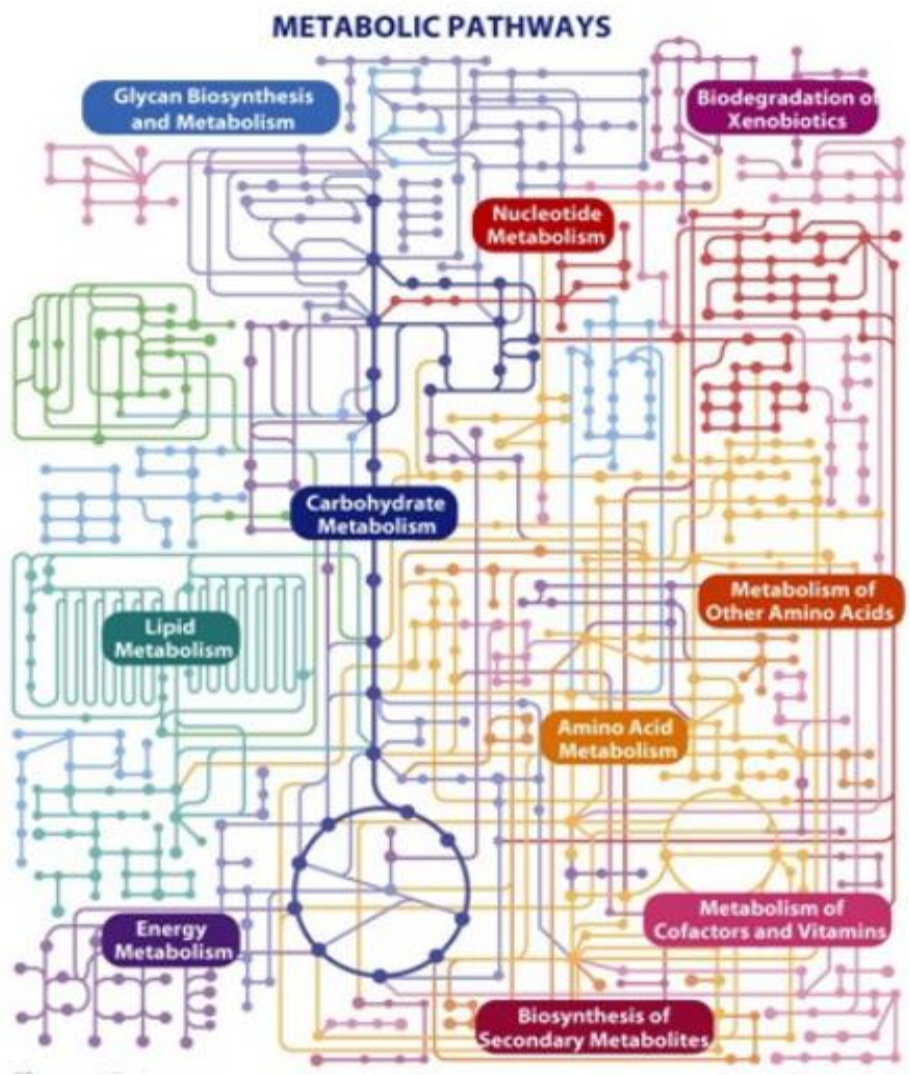
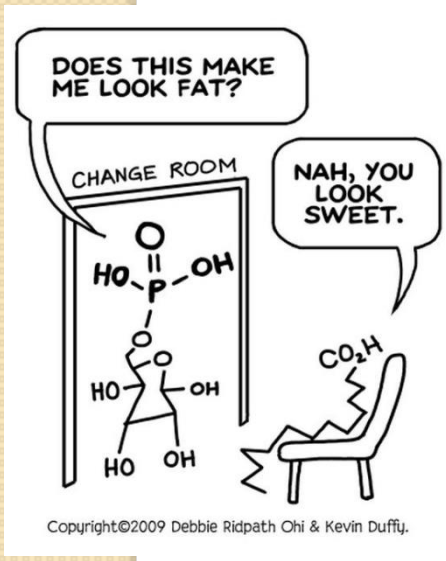
Gluconeogenesis
استحداث السكر

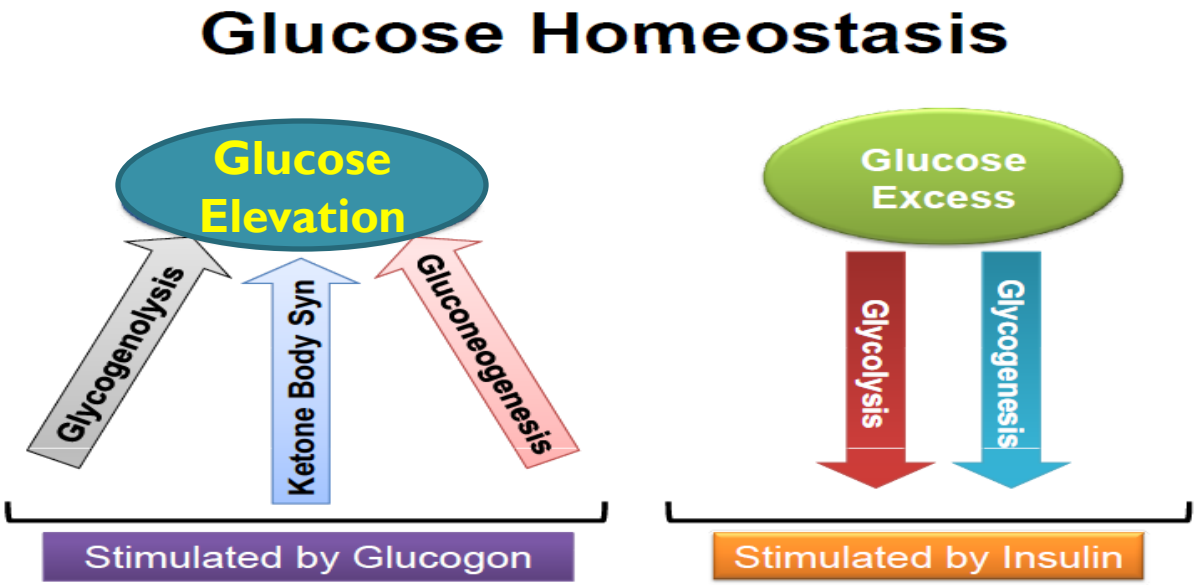


Gluconeogenesis and Glucose Homeostasis

Gluconeogenesis: استحداث السكر

Definition: Synthesis of glucose from non- carbohydrate precursors





Significance of Gluconeogenesis

- To maintain blood glucose level especially under conditions of starvation and in DM.
- Liver plays an important role in blood sugar homeostasis.
- Liver can replenish blood sugar through this pathway because glucose-6-phospahtase is present in liver

Sources of non- carbohydrate precursors مصادر طلائع استحداث السكر

1. Pyruvate - major precursor
2. Lactate –from muscle, forms pyruvate
3. Glucogenic amino acids
4. Glycerol
5. Propionyl CoA

Site of synthesis

- Liver is the major site (90%)
- Kidneys minor site (10%)
- Pathways occurs partly in mitochondria and cytoplasm.
- The gluconeogenesis pathway is not simple reversal of glycolysis.
- These are under reciprocal control so that Physiological conditions favoring one disfavor the other and vice versa.

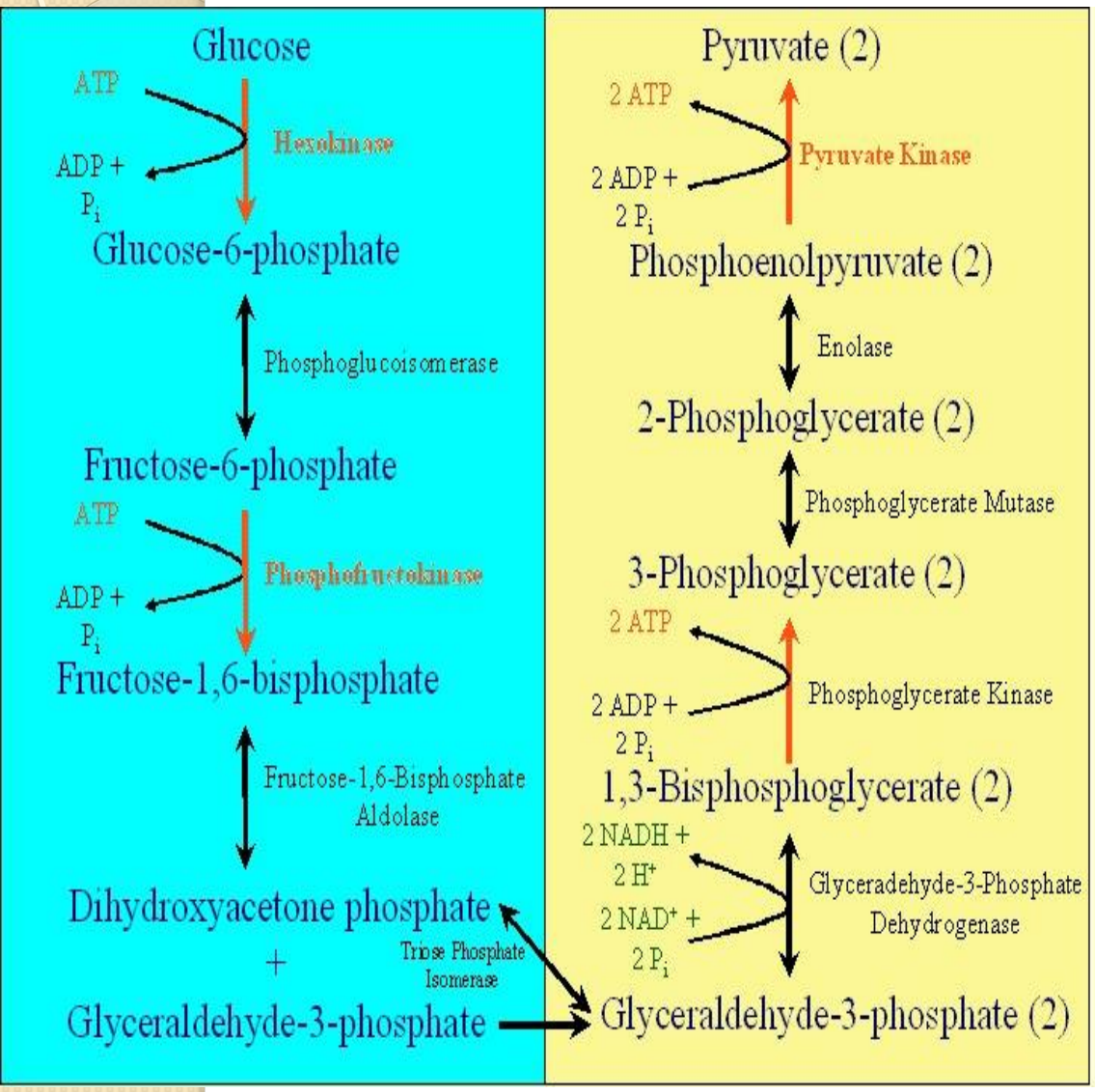
$$2\ \text{Pyruvate} + 2\ \text{NADH} + 4\ \text{ATP} + 2\ \text{GTP} + 6\ H_2O \rightarrow$$

$$\text{Glucose} + 2\ NAD^+ + 4\ \text{ADP} + 2\ \text{GDP} + 6\ P_i + 2H^+$$

Key enzymes of Gluconeogenesis

- Key Enzymes (4) :
  1. Pyruvate Carboxylase (PC)
  2. PEP Carboxykinase (PEPCK)
  3. Fructose 1,6 Bis phosphatase
  4. Glucose -6- Phosphatase

Gluconeogenesis is not reversal of Glycolysis:



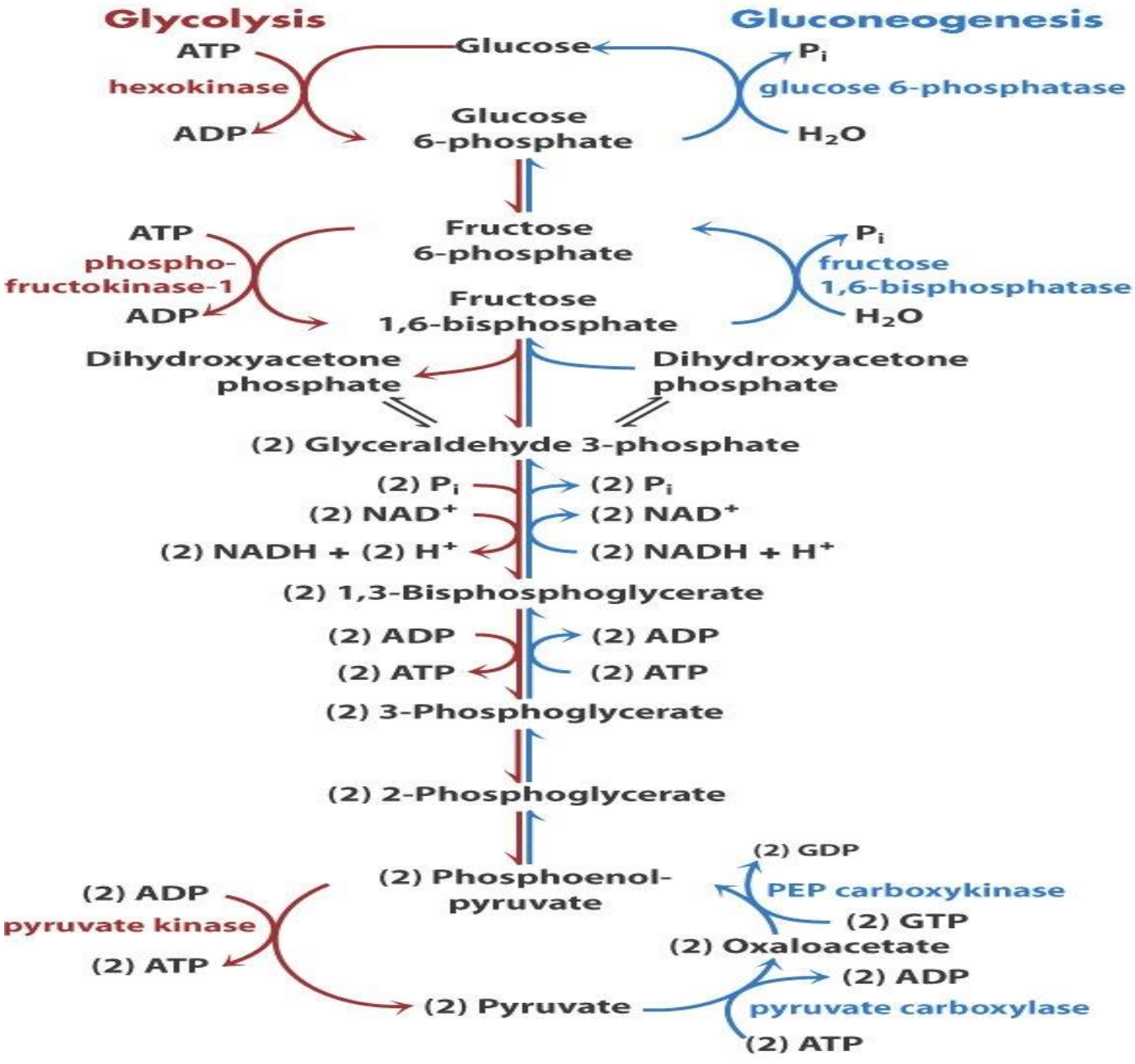
- ***Four unique enzymes*** (Key enzymes of Gluconeogenesis) are used to ***bypass*** *three* irreversible steps of glycolysis.

- The rest (7) of the steps use the same enzymes as glycolysis

In glycolysis, 3 irreversible kinase reactions are bypassed by 4 Key enzymes of Gluconeogenesis

Glycolysis		GNG
Hexokinase	Undone by	Glucose-6-Phosphatase
PFK	Undone by	Fructose -1,6-Bisphosphatase
Pyruvate Kinase	Undone by	Pyruvate Carboxylase AND PEP Carboxykinase

Glycolysis and Gluconeogenic pathway



Obstacle One

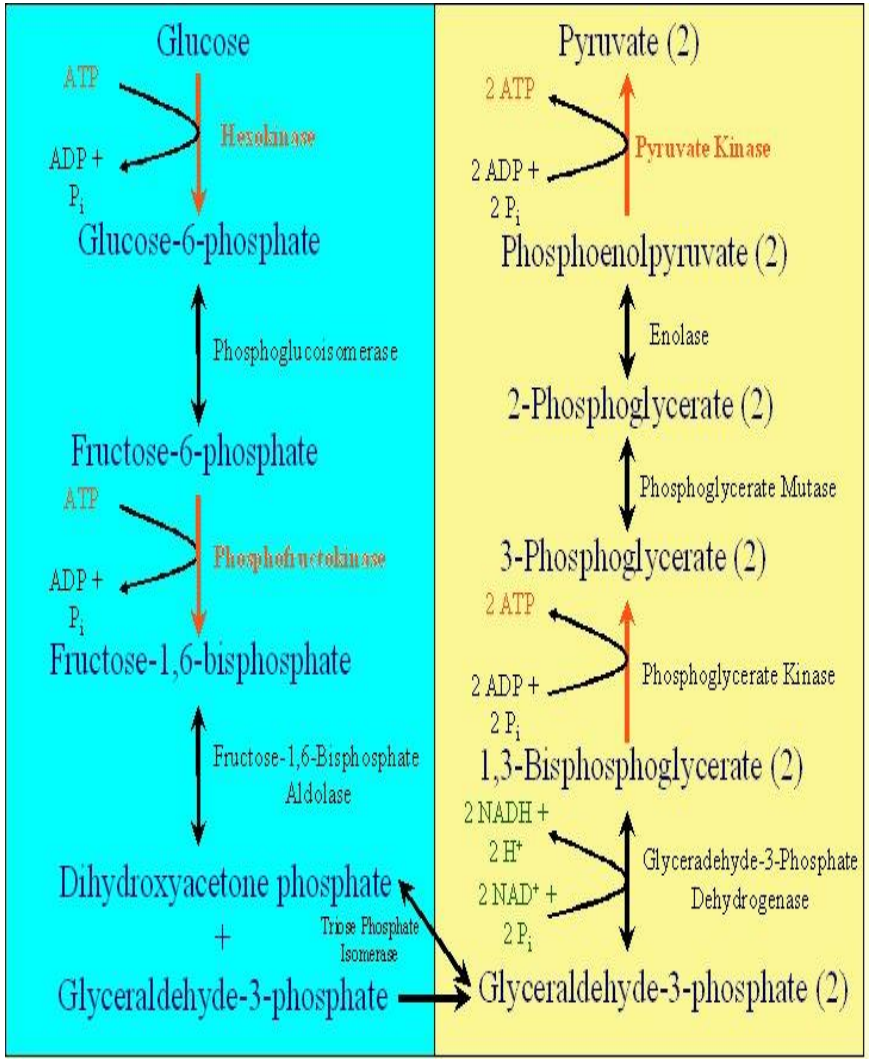
Pyruvate to Phosphoenolpyruvate ;

In glycolysis:

PEP ⟶ Pyruvate

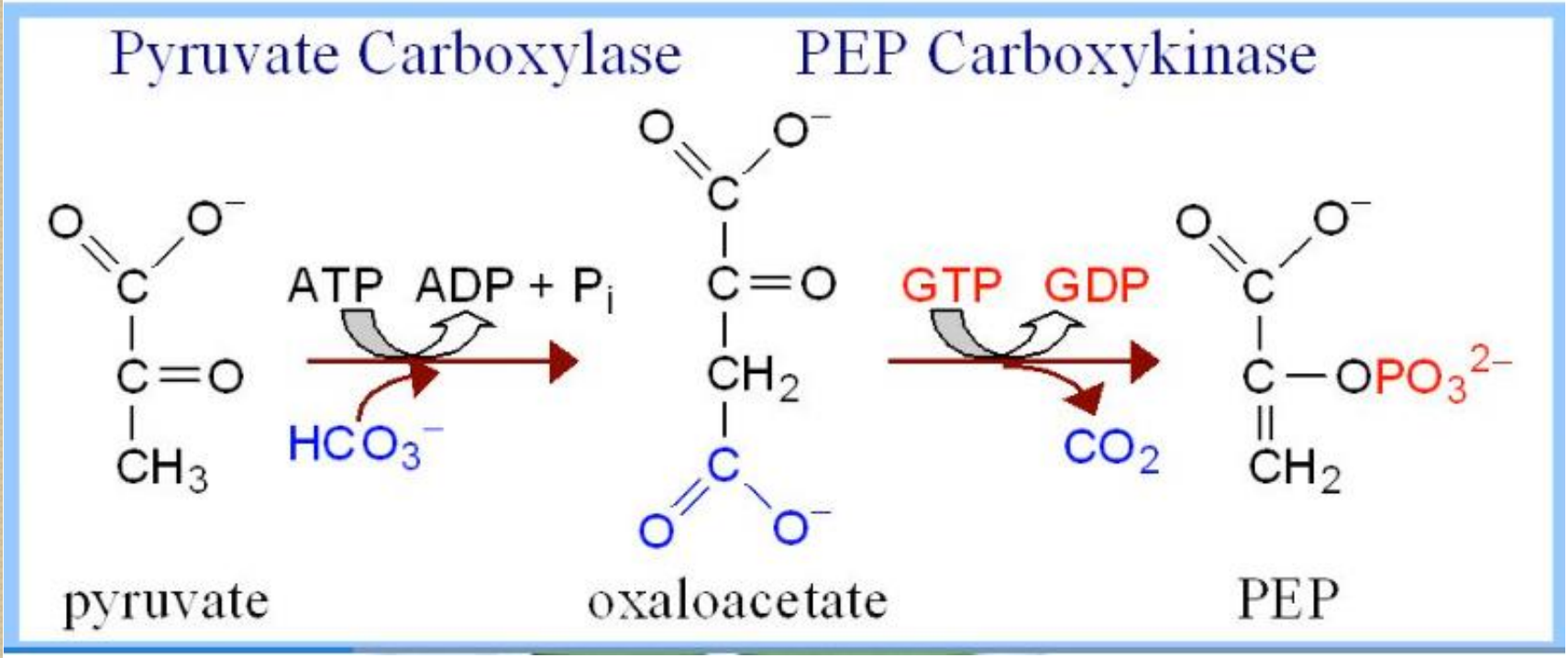
Enzyme: Pyruvate Kinase

- Highly irreversible reaction, requiring two enzymes to undo the reaction.



Conversion of Pyruvate to Phosphoenolpyruvate

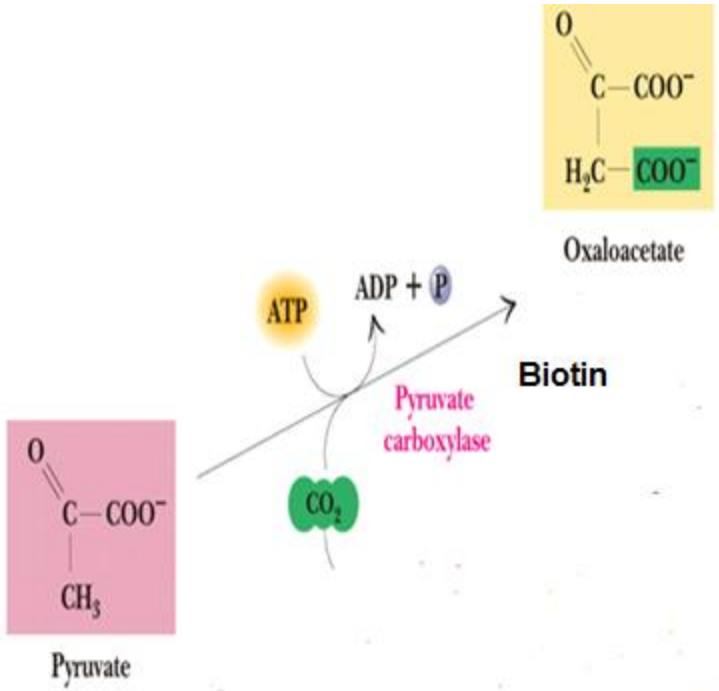
- **Enzymes involved:**
  - **Pyruvate carboxylase**
  - **PEP carboxykinase**



Conversion of Pyruvate →PEP

Thus, Part One:

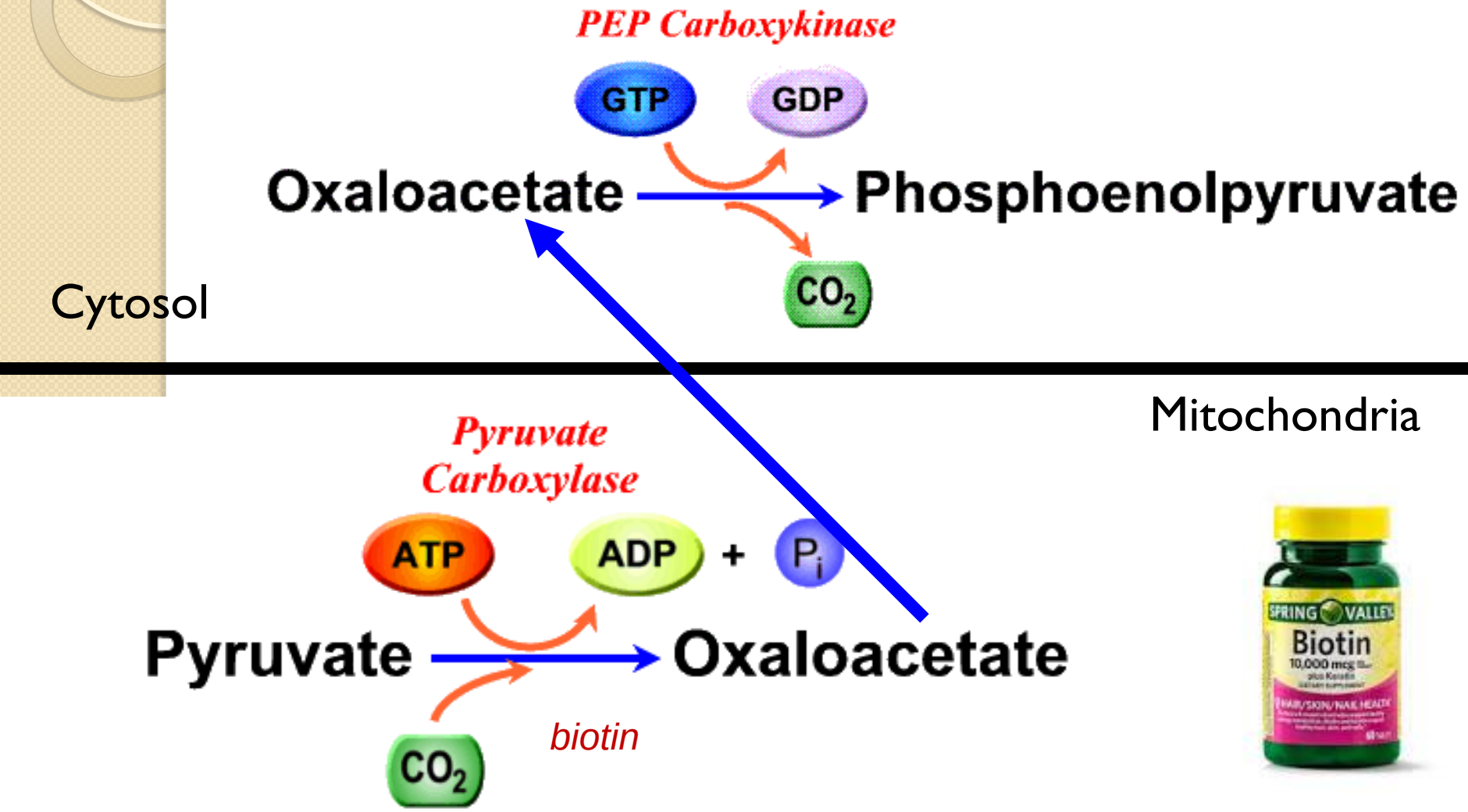
- Enzyme: Pyruvate Carboxylase
- (Carboxylation's reactions use CO_2 and the vitamin *biotin* as a cofactor)



Pyruvate → OAA

Found only in the Liver and Kidneys
NOT found in muscles
Location: Mitochondria
Requires 2 ATP

Reversal of PEP → Pyruvate



The GTP-dependent decarboxylation of oxaloacetate

Enzyme = **PEP carboxykinase**

cytosolic enzyme,

as all others

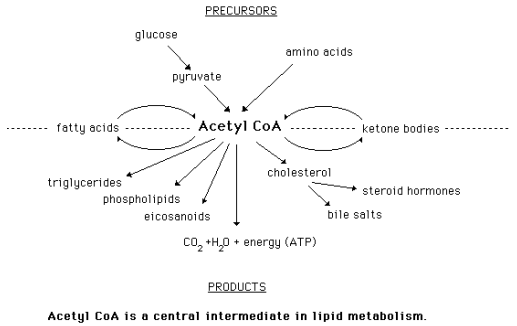
oxaloacetate + GTP

→phospho*enol*pyruvate + CO_2 + GDP

- uses GTP, not ATP.
- CO_2 added is last in this step.

Two Alternative Fates for Pyruvate

- Pyruvate can be a source of new glucose
  - Store energy as glycogen
  - Generate NADPH via pentose phosphate pathway
- Pyruvate can be a source of acetyl-CoA
  - Store energy as body fat
  - Make ATP via citric acid cycle
- Acetyl-CoA stimulates glucose synthesis by activating pyruvate carboxylase



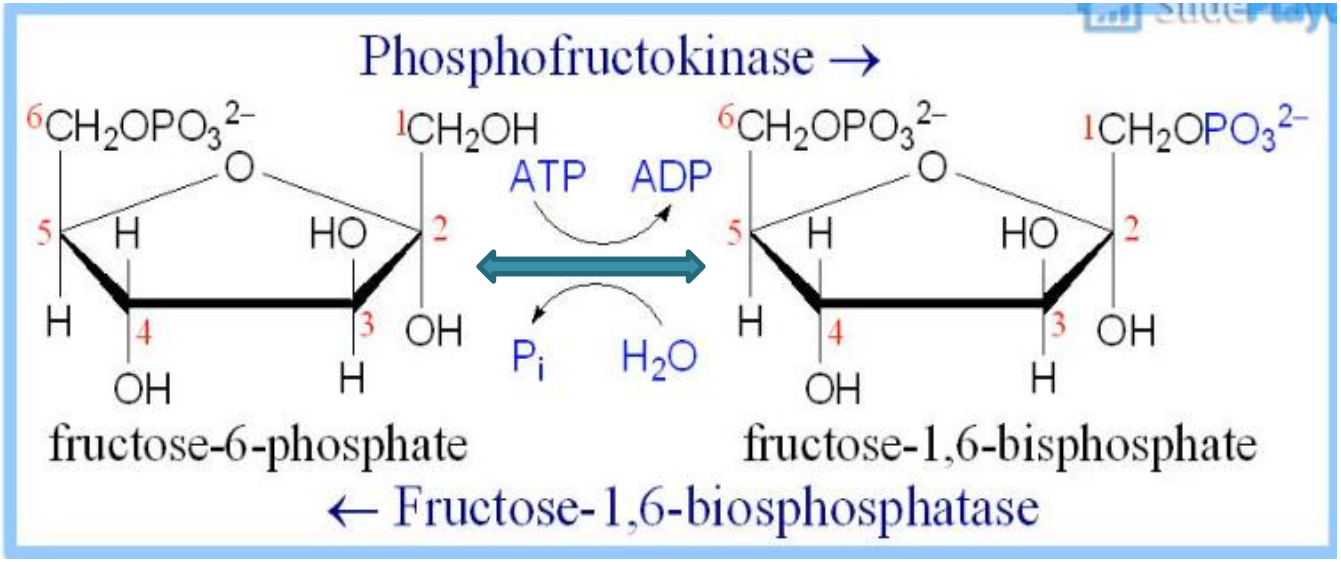
Acetyl CoA is a central intermediate in lipid metabolism.

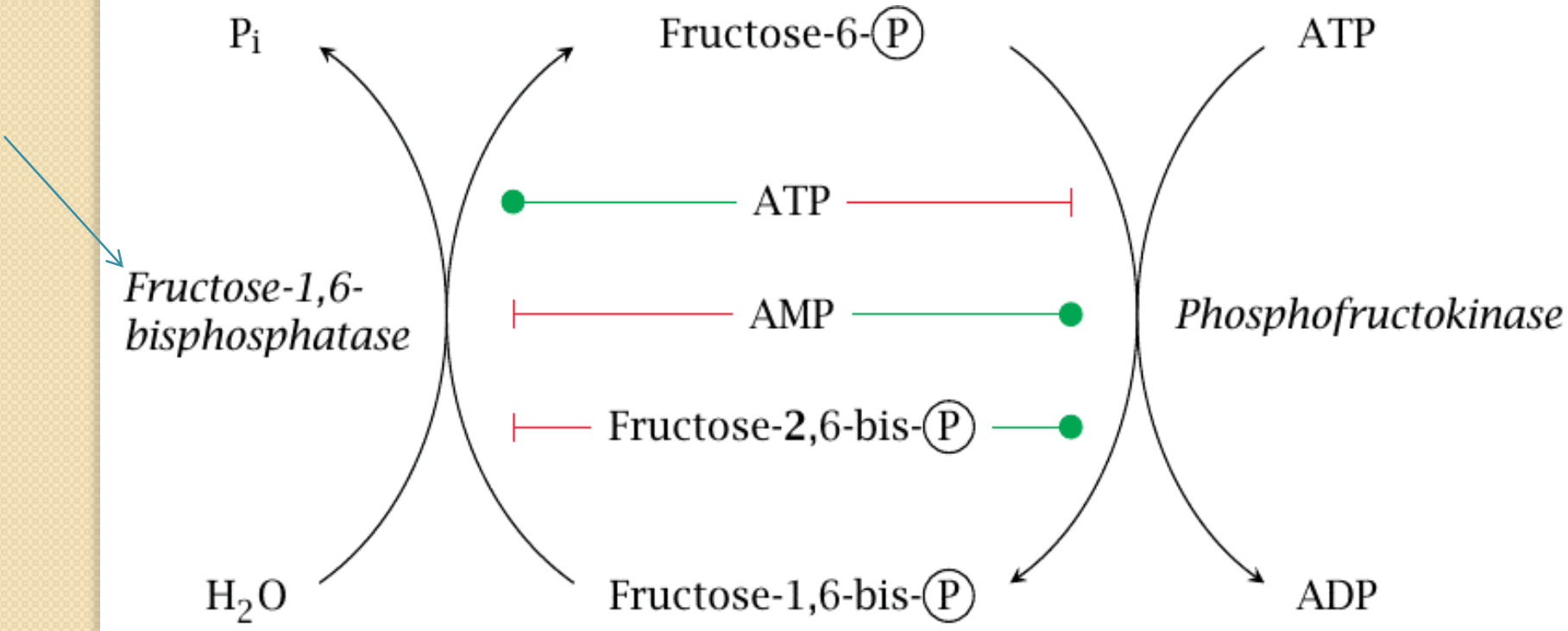
Obstacle number 2.

Fructose-1,6-*bis* phosphate to fructose-6-phosphate ;

Enzyme = **Fructose-1,6-*bis*phosphatase**

- Bypasses phosphofructokinase-I
- a simple hydrolysis.
- highly exergonic, irreversible

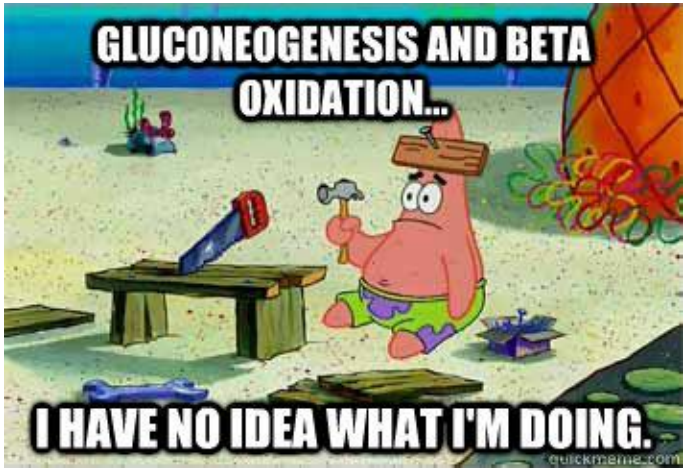


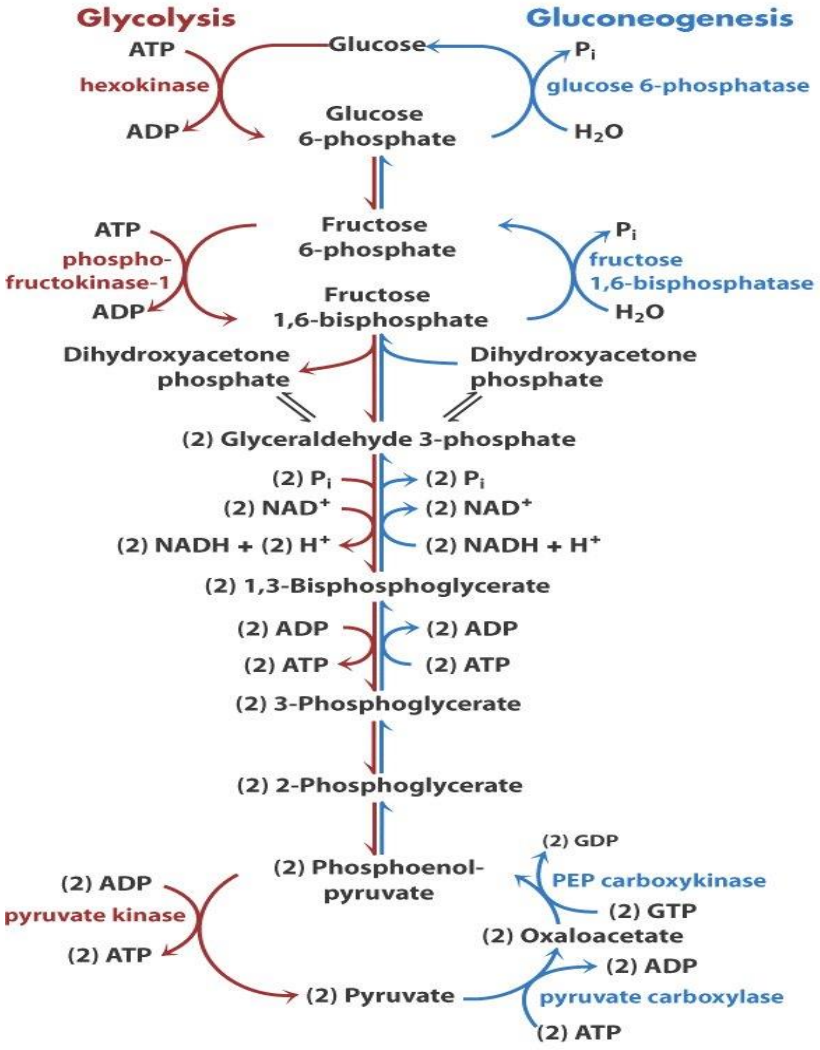


Fructose 1,6- bisphosphatase which converts fructose-1,6-bisphosphate to fructose 6-phosphate in gluconeogenesis is found in liver, kidneys and muscles

Obstacle number 3.
Glucose-6-phosphate to glucose.
Enzyme = *glucose-6-phosphatase*

- Bypasses hexokinase
- Highly exergonic, irreversible
- Absent in muscle
- Present in liver





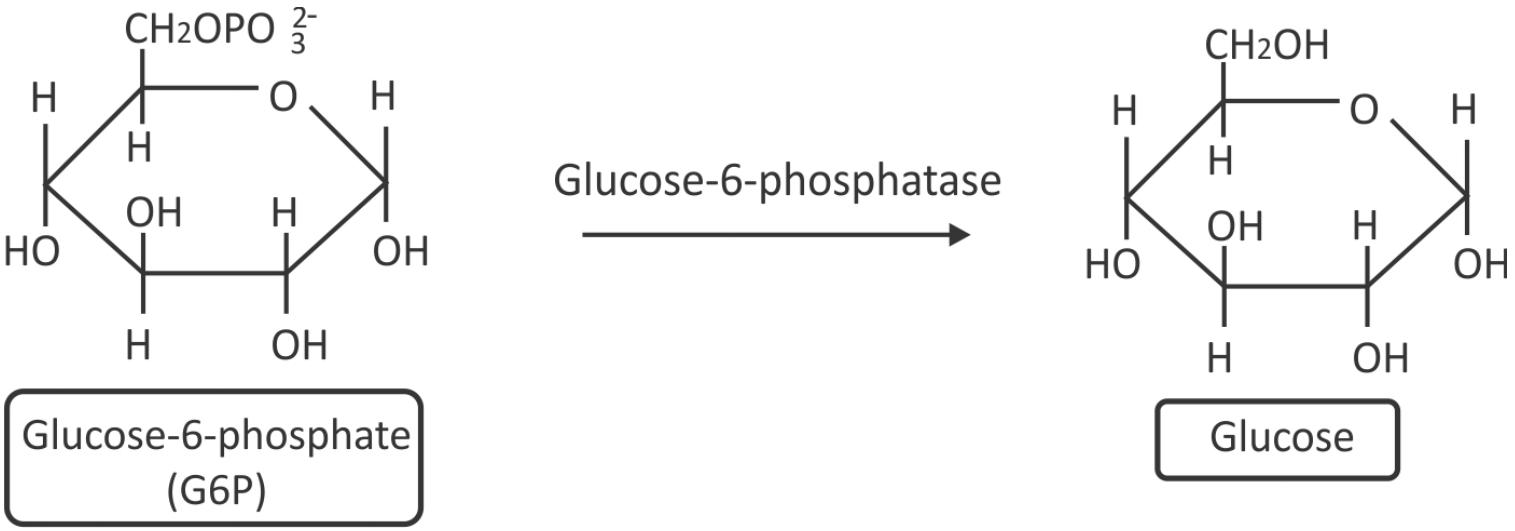
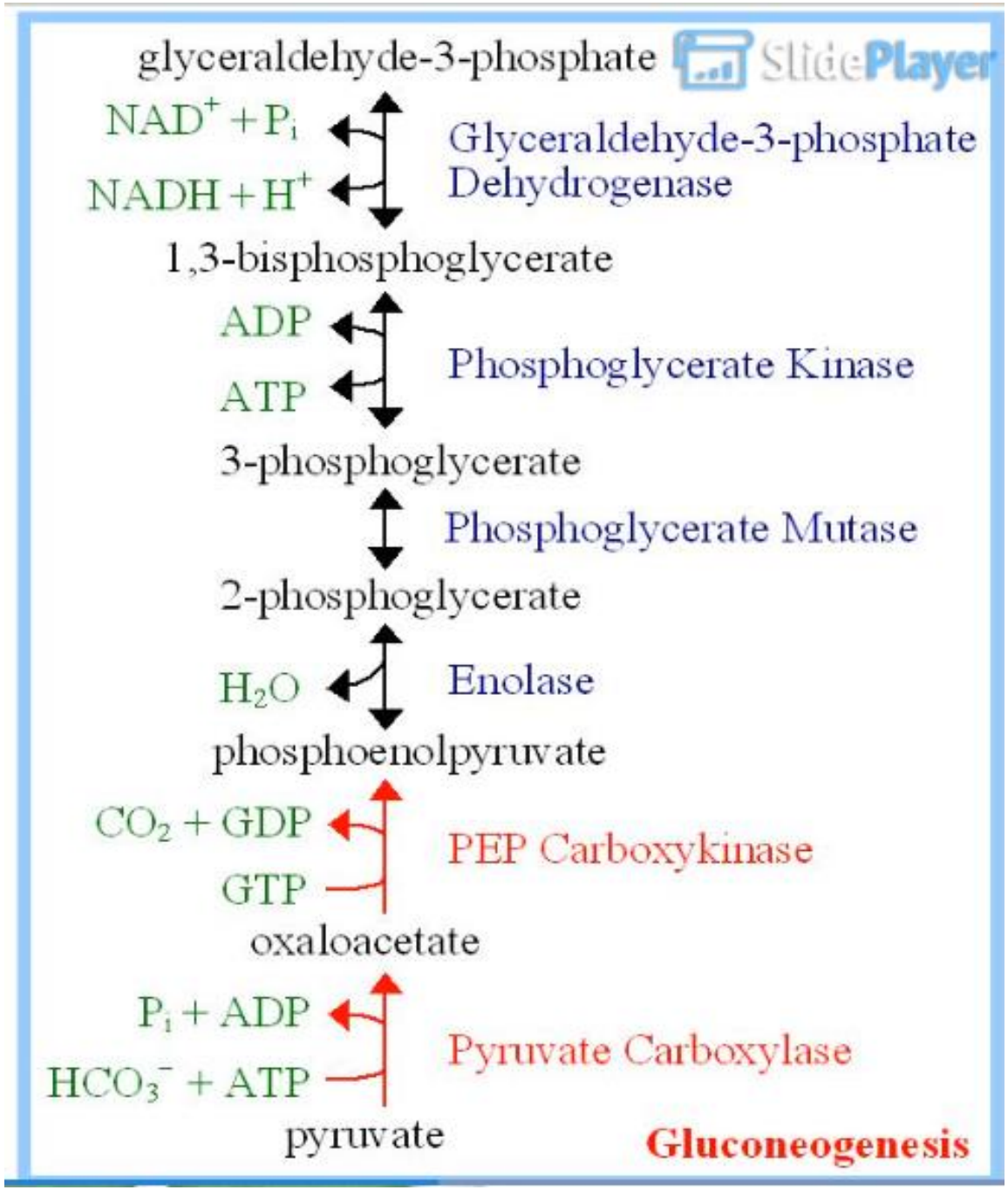


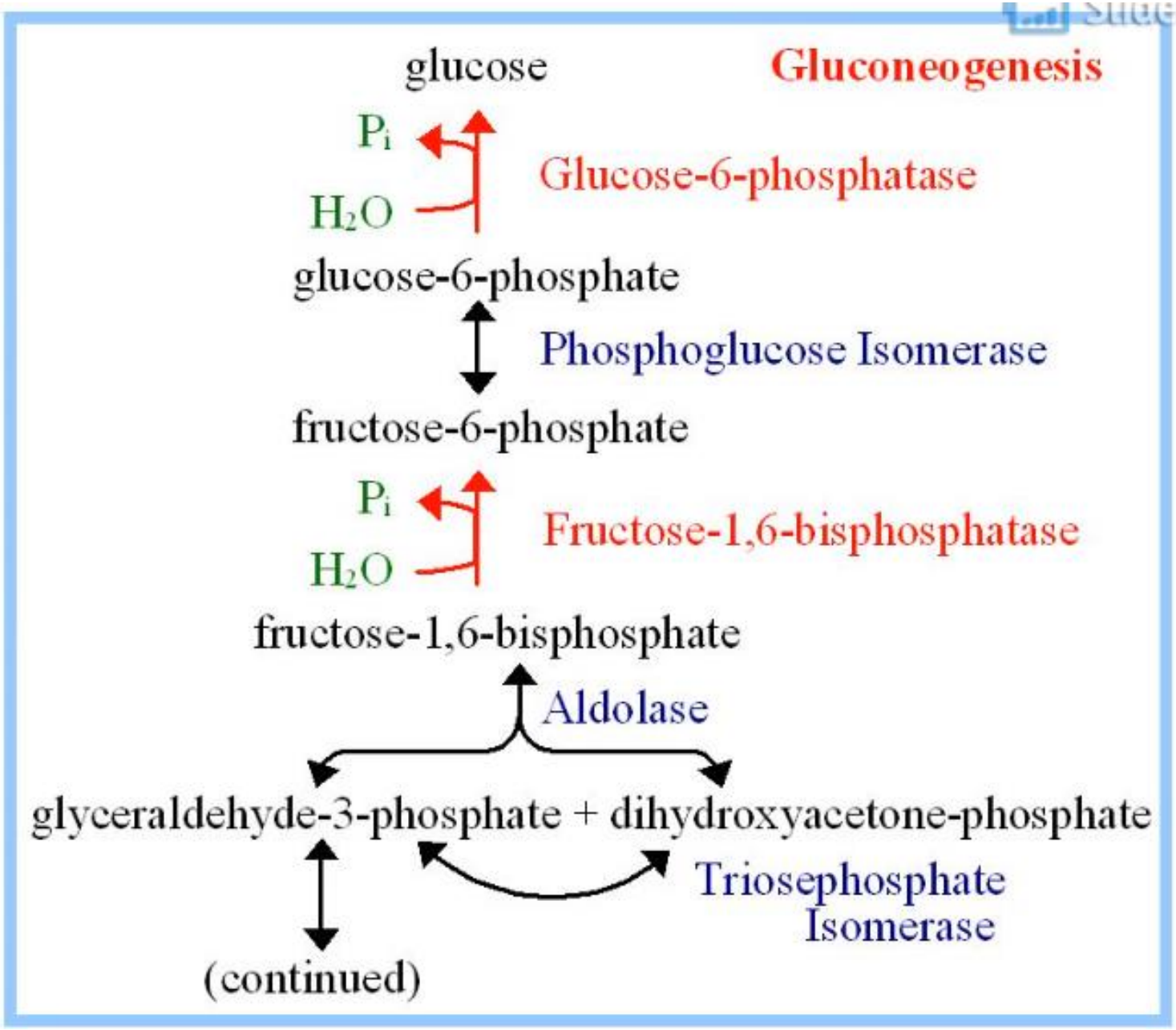
Fig. : Conversion of glucose–6 phosphate in glucose

G-6- Phosphatase which converts G-6p to Glucose is present in liver, kidney and small intestine, but absent in brain and muscles

Energy requirements

- 6 ATP are required to generate one glucose molecule.
- 2 Pyruvate → 2Oxaloacetate =2ATP
- 2 Oxaloacetate → PEP, 2GTP= 2ATP
- (2)3Phospho glycerate → (2)1,2 BPG = 2ATP
- Total = 6ATP


glyceraldehyde-3-phosphate
NAD+ + Pi
NADH + H+
Glyceraldehyde-3-phosphate Dehydrogenase
1,3-bisphosphoglycerate
ADP
ATP
Phosphoglycerate Kinase
3-phosphoglycerate
Phosphoglycerate Mutase
2-phosphoglycerate
H2O
Enolase
phosphoenolpyruvate
CO2 + GDP
GTP
PEP Carboxykinase
oxaloacetate
Pi + ADP
HCO3− + ATP
Pyruvate Carboxylase
pyruvate
Gluconeogenesis


Gluconeogenesis
glucose
Pi
H2O
Glucose-6-phosphatase
glucose-6-phosphate
Phosphoglucose Isomerase
fructose-6-phosphate
Pi
H2O
Fructose-1,6-bisphosphatase
fructose-1,6-bisphosphate
Aldolase
glyceraldehyde-3-phosphate + dihydroxyacetone-phosphate
Triosephosphate Isomerase
(continued)

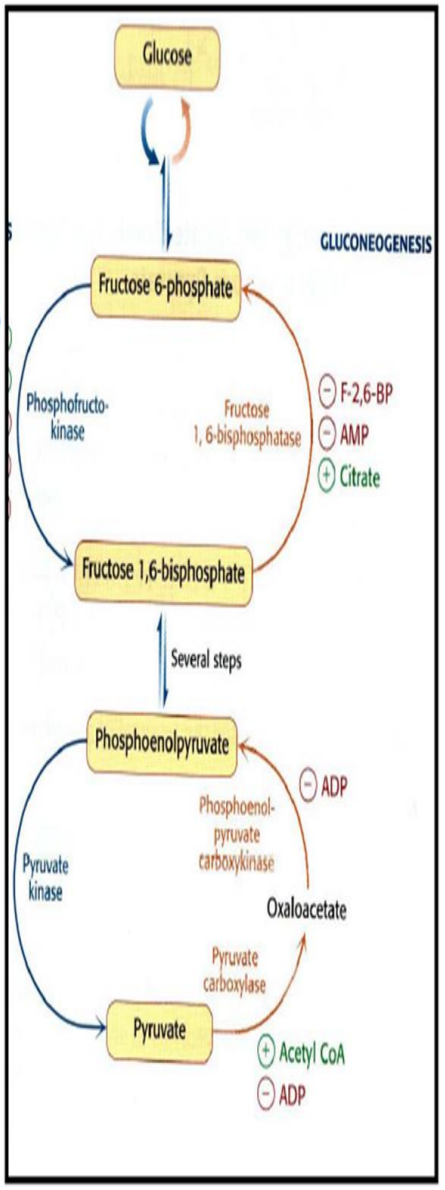
Acetyl CoA can not produce glucose

- Acetyl CoA cannot give rise to a net synthesis of glucose. This is due to the irreversible nature of the pyruvate dehydrogenase reaction, which converts pyruvate to acetyl CoA.

- **Pyruvate** —(Pyruvate dehydrogenase; NAD^+ → $NADH+H^+$)→ **acetyl CoA + CO_2**

Regulation

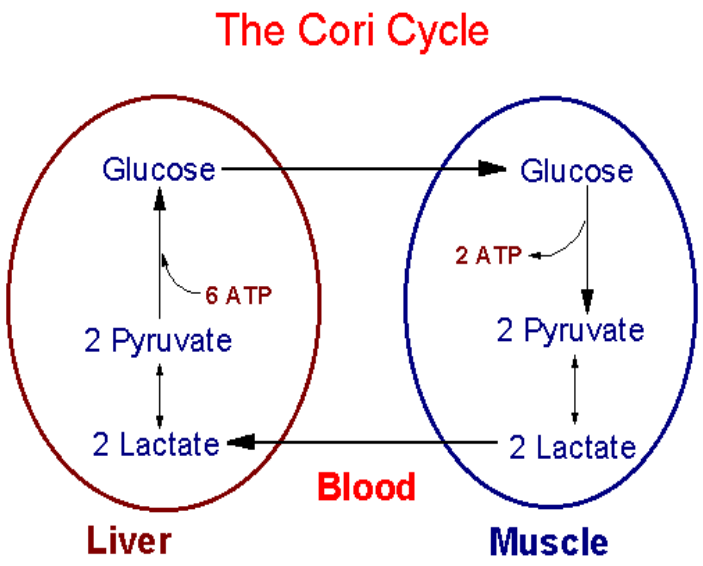
Regulation of Gluconeogenesis



Glucagon and Glucocorticoids: hormones released when glucose levels are ***low and increase GNG.***

The Cori's cycle or Lactic acid cycle

Carl Cori and Gerty Cori were awarded Nobel prize

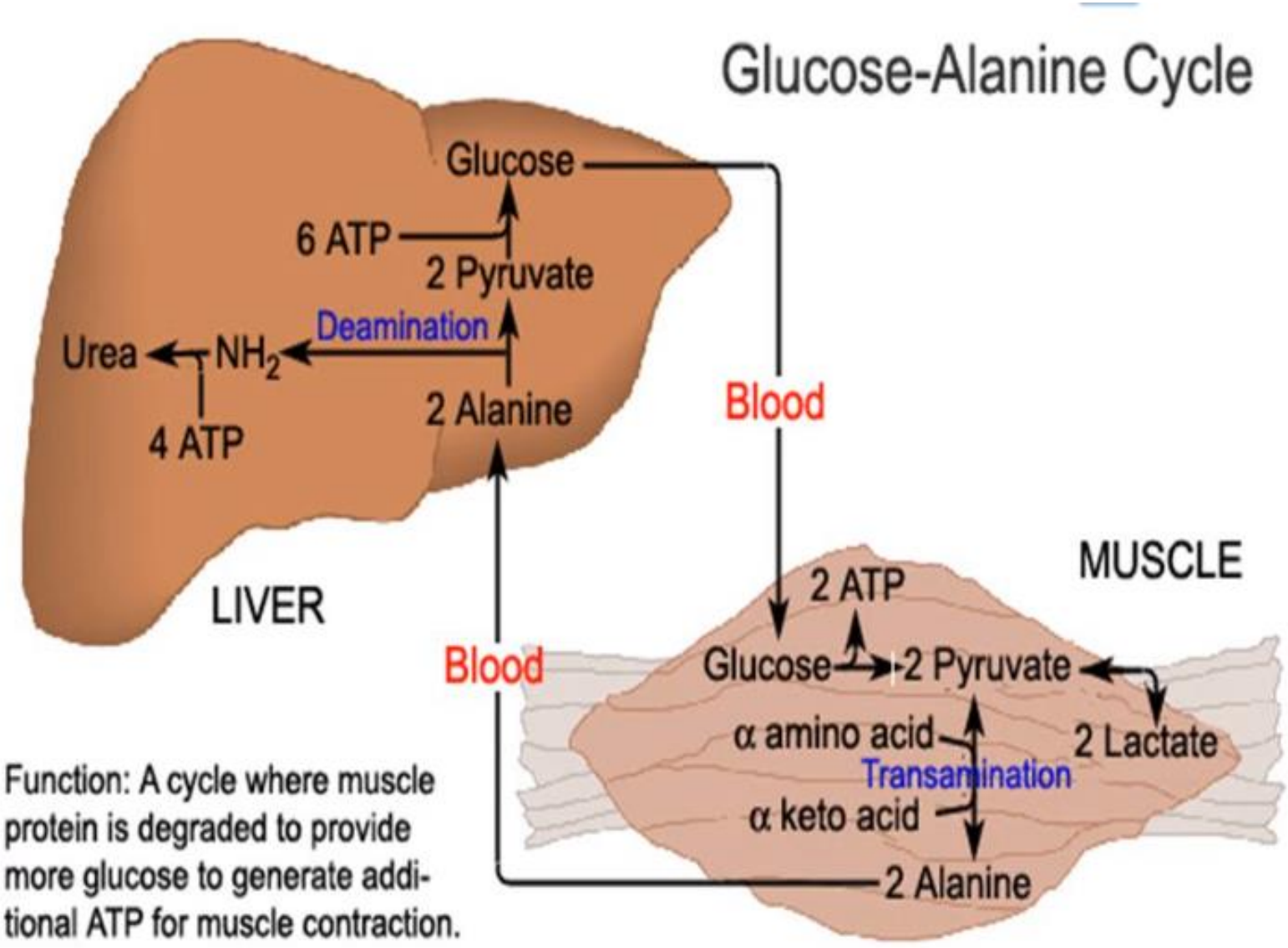


- Lactate formed in muscles or RBC transported to liver.
- In liver cell LDH converts lactate to pyruvate.
- Pyruvate enters GNG to form glucose.

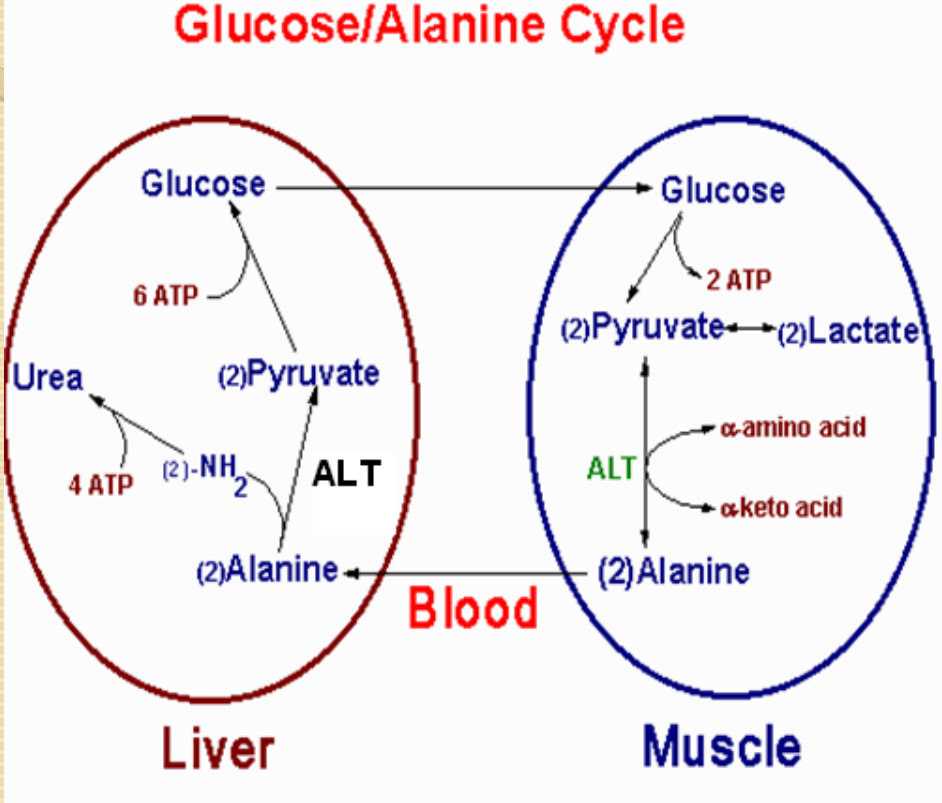
- The **Cori Cycle** operates during **exercise**.
- Lactate is efficiently reutilized by the body

The Glucose – Alanine Cycle

- The Gluconeogenic cycle that uses Alanine to move Pyruvate from the cell to the liver.
- This cycle maintains blood glucose at the cost of muscle amino acids.
  - Alanine may provide up to 5% of the total fuel used during exercise.


Glucose-Alanine Cycle
Glucose
6 ATP
2 Pyruvate
Deamination
Urea
NH_2
4 ATP
2 Alanine
LIVER
Blood
Blood
MUSCLE
2 ATP
Glucose
2 Pyruvate
α amino acid
2 Lactate
Transamination
α keto acid
2 Alanine
Function: A cycle where muscle protein is degraded to provide more glucose to generate additional ATP for muscle contraction.

In starvation



- Alanine is transported to liver , transaminated to pyruvate and converted to glucose.
- Glucose enter the glycolysis to form pyruvate which inturn transaminated to Alanine.

Substrates for Gluconeogenesis

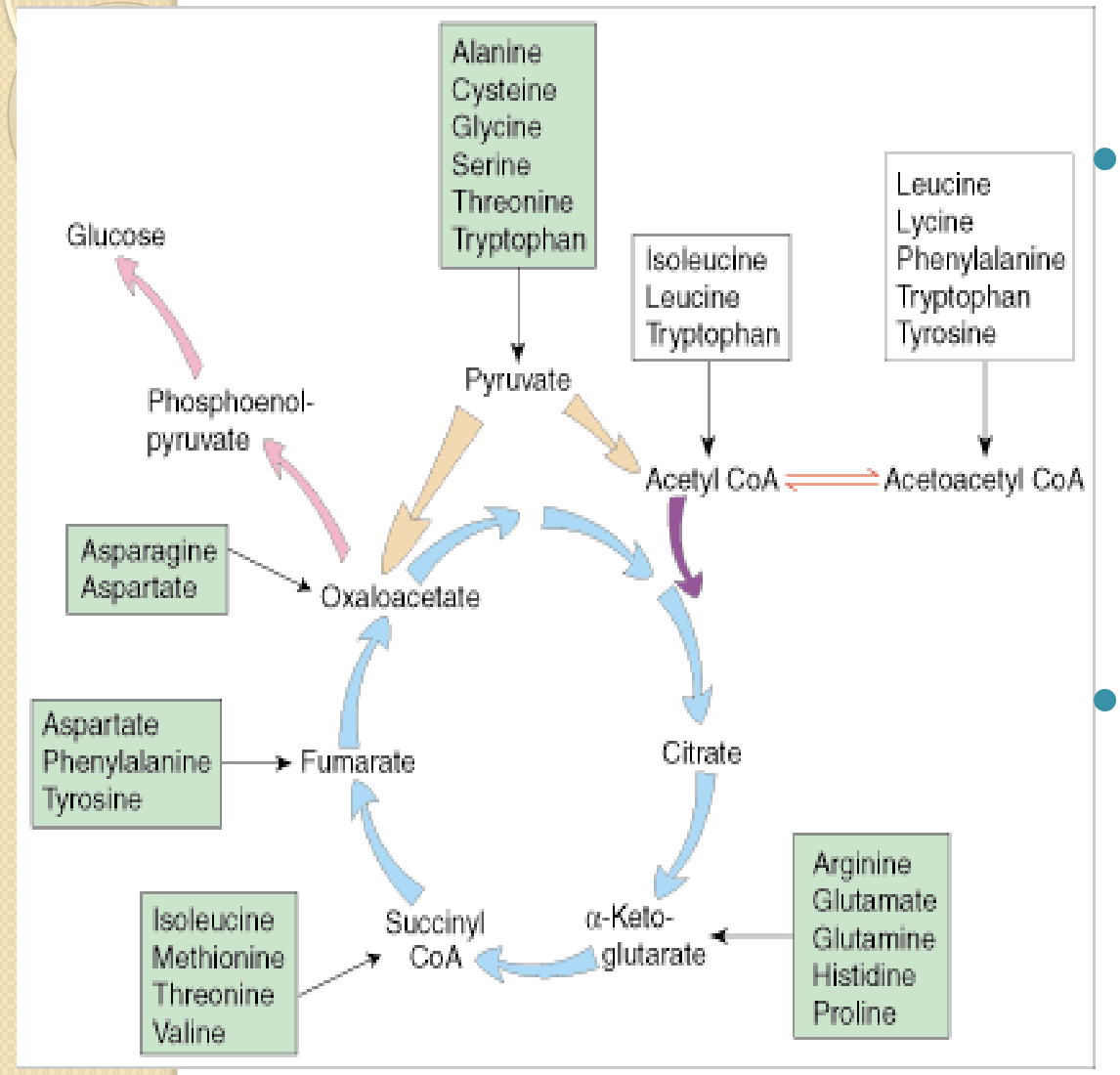
1- Lactate (Lactic acid):

- In vigorous skeletal muscle activity, large amount of lactic acid produced ⟶ pass to liver through blood stream ⟶ converted into pyruvic and lastly to glucose reach muscle again through blood stream to provide energy **(Cori cycle)**.

2- Glucogenic amino acids:

- Amino acids by deamination can be converted into keto acids as pyruvic, ketoglutaric and oxaloacetic acid.
- Proteins are considered as one of the main sources of blood glucose especially after 18 hr due to depletion of liver glycogen.

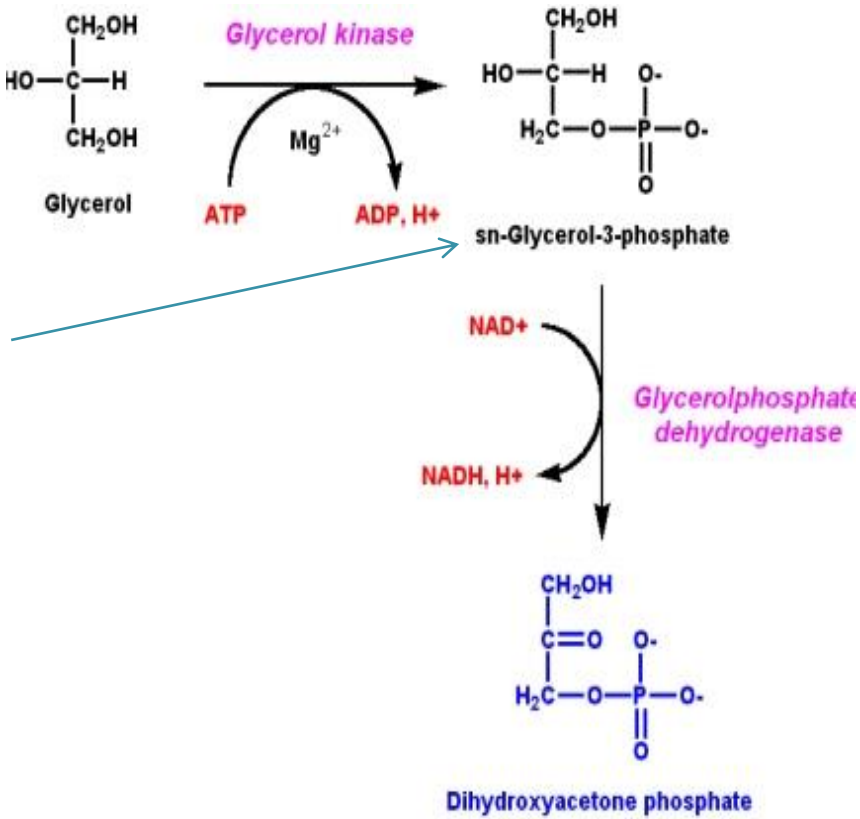
Glucogenic Amino Acids



- Glucogenic AA are transaminated to TCA cycle intermediates and form OAA and pyruvate.
- Pyruvate can also be turned into the amino acid Alanine.

Glycerol: liberated in the adipose tissue by hydrolysis of fats (TAG)

Glycerol: is Phosphorylated in the liver by ATP to glycerol-3 phosphate which is then oxidised to DHAP and channeled into **glycolysis.**

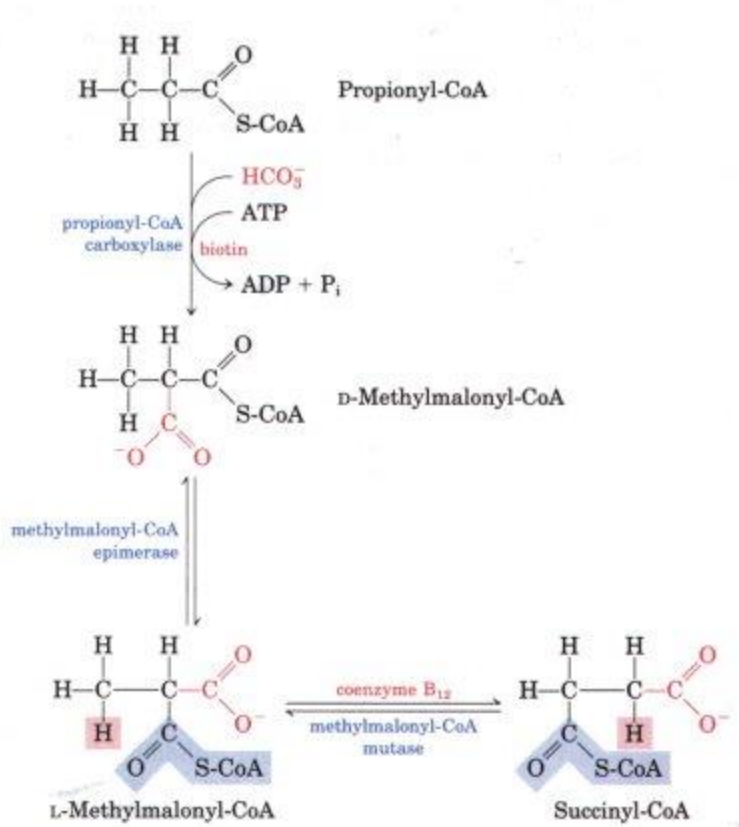


Propionyl CoA: formed from odd chain FA

- Propionyl CoA: by biotin dependent carboxylation is converted to

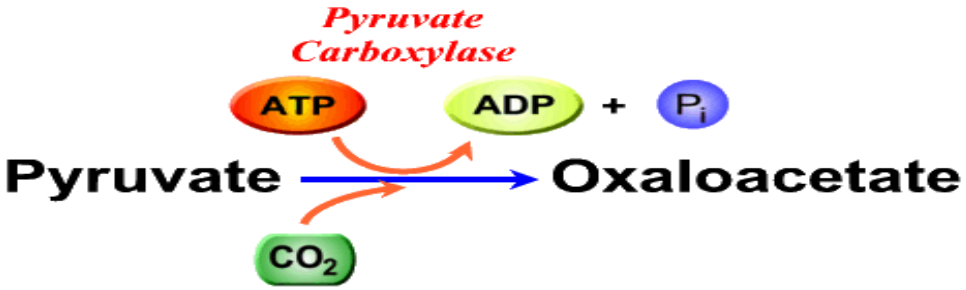
Succinyl CoA and enters GNG via TCA .

- Even chain FA are not substrates.



Disorders (cont.)

1. Pyruvate carboxylase deficiency : first step of GNG



- Lack of OAA affects the function of Krebs cycle
- Presents with LA
- Fasting results in hypoglycemia and LA.
- Diagnosis : Pyruvate carboxylase assay in cultured skin fibroblast.
- Prognosis : rarely survive > 3 months

Disorders

2. Fructose -1,6 bisphosphate: deficiency leads to imparied GNG and accumulation of precursors of GNG lactate pyruvate, alanine, ketones.

- Acute episodes are precipitated by infection and fasting.
- Diagnosis: F-1,6BP assay in leucocytes and liver homogenate