

# Gluconeogenesis

(Production of glucose from non-carbohydrate precursors)

Dr. Diala Abu-Hassan

Textbook:

Lippincott's Illustrated reviews: Biochemistry

# Glucose Synthesis is Required for Survival

- Brain is dependent on glucose 120g/day
  - Body glucose reserve is limited
    - ≈ 20 g (extra cellular fluid)
    - ≈ 75 g ( liver glycogen); enough for 16 hours
    - ≈ 400 g (muscle glycogen); for muscle use only
- Main source of energy for resting muscle in post-absorptive state
- 70 Kg man has ≈ 15 Kg fat
    - Fatty acids can not be converted to glucose
    - Utilization of FA is increased 4-5 X in prolonged fasting
    - In prolonged fasting; FA → ketone bodies at high rate

# Gluconeogenesis occurs mainly in the liver

Tissues that do not oxidize glc. completely  
e.g. **RBCs**  
Exercising muscle

Muscle  
Glucogenic A.As

Adipose  
tissue

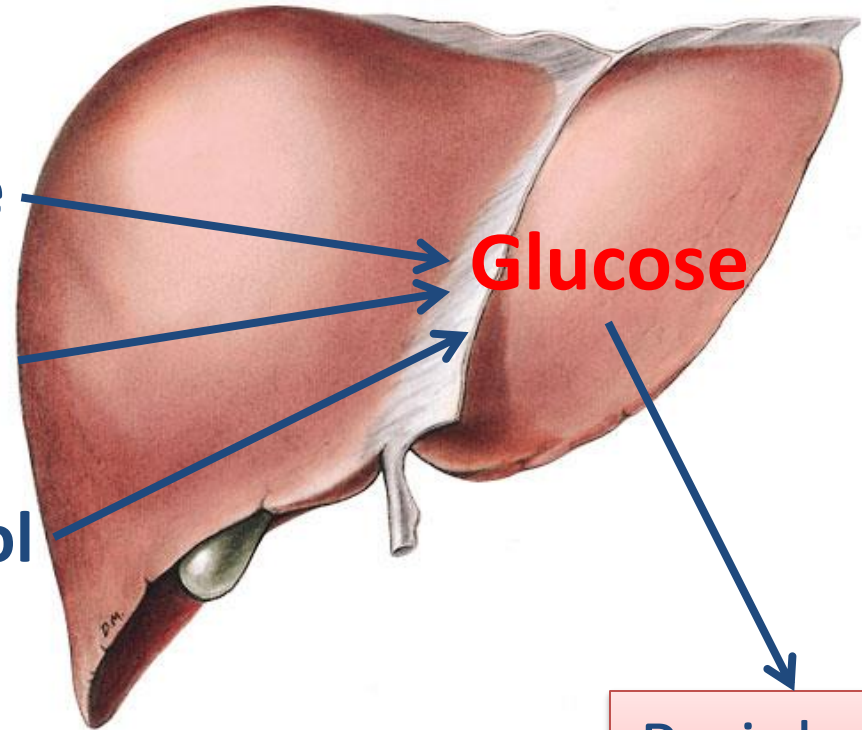
Lactate

Alanine

Glycerol

**Glucose**

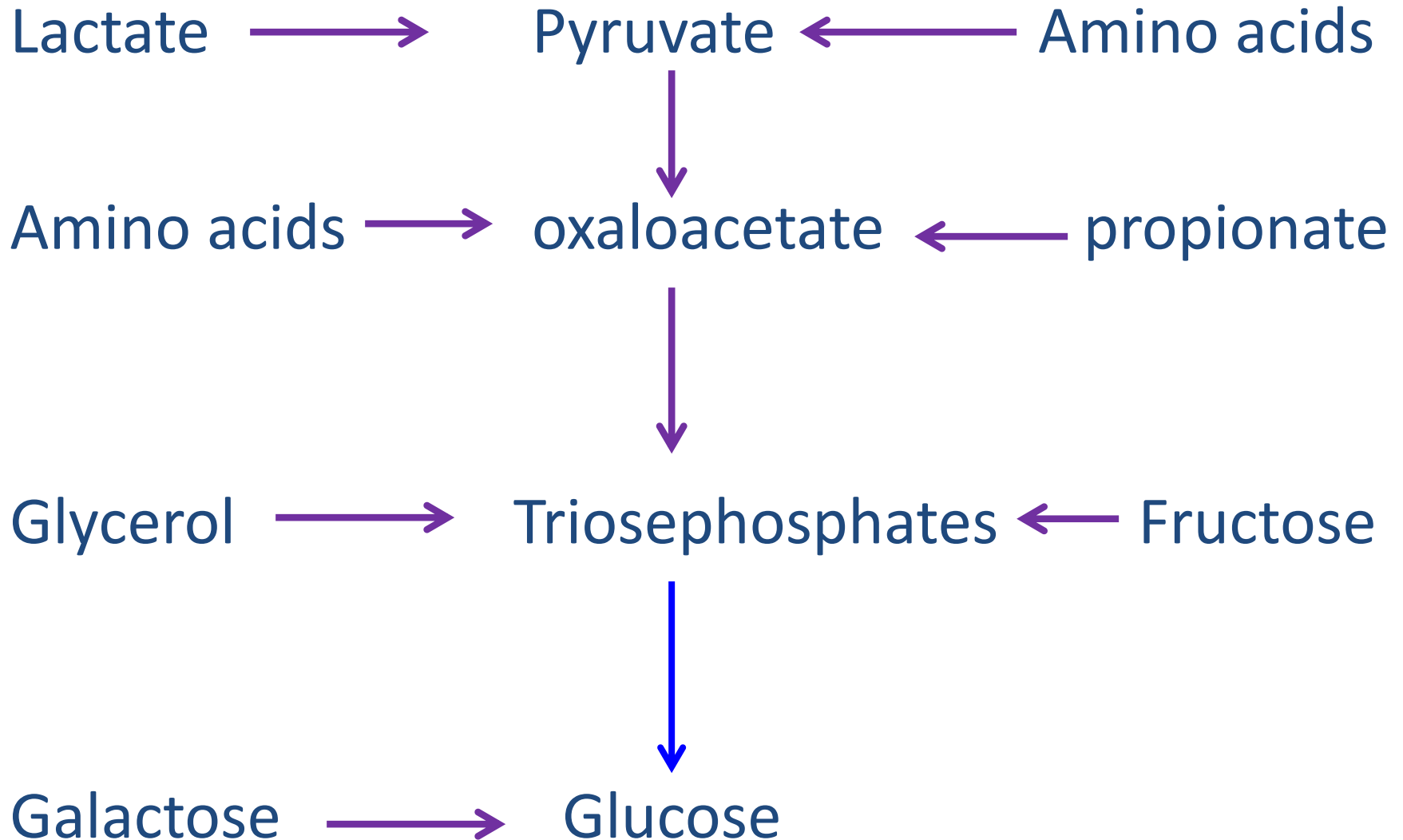
Peripheral  
tissues



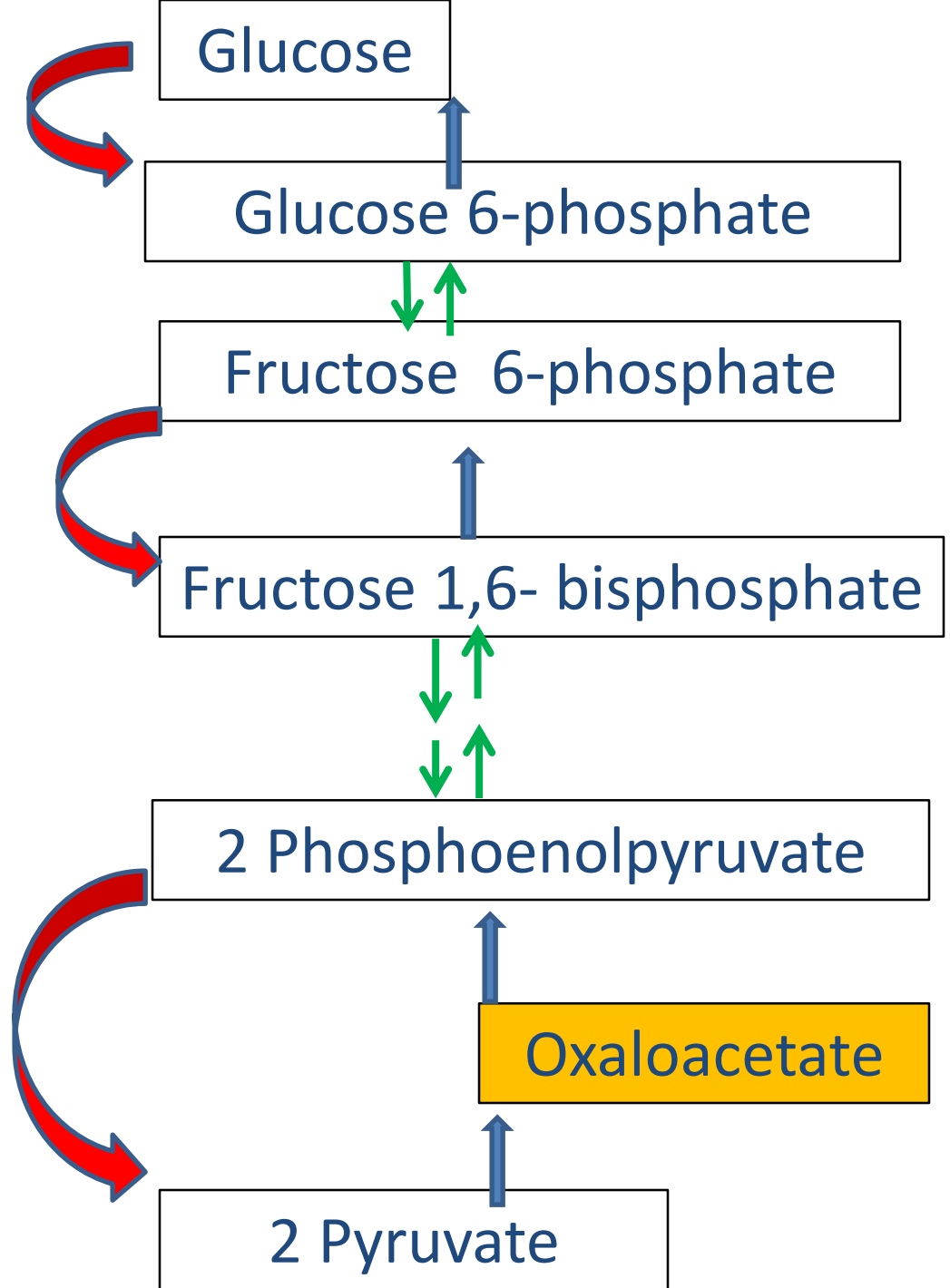
# Where and when does gluconeogenesis occur?

- During an overnight fast, ~ 90% of gluconeogenesis occurs in the liver and 10% by the kidneys
- During prolonged fasting kidneys become major glucose-producing organs (40% of total glucose production)

# Entrance of substrates into gluconeogenesis



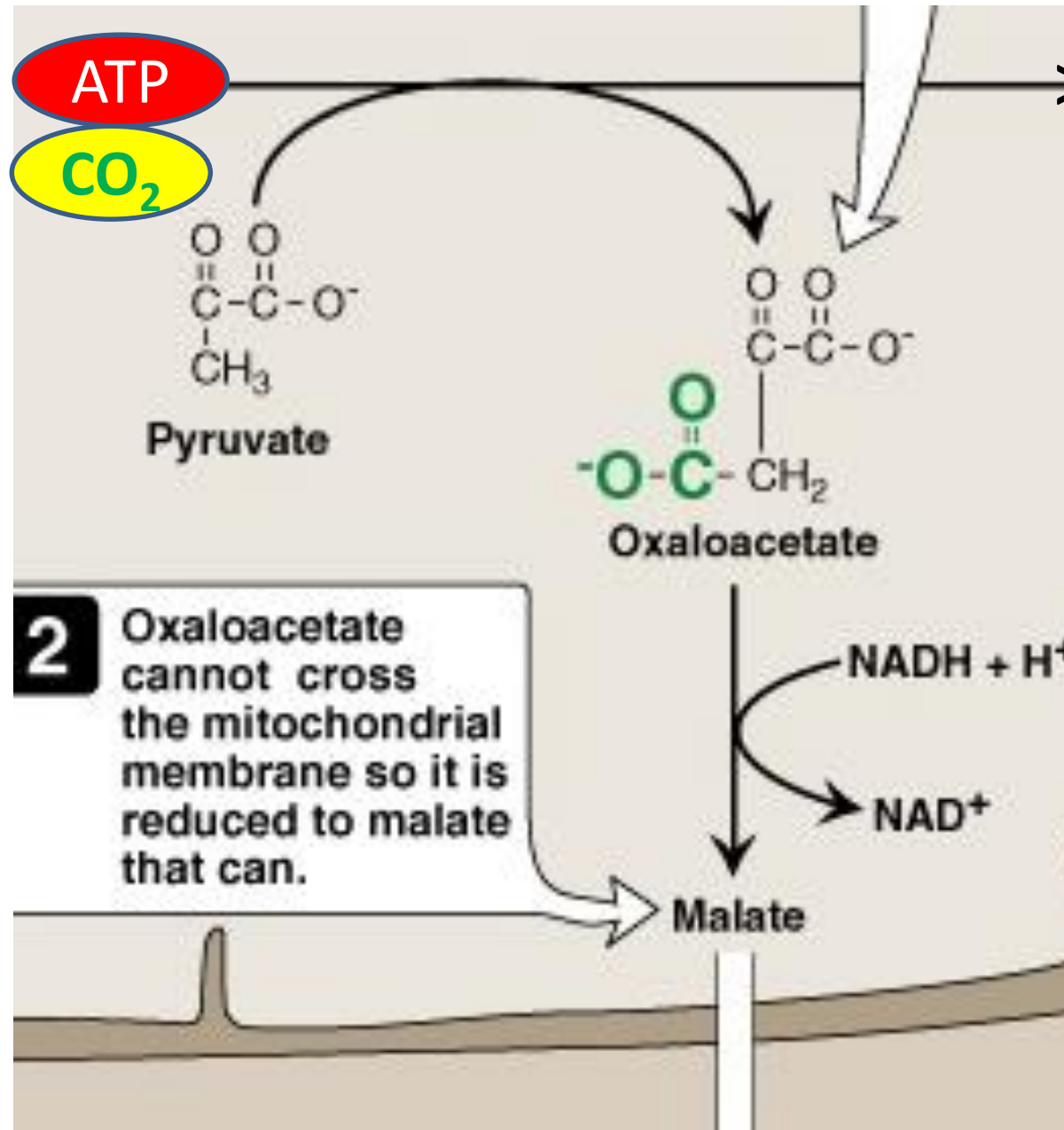
**Gluconeogenesis  
is the opposite of  
glycolysis BUT**



# Reversing the irreversible steps

1. From pyruvate to phosphoenolpyruvate (PEP)

# Carboxylation of Pyruvate Produces Oxaloacetate (OAA)



- By pyruvate carboxylase
- In mitochondria
- Allosterically activated by Acetyl Co A

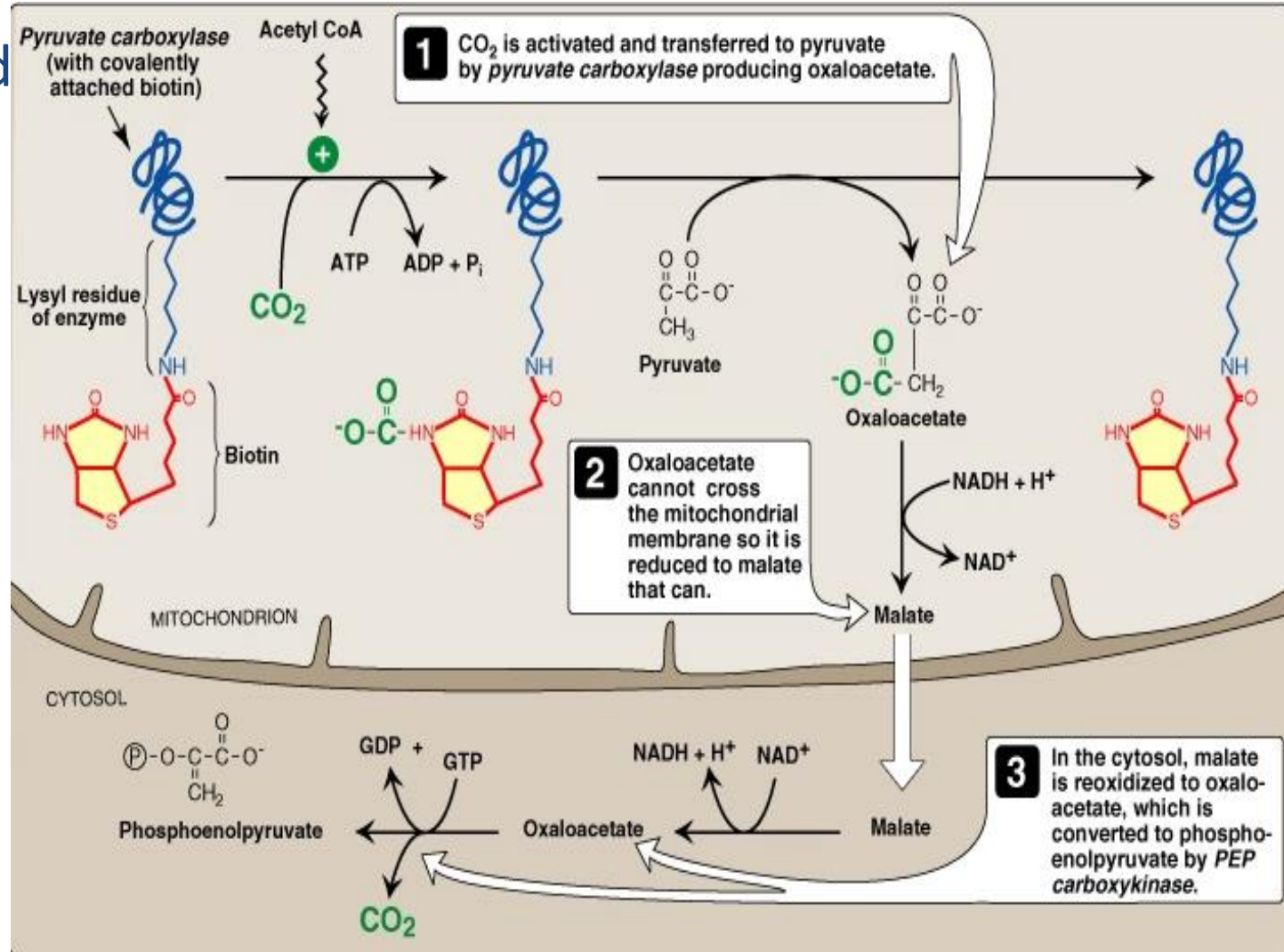


# From OAA to PEP

- Enzyme is found in both cytosol and mitochondria

- The generated PEP in the mitochondria is transported to the cytosol by a specific transporter

- The PEP that is generated in the cytosol requires the transport of OAA from the mitochondria to the cytosol

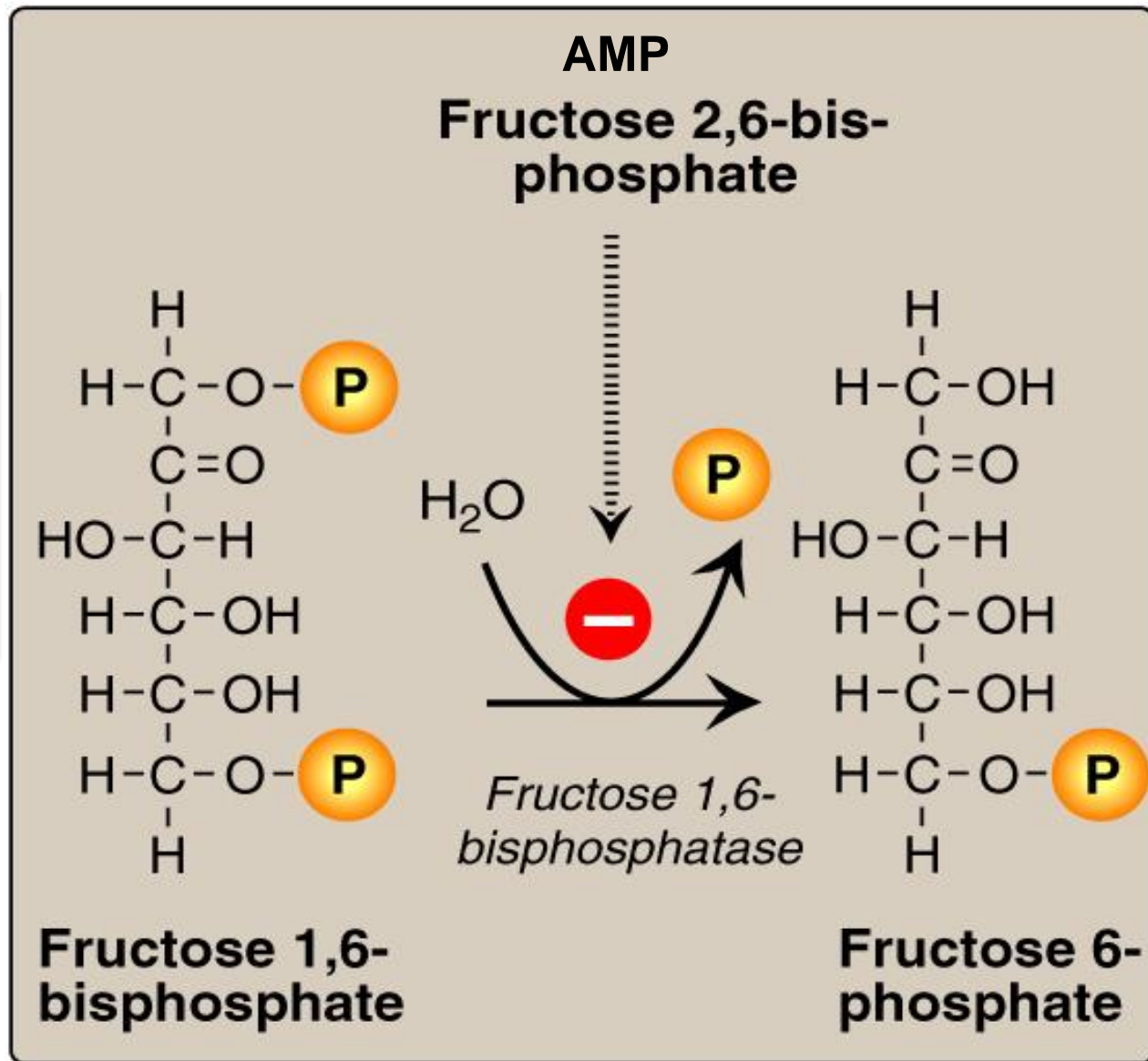


# Reversing the irreversible steps

2. From fructose-1,6-bisphosphate to fructose-6-phosphate

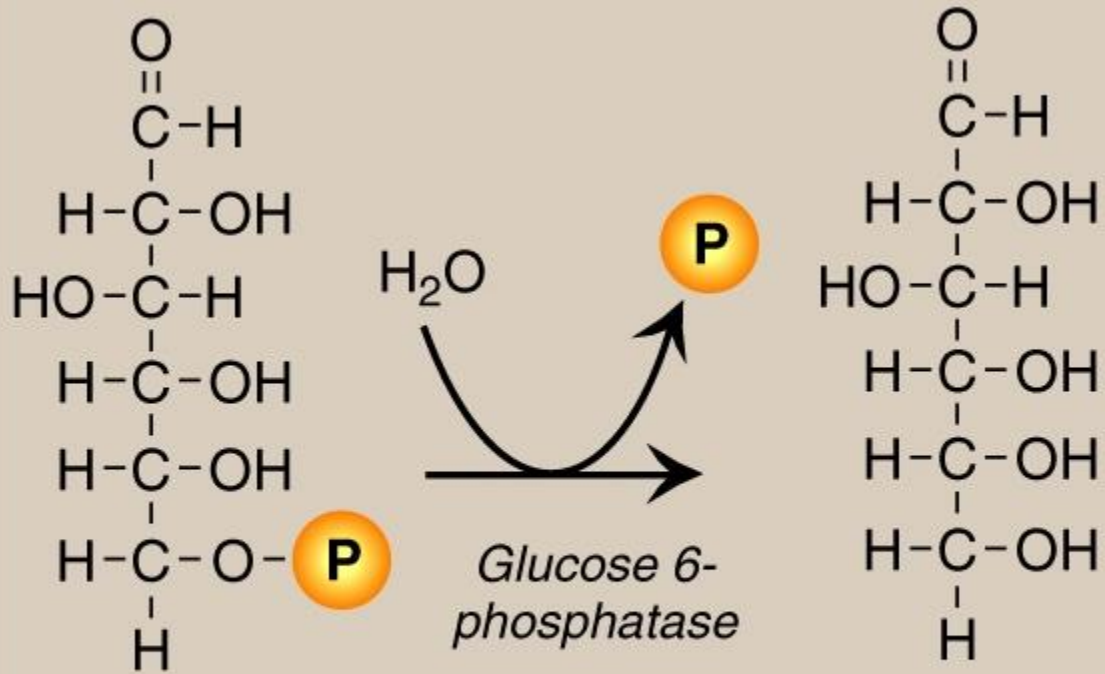
# Dephosphorylation of fructose 1,6-bisphosphate

This reaction bypasses the irreversible phosphofructokinase -1 reaction



# Reversing the irreversible steps

3. From glucose-6-phosphate to glucose



**Glucose 6-phosphate**

**D-Glucose**

## Dephosphorylation of glucose 6-phosphate

- Bypasses the irreversible hexokinase reaction
- Only in liver and kidney
- Glucose 6-phosphate translocase is needed to transport G-6-P across the ER membrane

## Glucose 6-phosphatase in Endoplasmic Reticulum (ER)

Hint: Muscle lacks glucose 6-phosphatase, and therefore muscle glycogen can not be used to maintain blood glucose levels.

# Formation vs. Hydrolysis of Glucose 6-phosphate

- Formation



**Hexokinase**

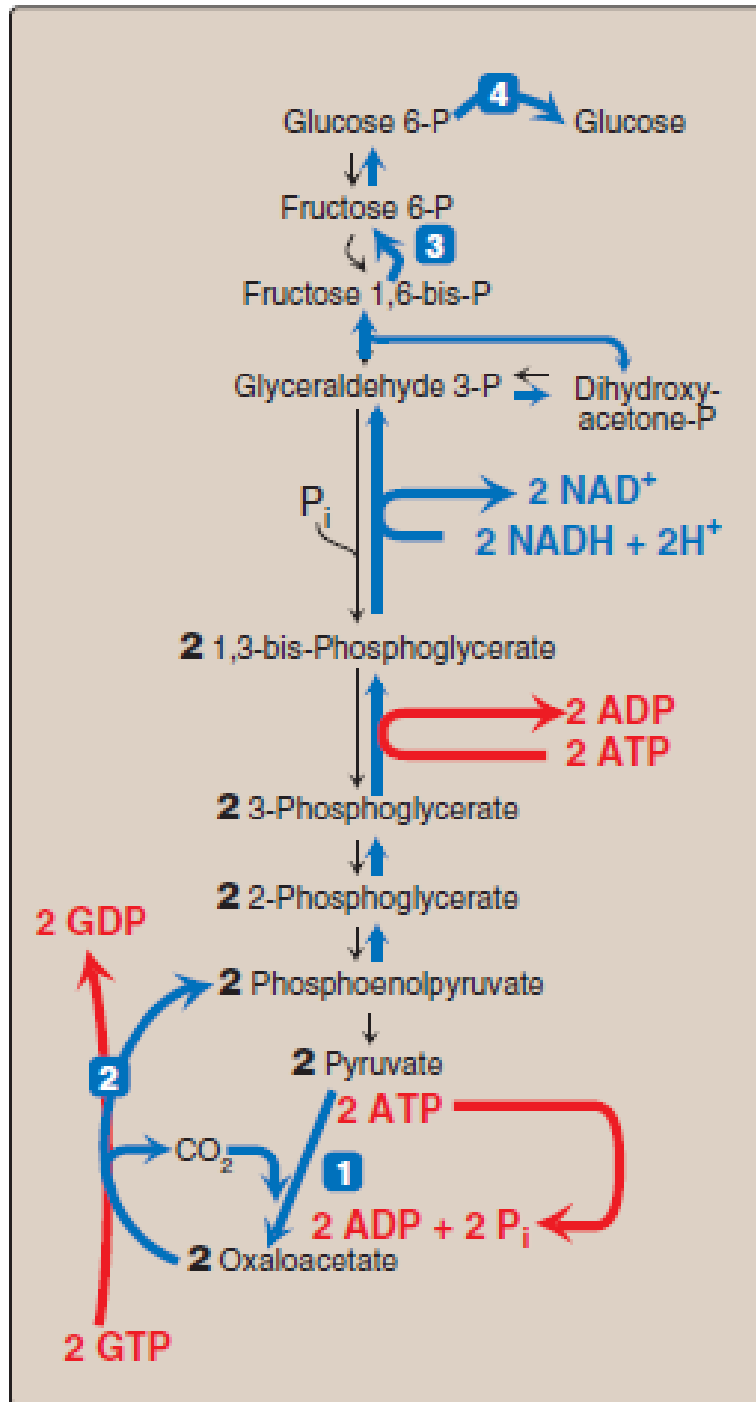


- Hydrolysis

**Phosphatase**

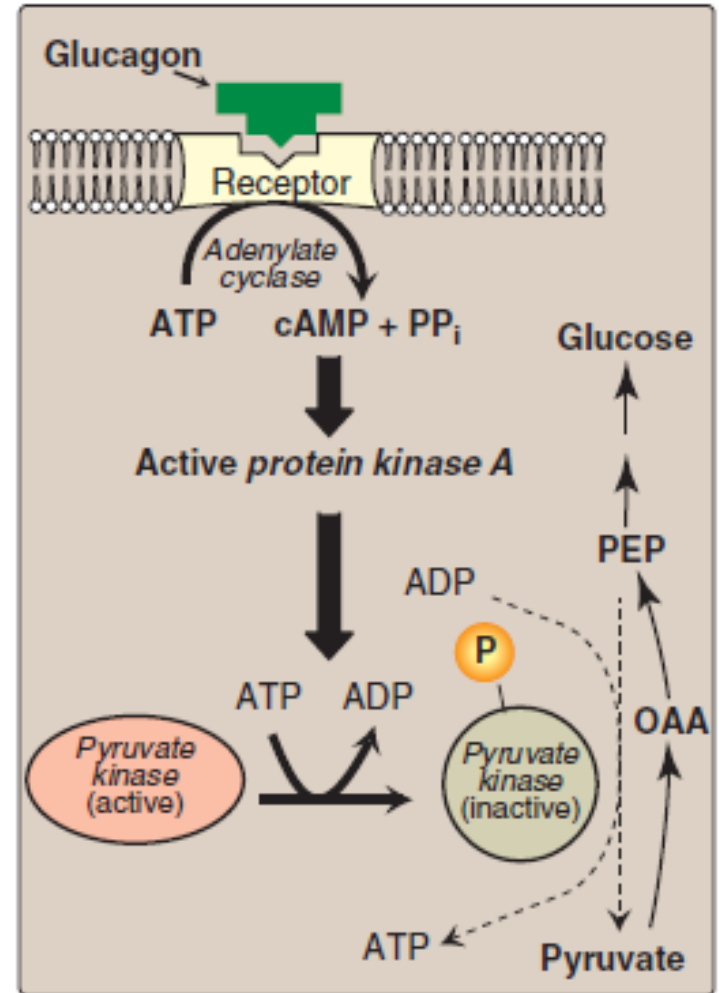


# Energy requirements of gluconeogenesis



# Regulation of gluconeogenesis

- Mainly by:
  1. The circulating level of glucagon
  - Glucagon lowers the level of fructose 2,6-bisphosphate, resulting in activation of fructose 1,6-bisphosphatase and inhibition of PFK-1
  - Inhibition of pyruvate kinase
  - Glucagon increases the transcription of the gene for PEP-carboxykinase
- 2. The availability of gluconeogenic substrates



3. Slow adaptive changes in enzyme activity due to an alteration in the rate of enzyme synthesis or degradation, or both