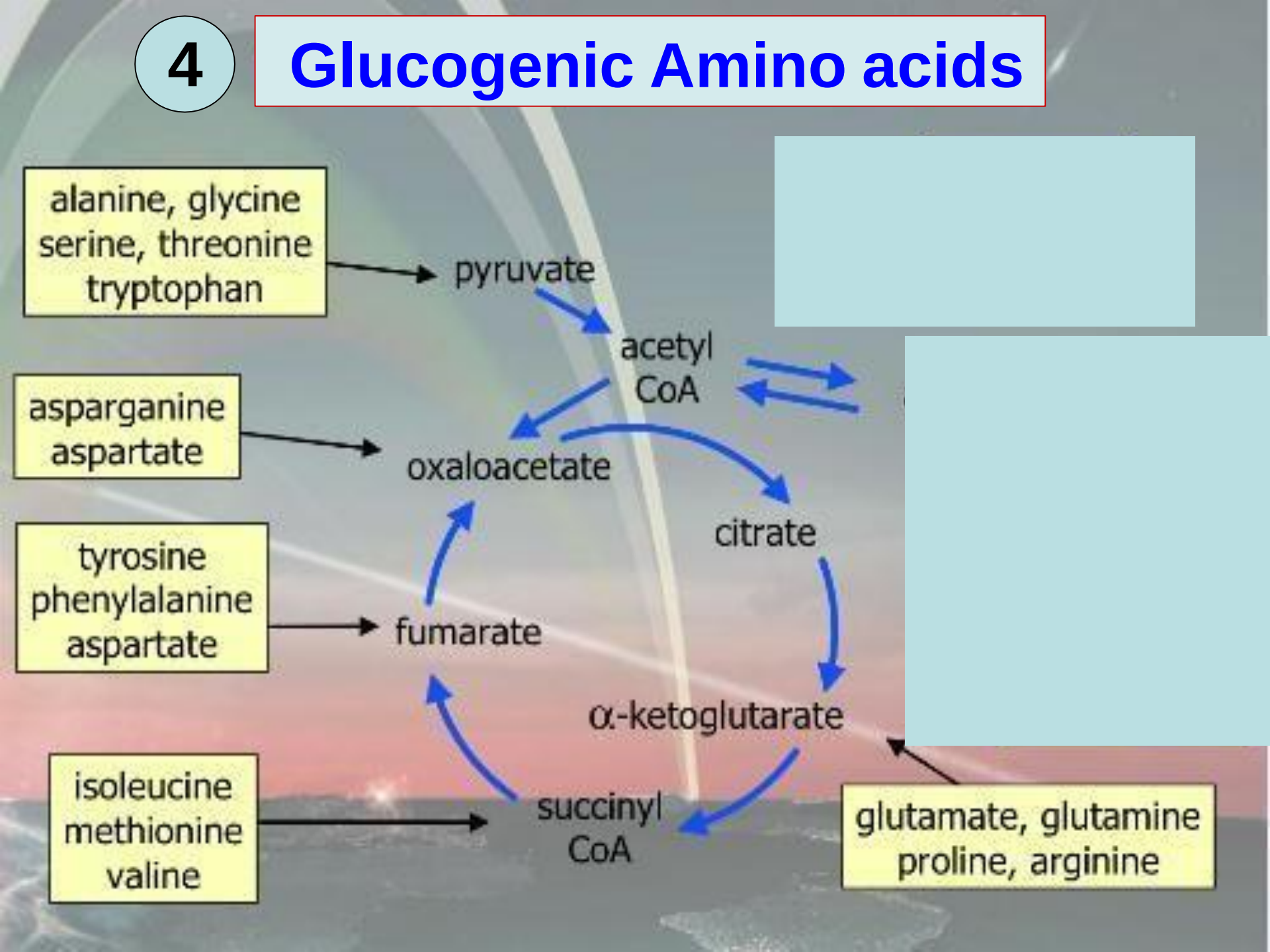
- **Conversion of Propionyl CoA to Succinyl CoA**



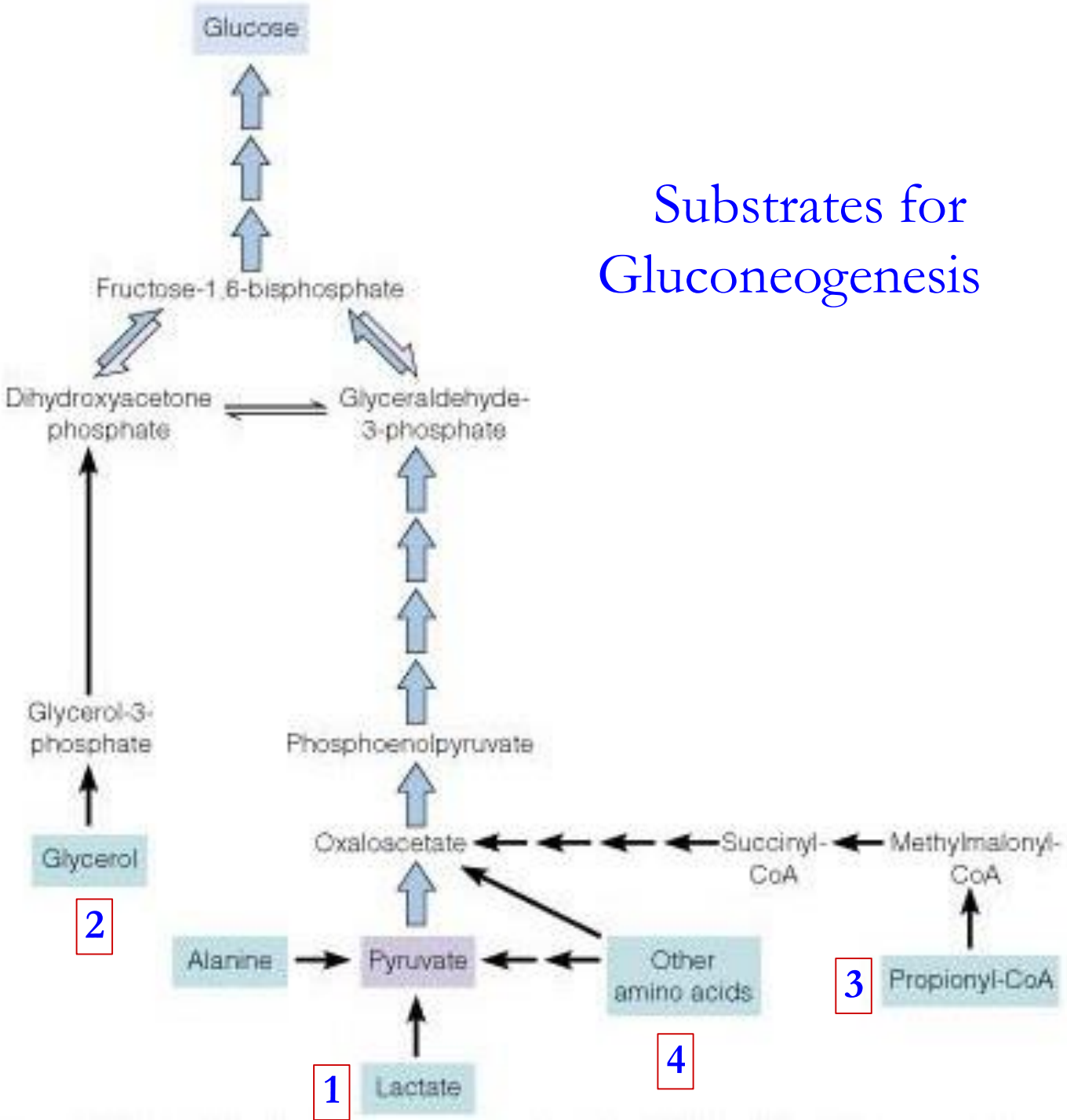
4 Glucogenic Amino acids

Proteins are the most important sources of glucose during fasting after the liver glycogen is depleted, 58% of proteins are convertible to glucose. The glucogenic amino acids are deaminated giving pyruvate or intermediates of kreb's cycle, all of which can be transformed into oxaloacetate that is convertible to glucose by reversal of glycolysis

4 Glucogenic Amino acids



Substrates for Gluconeogenesis



Gluconeogenesis

Gluconeogenesis removes the blood lactate produced by the erythrocytes and skeletal muscle, and the glycerol produced by adipose tissue or absorbed from the intestine.

Steps of gluconeogenesis: By reversal of glycolysis.

The three irreversible steps of glycolysis can be reversed as follows:

Enzymes of Gluconeogenesis

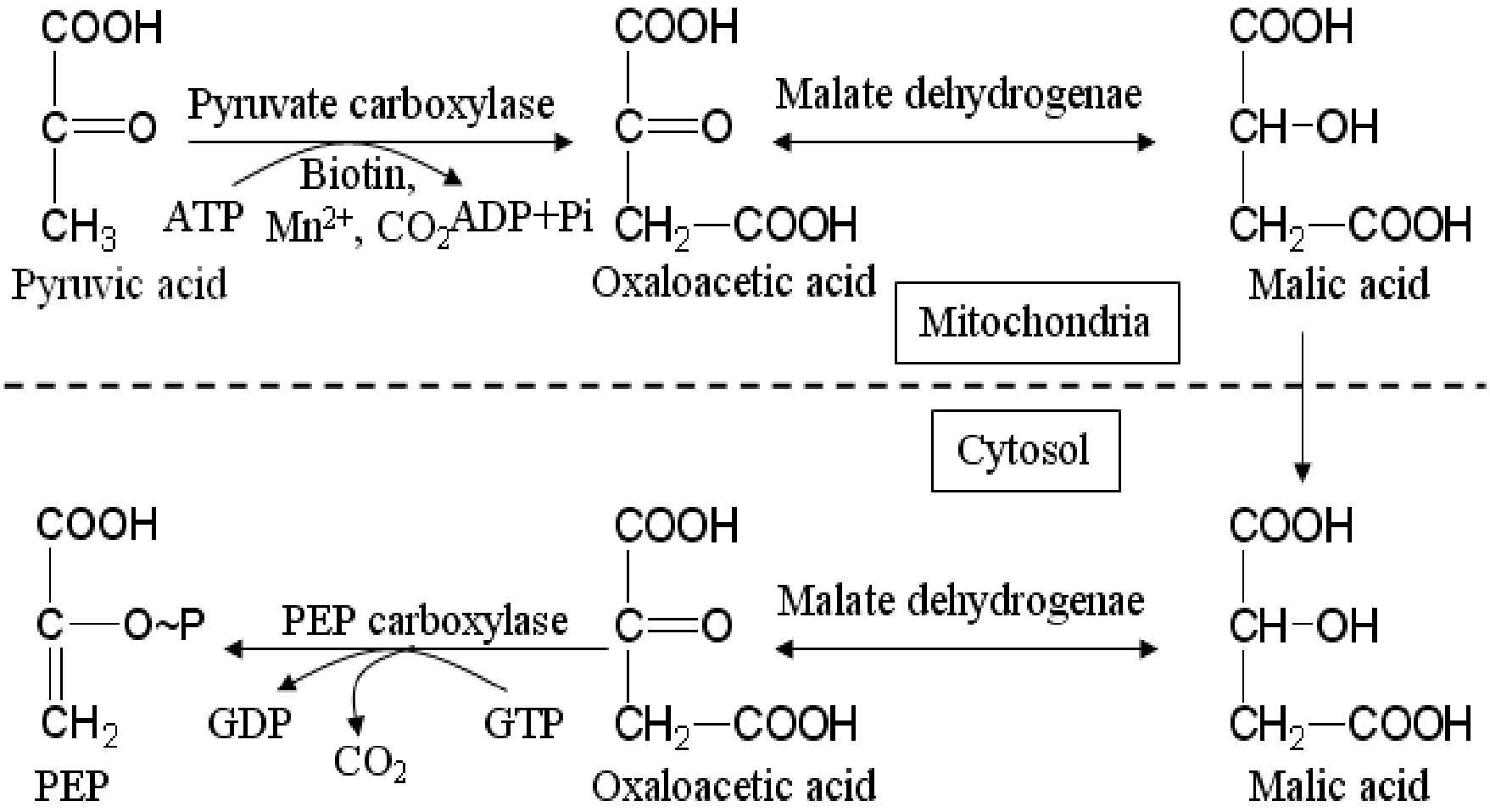
1. **Pyruvate Carboxylase (Mitochondria):**
   Converts pyruvate to oxaloacetate
2. **Phosphoenolpyruvate Carboxykinase (PEP Carboxykinase):**
   - **Converts oxaloacetate to PEP**
3. **Fructose–1,6–diphosphatase:**
   - **To reverse F–1,6–diP into F–6–P**
4. **Glucose–6–phosphatase (Absent in muscles):**
   - **To reverse Glucose–6–P into Free Glucose**

1. Pyruvate kinase: This reaction is reversed by 2 enzymes:

A- Pyruvate carboxylase: (A mitochondrial enzyme). Lactate is first converted to pyruvate by lactate dehydrogenase. This occurs in the cytoplasm. Pyruvic acid produced is then transported across the mitochondrial membrane to the mitochondria. Pyruvic carboxylase will then act on pyruvate converting it to oxaloacetate.

B- Phosphoenol pyruvate carboxykinase: The enzyme is present in the cytoplasm. Oxaloacetate cannot diffuse through the mitochondrial membrane to the cytosol. This problem can be solved by the dicarboxylic acid shuttle. Oxaloacetate is converted to malate (the mitochondrial membrane is permeable to malate) which can diffuse to the cytosol where it becomes reconverted to oxaloacetate. The phosphoenol pyruvic carboxykinase will act on oxaloacetate converting it into phosphoenol pyruvic

Gluconeogenesis



2. Phosphofructokinase reaction:

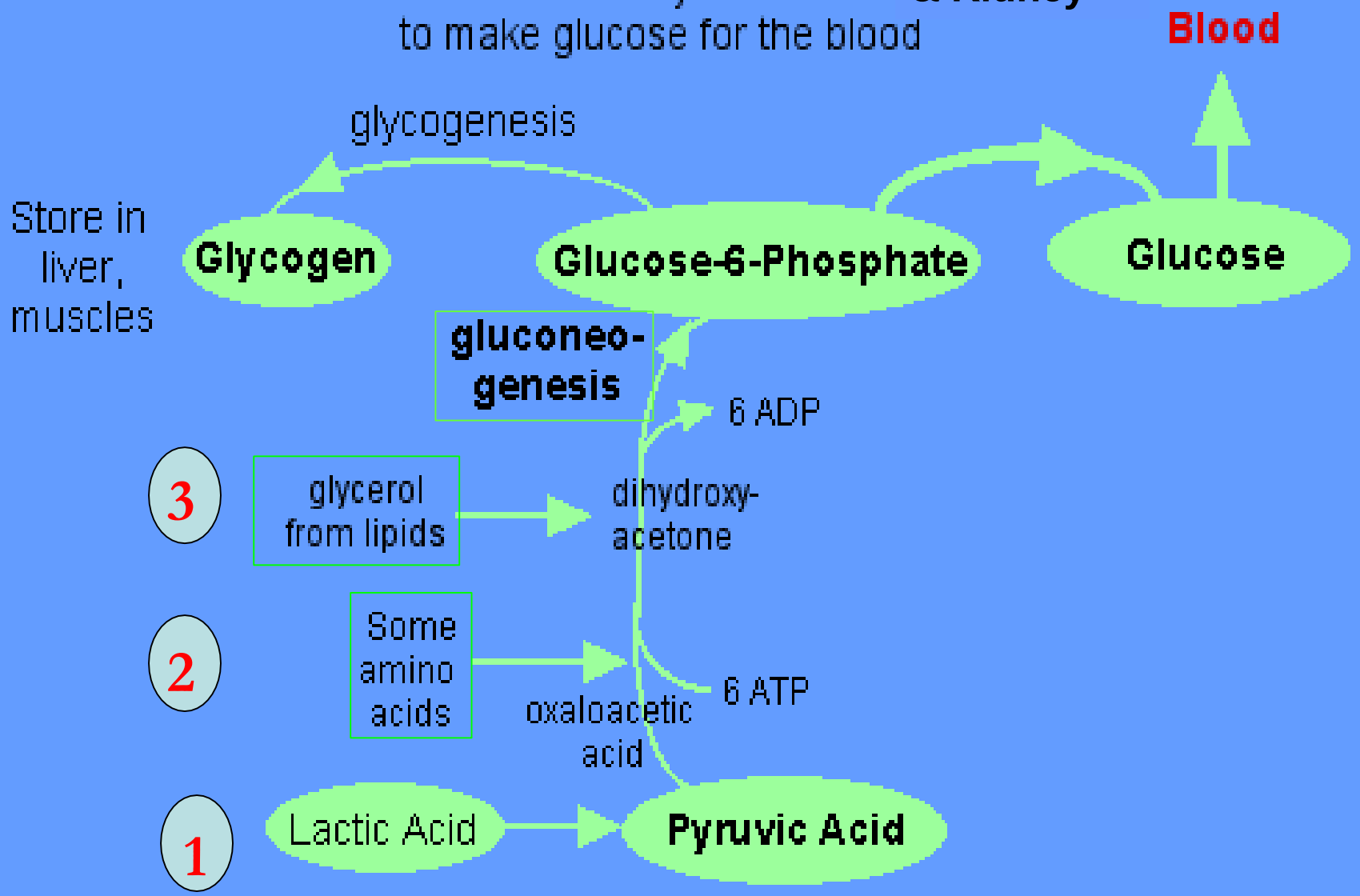
This is reversed by fructose 1, 6-diphosphatase enzyme.

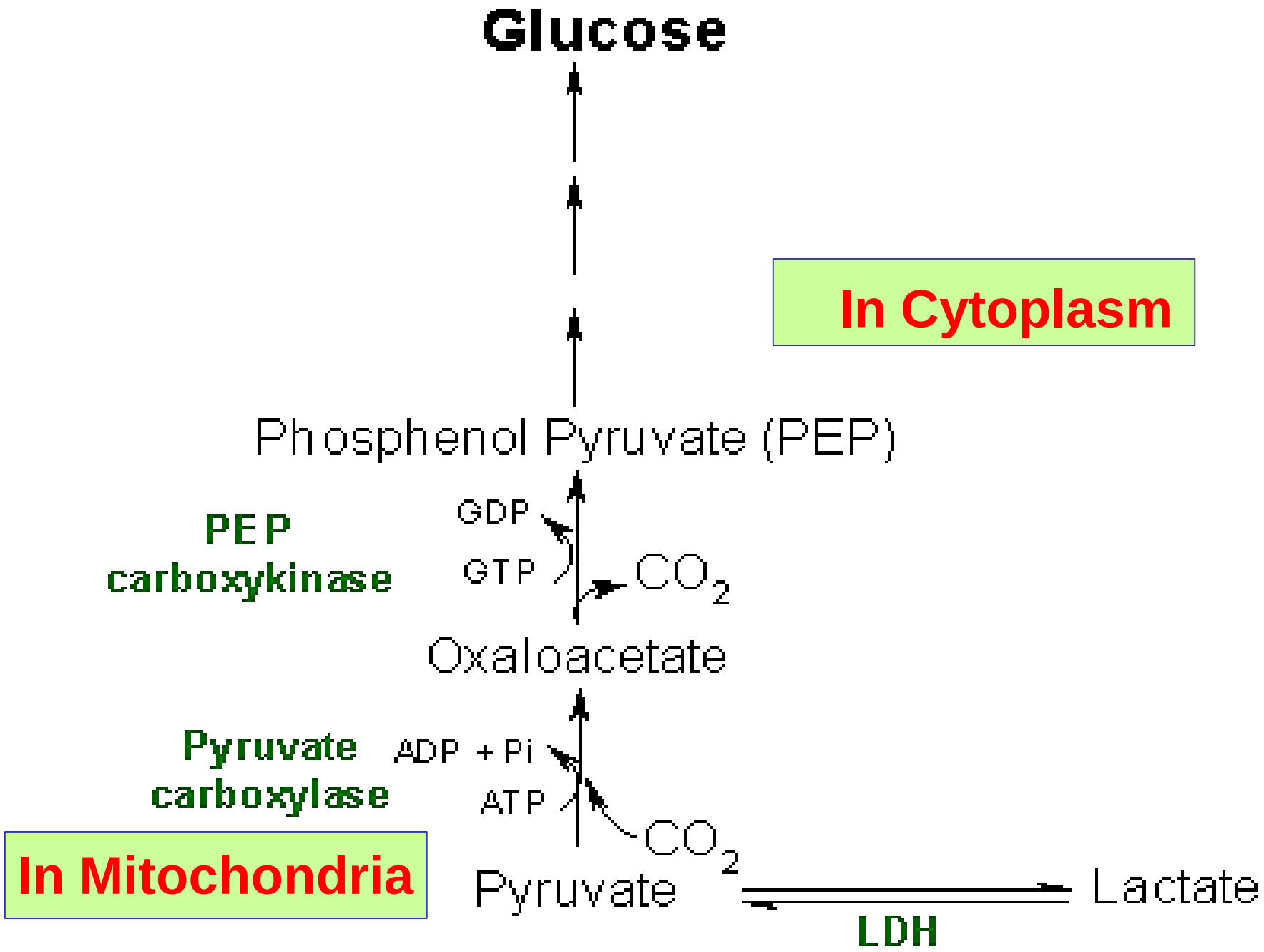
3. Glucokinase reaction:

This is reversed by glucose 6- phosphatase. This enzyme is found in the liver, with small amounts in the kidney. So glucose is produced from gluconeogenesis only in liver and kidney.

Gluconeogenesis

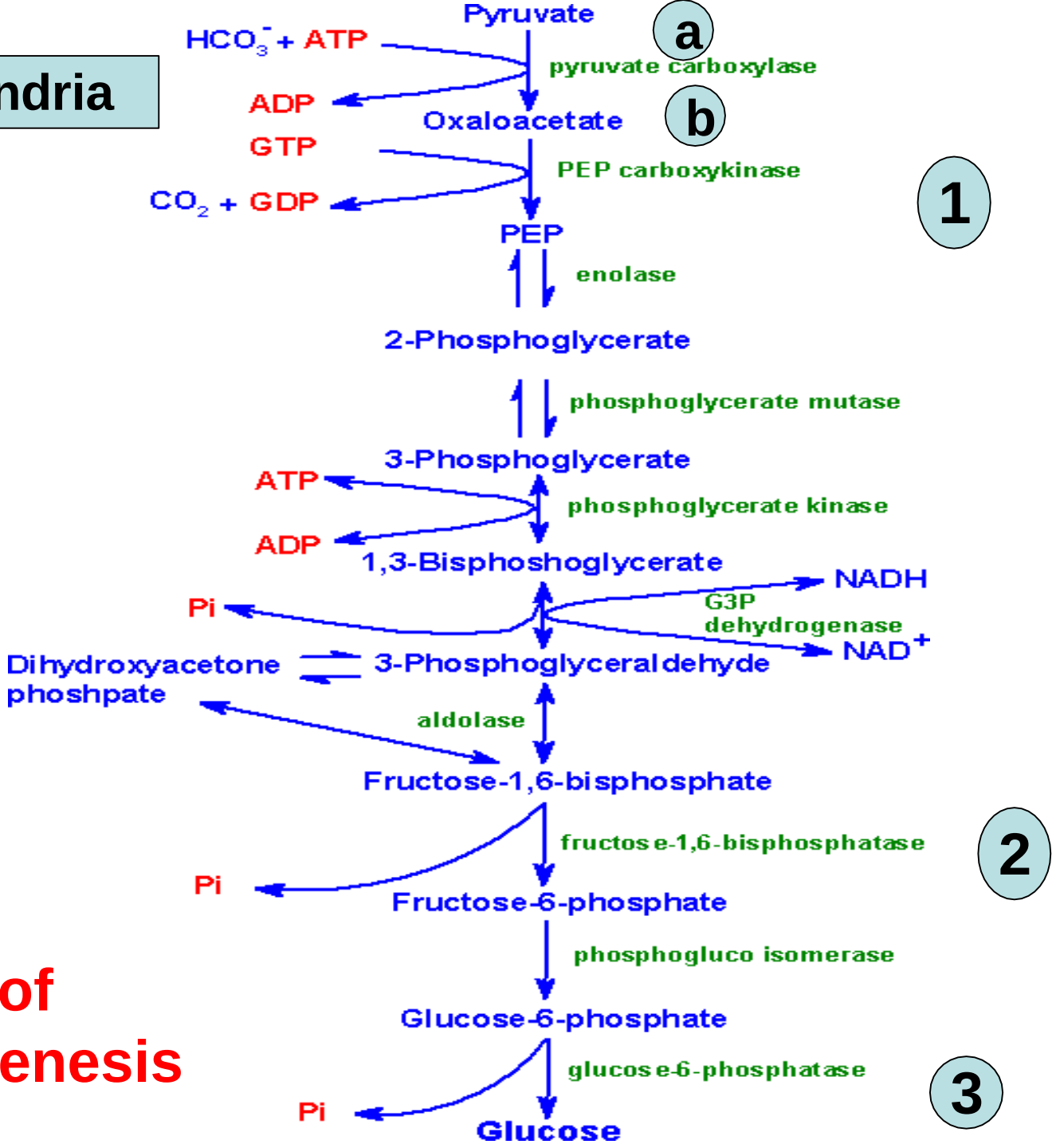
Occurs mainly in the liver **& Kidney**
to make glucose for the blood




Glucose
In Cytoplasm
Phosphenol Pyruvate (PEP)
PEP carboxykinase
GDP
GTP
CO_2
Oxaloacetate
Pyruvate carboxylase
ADP + Pi
ATP
CO_2
In Mitochondria
Pyruvate
Lactate
LDH

Steps of Gluconeogenesis

In mitochondria



Regulation of Gluconeogenesis

1. After carbohydrate diet, Insulin inhibits the synthesis of enzymes of gluconeogenesis
2. During starvation, glucocorticoids, growth hormone, glucagon and adrenaline stimulate the synthesis of enzymes of gluconeogenesis
3. Acetyl CoA is an allosteric activator of pyruvate carboxylase, so oxaloacetate accumulate
4. Citrate & ATP stimulate fructose–1,6–diphosphatase
5. Fructose–2,6–diphosphate & AMP inhibit fructose––1,6diphosphatase