B.Sc-4th sem

Unit-2 (CC-410)

GLUCONEOGENESIS

BY

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Definition

- The synthesis of glucose from non-carbohydrate compounds is known as gluconeogenesis.
- The major substrates/precursors for gluconeogenesis:
- Lactate, pyruvate, glucogenic amino acids, propianate and glycerol.

- **Site:**
- Gluconeogenesis occurs mainly in the liver, and to a lesser extent in the renal cortex.
- The pathway is partly mitochondrial & partly cytoplasmic.
- About 1 kg glucose synthesized everyday

Importance of gluconeogenesis

- Brain & CNS, erythrocytes, testes & kidney medulla are dependent on glucose for continuous supply for energy.
- Human brain alone requires about 120 g of glucose per day, out of about 160 g needed by the entire body.
- Glucose is the only source that supplies to the skeletal muscle, anaerobic conditions.

- During starvation gluconeogenesis maintains the blood glucose level.
- The stored glycogen is depleted within the first 12-18 hours of fasting.
- On prolonged starvation, the gluconeogenesis is speeded up & protein catabolism provides the substrates, namely glucogenic amino acids.

Reactions of gluconeogenesis

- Gluconeogeenesis closely resembles the reversed pathway of glycolysis.
- The 3 irreversible steps of glycolysis are catalysed by the 3 enzymes.
- Hexokinase
- PFK
- Pyruvate kinase

- These three stages bypassed by alternate enzymes specific to gluconeogenesis.
- These are:
- Pyruvate carboxylase
- Phosphoenol pyruvate carboxy kinase
- Fructose-1-6-bisphosphatase
- Glucose-6-phosphatase

Conversion of pyruvate to phosphoenol pyruvate

- Takes place in two steps pyruvate carboxylase is a biotin dependent mitochondrial enzyme that converts pyruvate to oxaloacetate in presence of ATP & CO_2
- This enzyme regulates gluconeogenesis & requires acetyl CoA for its activity.

- Oxaloacetate is synthesized in the mitochondrial matrix.
- It has to be transported to the cytosol.
- Due to membrane impermeability, oxaloacetate cannot diffuse out of the mitochondria.
- It is converted to malate & transported to cytosol.
- In the cytosol, oxaloacetate is regenerated.

- The reversible conversion of oxaloacetate to malate is catalysed by MDH, present in mitochondria & cytosol
- In the cytosol, phosphoenolpyruvate carboxykinase converts oxaloacetate to phosphoenol pyruvate.

- **GTP or ITP (not ATP) is used in this reaction and the CO_2 is liberated.**
- **For the conversion of pyruvate to phosphoenol pyruvate, 2ATP equivalents are utilized.**

Conversion of Fructose 1,6-bisphosphate to fructose 6-phosphate

- **Phosphoenolpyruvate undergoes the reversal of glycolysis until Fructose 1,6-bisphosphate is produced.**
- **The enzyme Fructose 1,6-bisphosphatase converts Fructose 1,6-bisphosphate to Fructose 6-phosphate & it requires Mg^{2+} ions.**
- **This is also a regulatory enzyme.**

Conversion of glucose 6-phosphate to glucose

- Glucose 6-phosphatase catalyses the conversion of glucose 6-phosphate to glucose.
- It is present in liver & kidney but absent in muscle, brain and adipose tissue.
- Liver can replenish blood sugar through gluconeogenesis, glucose 6- phosphatase is present mainly in liver.

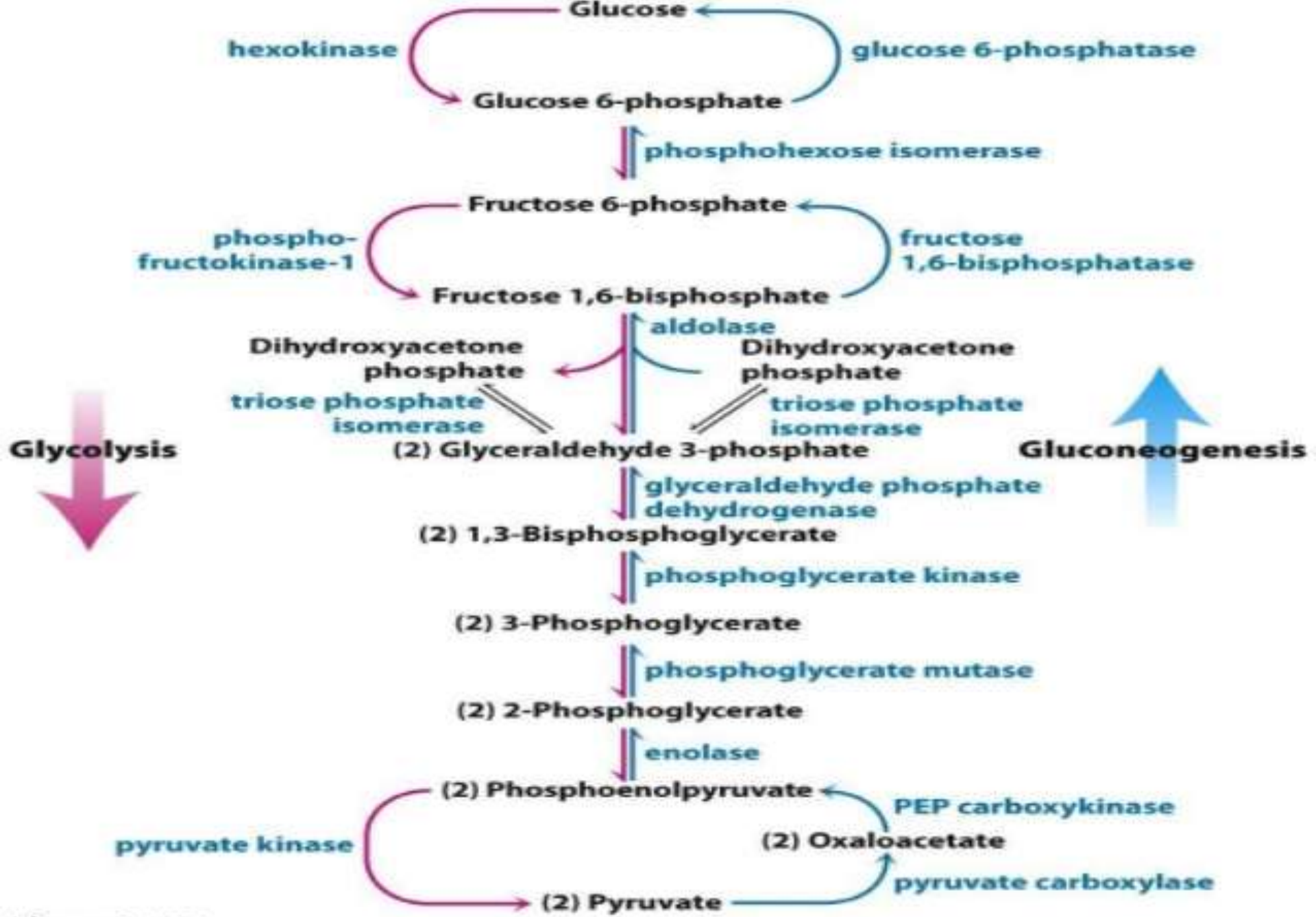
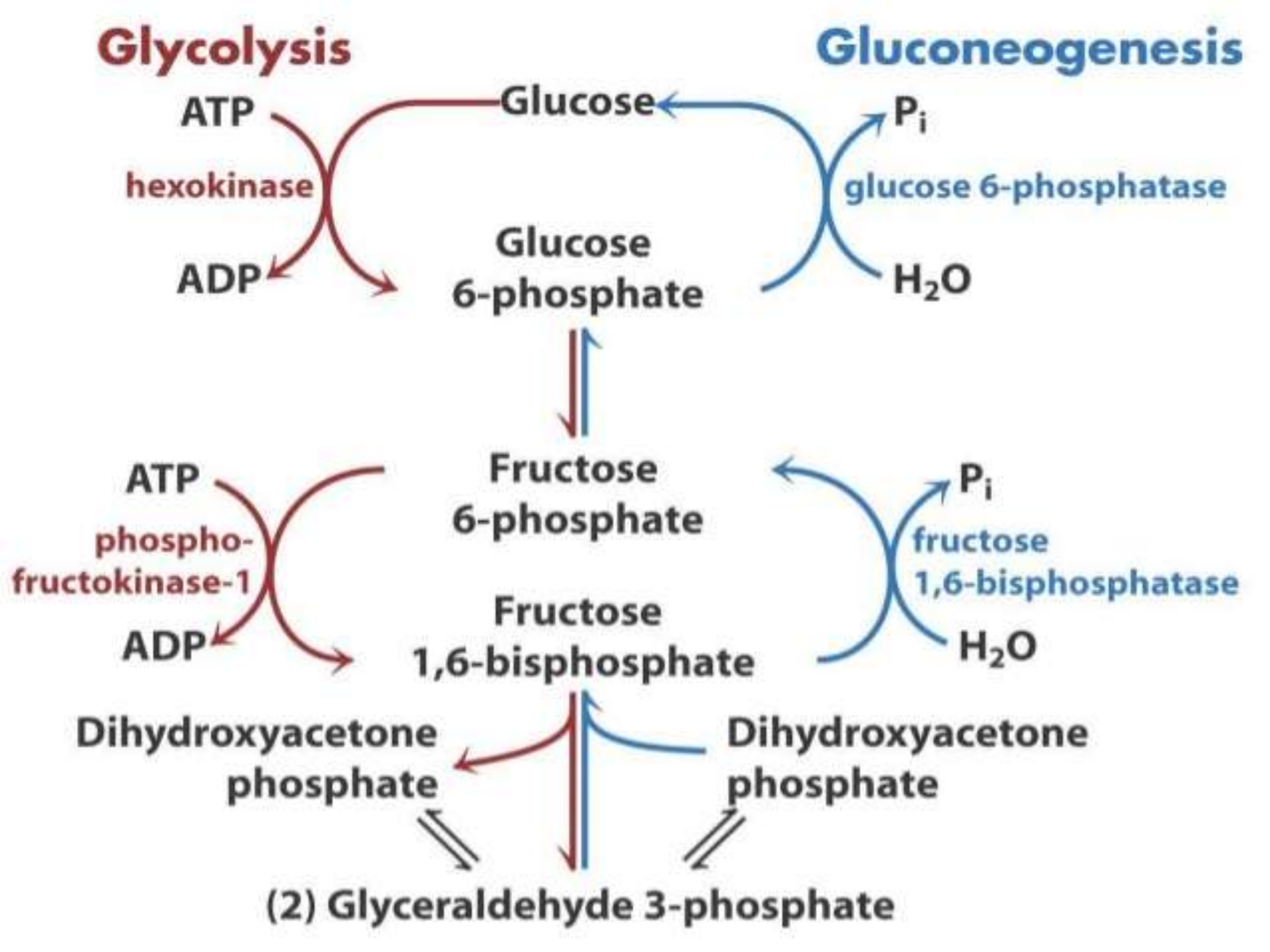
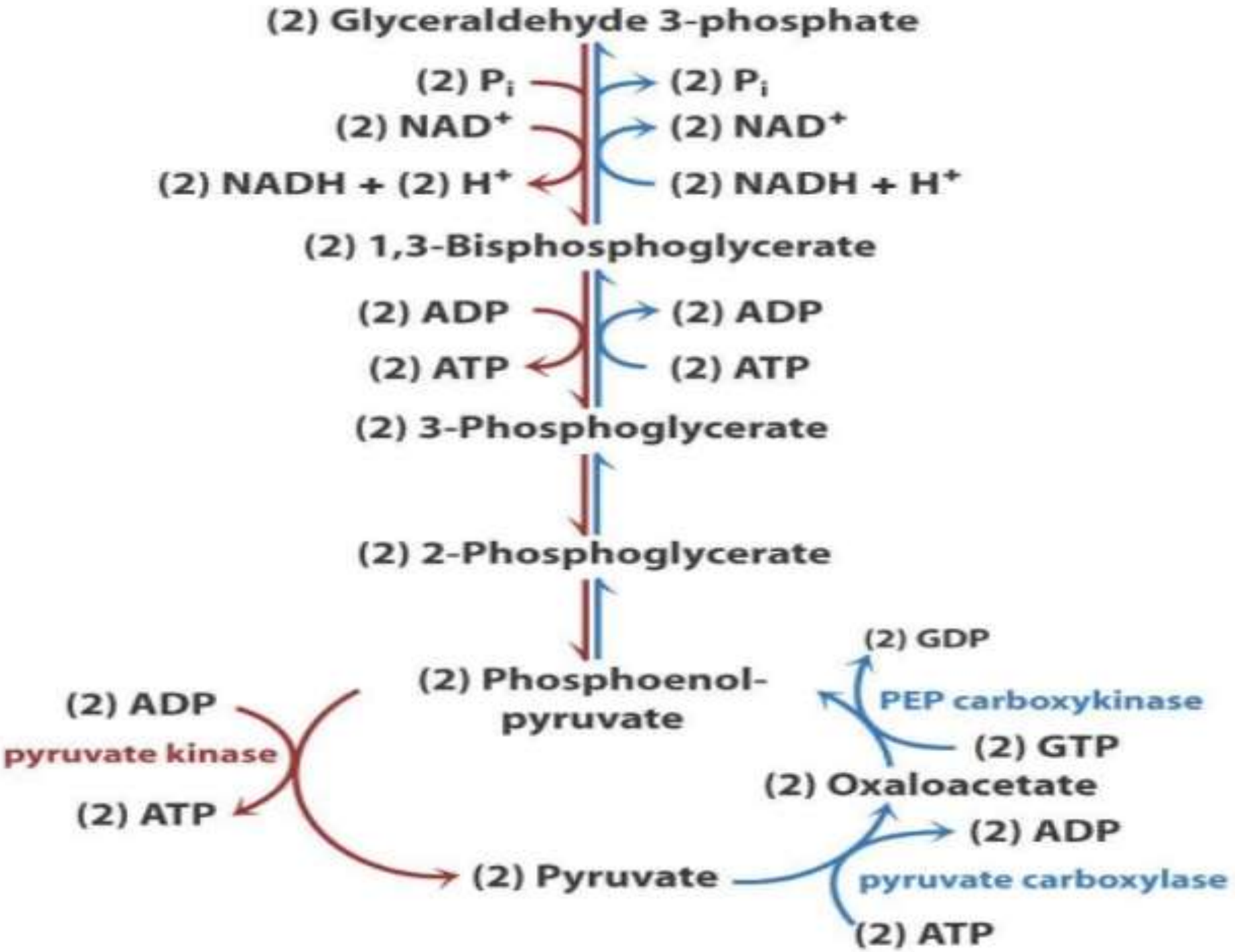


Figure 15-11
Lehninger Principles of Biochemistry, Fifth Edition


Glycolysis
Gluconeogenesis
ATP
Glucose
P_i
hexokinase
glucose 6-phosphatase
ADP
Glucose
6-phosphate
H_2O
Fructose
6-phosphate
ATP
P_i
phospho-
fructokinase-1
fructose
1,6-bisphosphatase
ADP
Fructose
1,6-bisphosphate
H_2O
Dihydroxyacetone
phosphate
Dihydroxyacetone
phosphate
(2) Glyceraldehyde 3-phosphate


(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) NAD^+
(2) NADH + (2) H^+
(2) P_i
(2) NAD^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenol-pyruvate
(2) ADP
pyruvate kinase
(2) ATP
(2) Pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) Oxaloacetate
(2) ADP
pyruvate carboxylase
(2) ATP

Regulation of gluconeogenesis

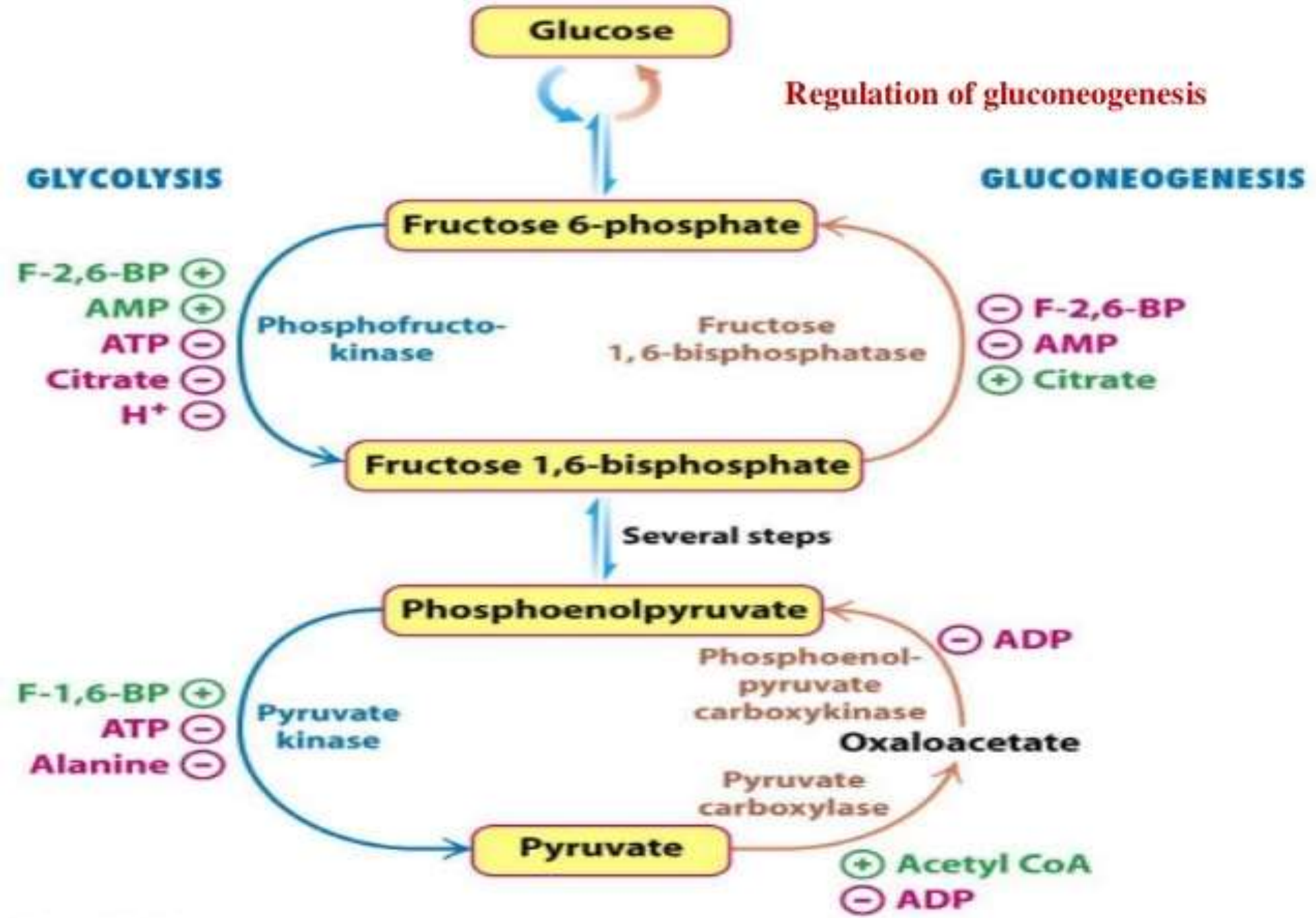
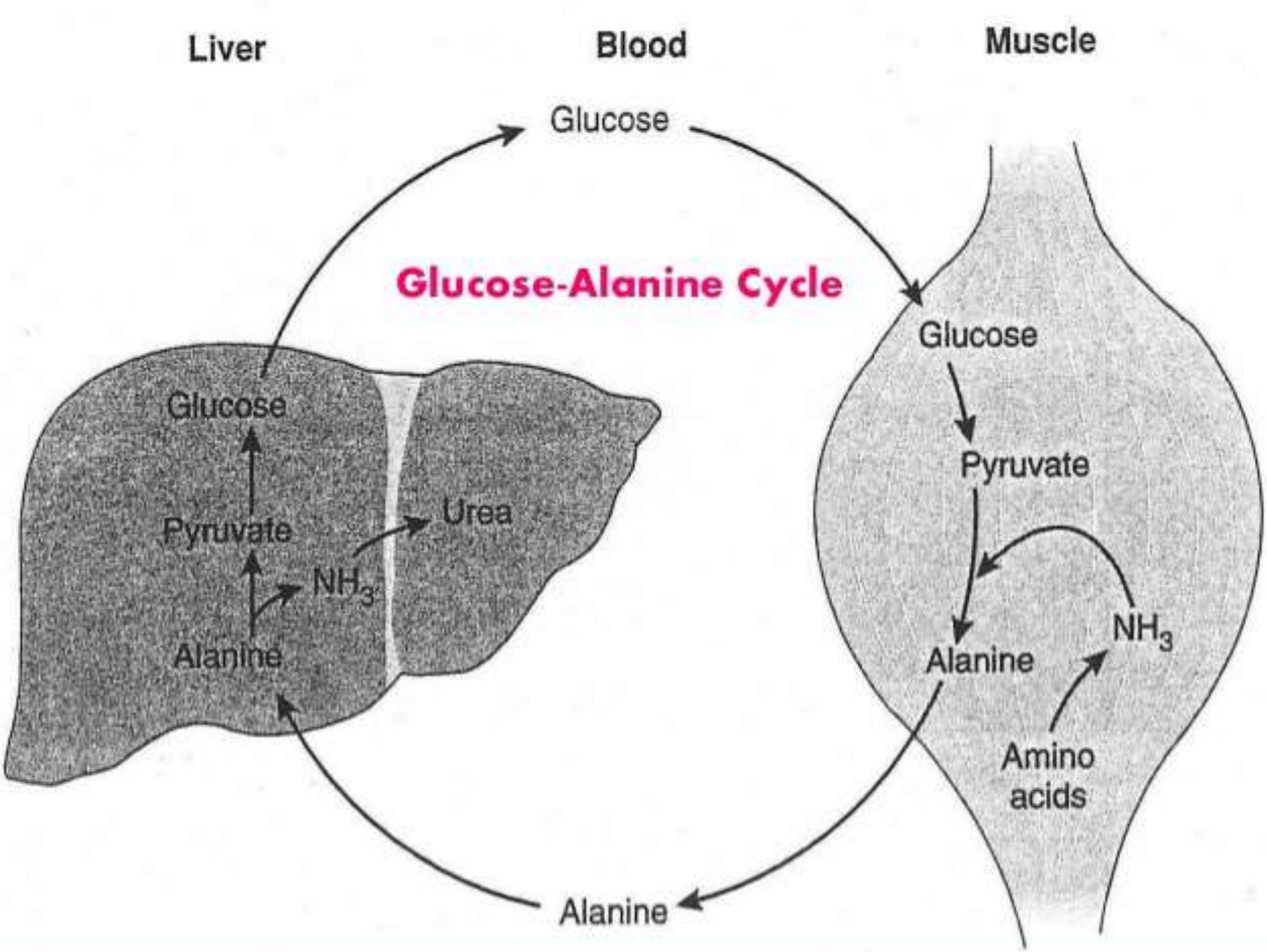


Figure 16-28
Biochemistry, Sixth Edition

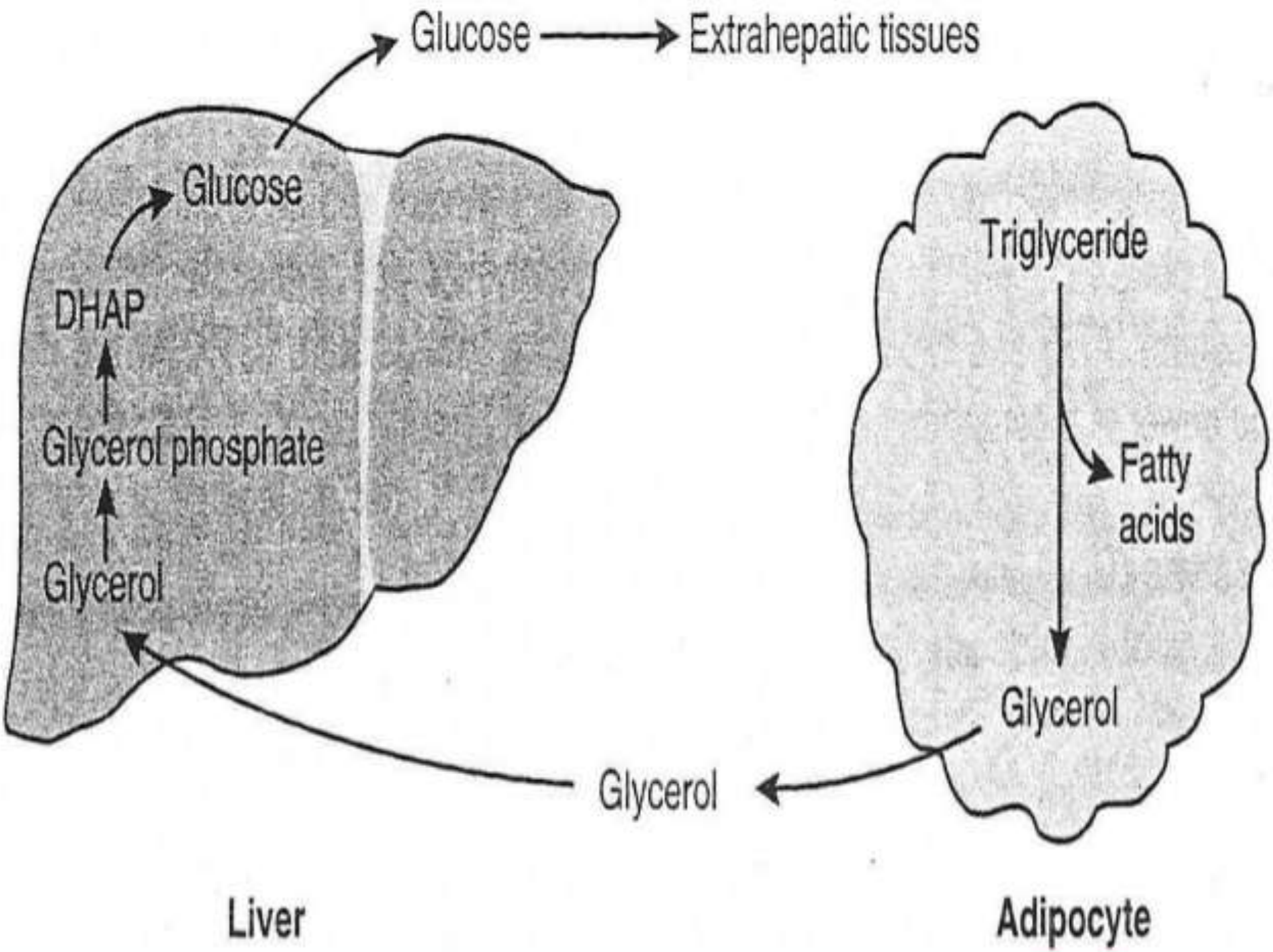
Gluconeogenesis from amino acids

- The carbon skeleton of glucogenic amino acids (all except leucine & lysine) results in the formation of pyruvate or the intermediates of citric acid cycle.
- Which, ultimately, result in the synthesis of glucose.


Liver
Blood
Muscle
Glucose
Glucose-Alanine Cycle
Glucose
Pyruvate
Urea
NH3
Alanine
Glucose
Pyruvate
NH3
Alanine
Amino acids
Alanine

Gluconeogenesis from glycerol

- Glycerol is liberated in the adipose tissue by the hydrolysis of fats (triacylglycerols).
- The enzyme glycerokinase (found in liver & kidney, absent in adipose tissue) activates glycerol to glycerol 3- phosphate.
- It is converted to DHAP by glycerol 3-phosphate dehydrogenase.
- DHAP is an intermediate in glycolysis.


Glucose
Extrahepatic tissues
Glucose
DHAP
Glycerol phosphate
Glycerol
Triglyceride
Fatty acids
Glycerol
Glycerol
Liver
Adipocyte

Gluconeogenesis from propionate

- Oxidation of odd chain fatty acids & the breakdown of some amino acids (methionine, isoleucine) yields a three carbon propionyl CoA.
- Propionyl CoA carboxylase acts on this in the presence of ATP & biotin & converts to methyl melonyl CoA

- Which is then converted to succinyl CoA in the presence of B_{12}.
- Succinyl CoA formed from propionyl CoA enters gluconeogenesis.

Gluconeogenesis from lactate (CORI cycle)

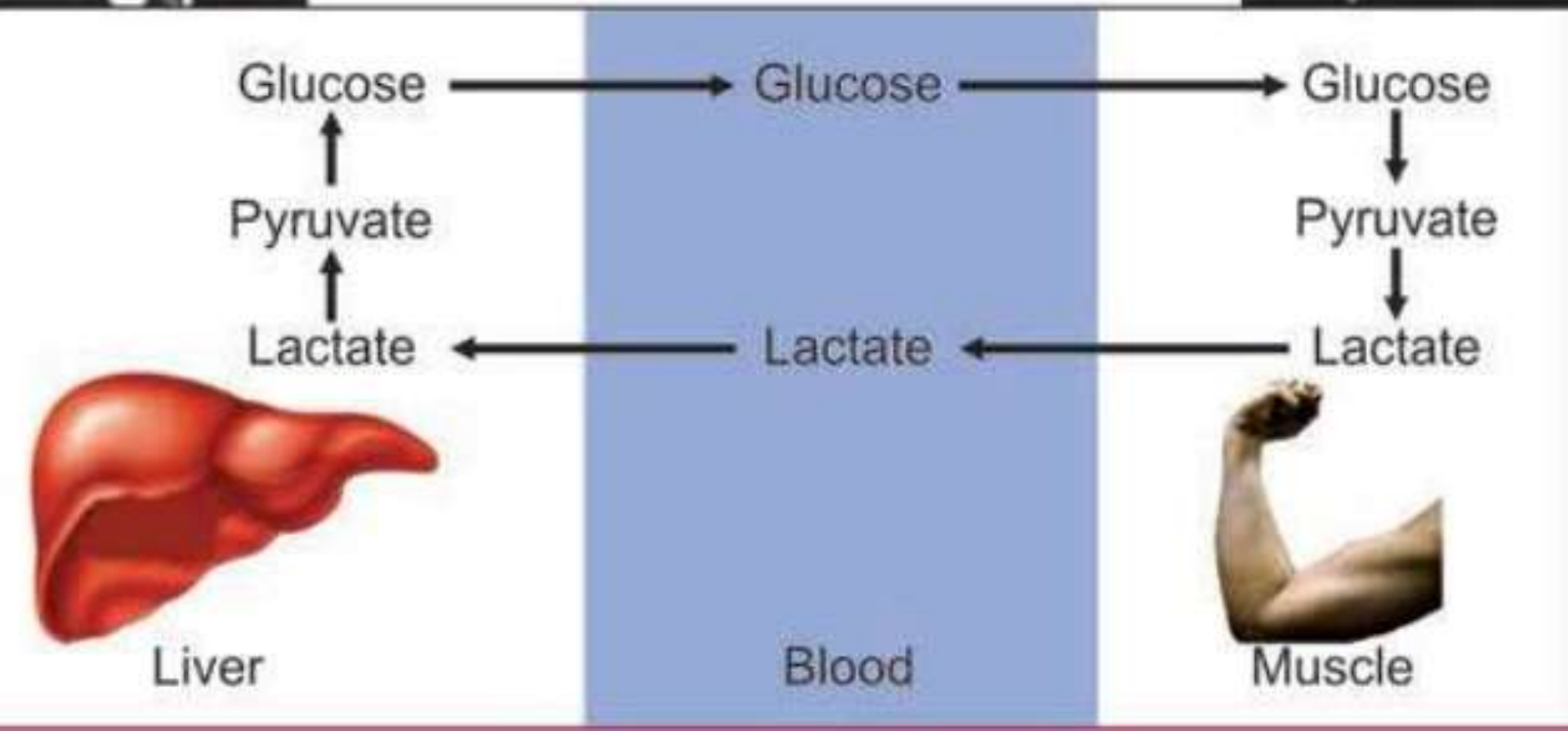
- **Definition:**
- It is a process in which glucose is converted to Lactate in the muscle and in the liver this lactate is re-converted to glucose.
- In an actively contracting muscle, pyruvate is reduced to lactic acid which may tend to accumulate in the muscle.
- To prevent lactate accumulation, body utilizes cori cycle.

- This lactic acid from muscle diffuses into the blood.
- Lactate then reaches liver, where it is oxidised to pyruvate.
- It is entered into gluconeogenesis.
- Regenerated glucose can enter into blood and then to muscle.
- This cycle is called cori cycle.

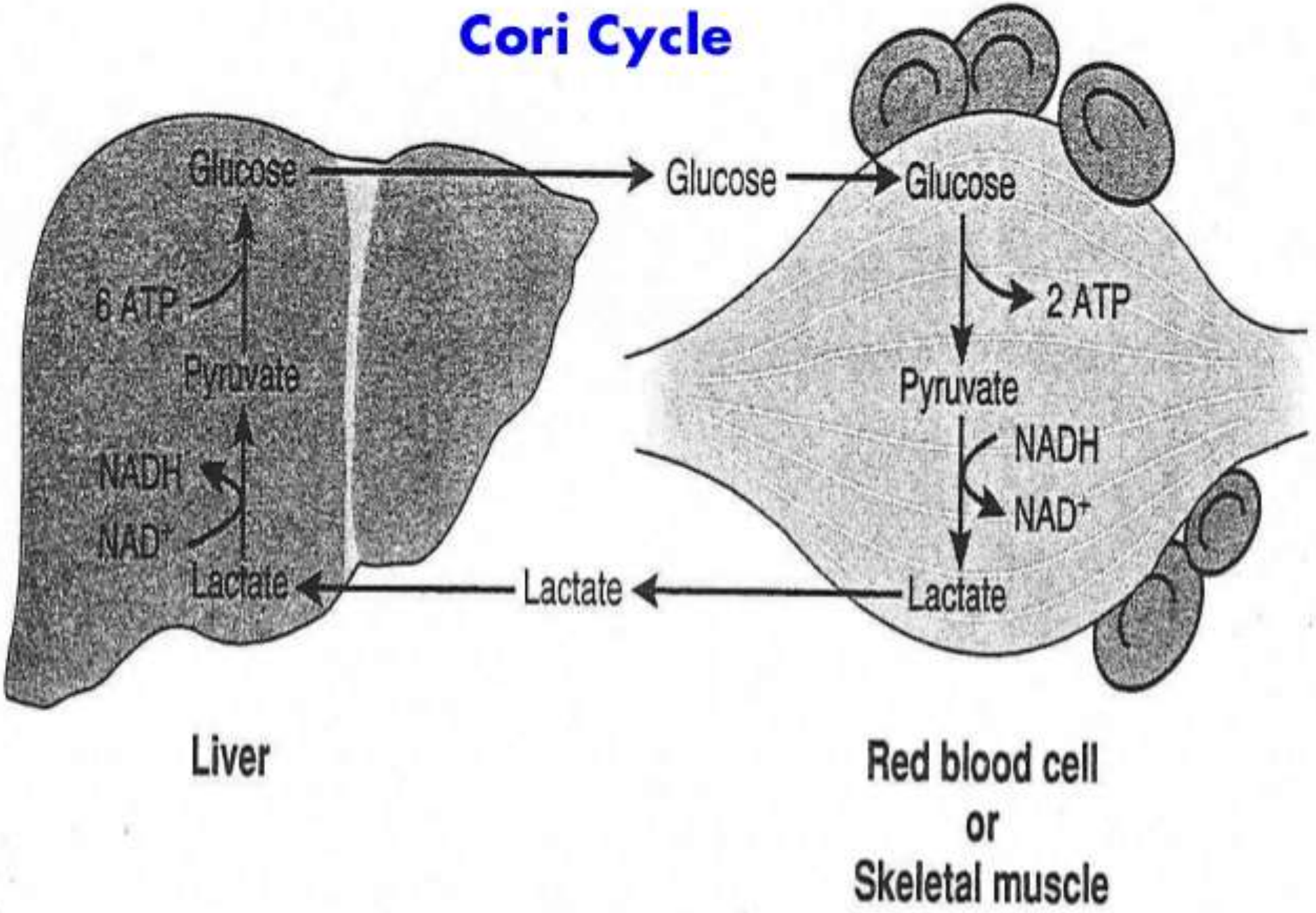
Cori Cycle

Carl Cori
NP 1947
1896-1984

Gerty Cori
NP 1947
1896-1957



Cori Cycle


Glucose
Glucose
Glucose
6 ATP
2 ATP
Pyruvate
Pyruvate
NADH
NADH
NAD+
NAD+
Lactate
Lactate
Lactate
Liver
Red blood cell
or
Skeletal muscle

Regulation of Gluconeogenesis

- Gluconeogenesis & glycolysis are reciprocally regulated
- One pathway is relatively inactive when the other is active.
- Regulatory enzymes:
- Pyruvate Carboxylase.
- Fructose-1,6-bisphosphatase.
- ATP.
- Hormonal Regulation of Gluconeogenesis.

Pyruvate Carboxylase

- It is an allosteric enzyme.
- Acetyl CoA is an activator of pyruvate carboxylase so that generation of oxaloacetate is favored when acetyl CoA level is high.

Fructose-1,6-bisphosphatase

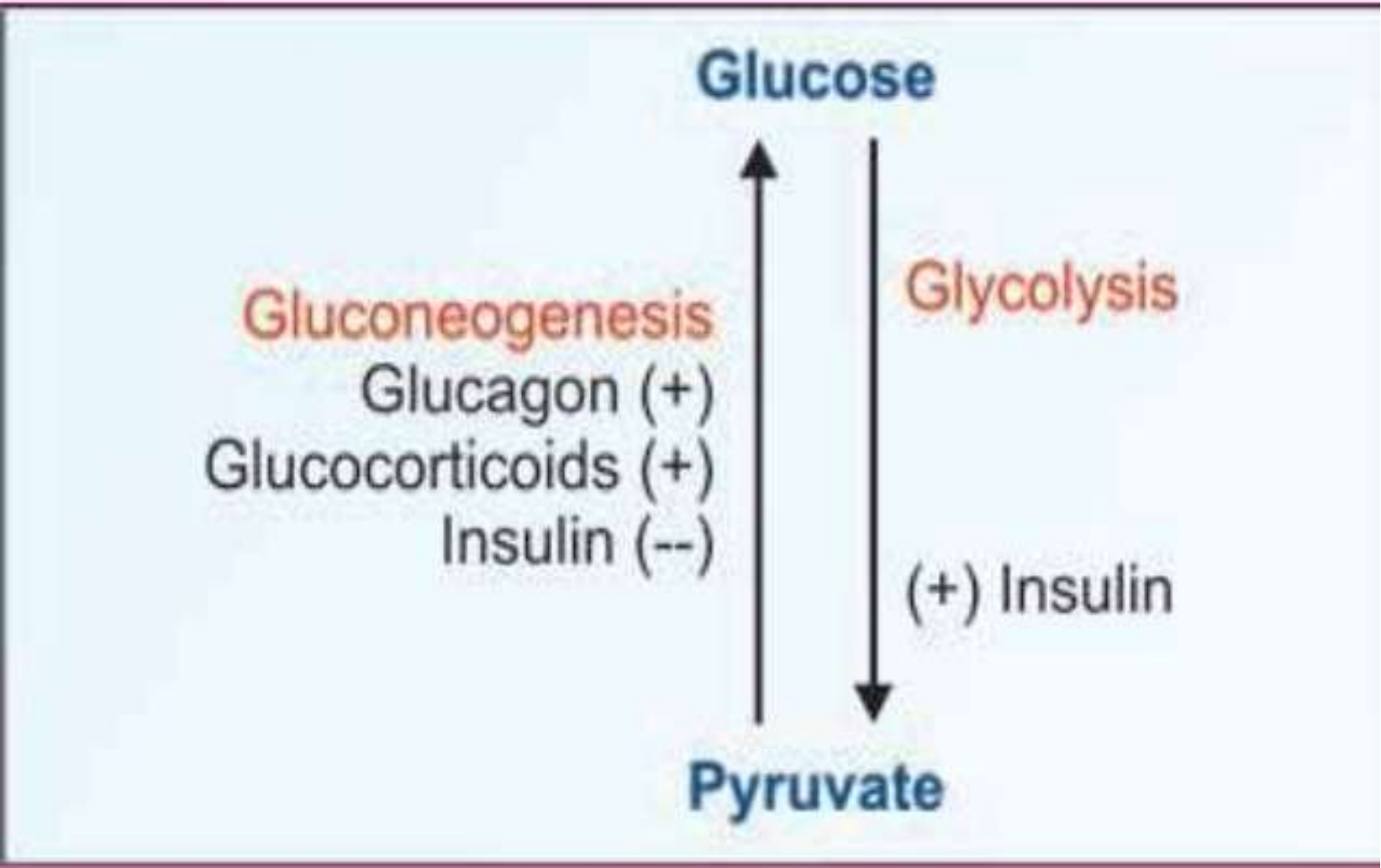
- Citrate is an activator.
- Fructose-2,6-bisphosphate & AMP are inhibitors.
- All these three effectors have an exactly opposite effect on the phosphofructokinase (PFK).
- ATP:
- Gluconeogenesis is enhanced by ATP.

Hormonal Regulation of Gluconeogenesis

- Glucagon & glucocorticoids increase gluconeogenesis
- Glucocorticoids induce the synthesis of hepatic amino transferases & provides substrate for gluconeogenesis.

- The high glucagon-insulin ratio favors induction of synthesis of gluconeogenic enzymes (PEPCK, Fructose-1,6-bisphosphatase & glucose-6-phosphatase).
- At the same time, synthesis of glycolytic enzymes HK, PFK & PK are depressed.

Hormonal regulation of gluconeogenesis



THANK YOU