Gluconeogenesis

(Production of glucose from non-carbohydrate precursors)

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Textbook:

Lippincott's Illustrated reviews: Biochemistry

Glucose Synthesis is Required for Survival

- Brain is dependent on glucose 120g/day
- Body glucose reserve is limited

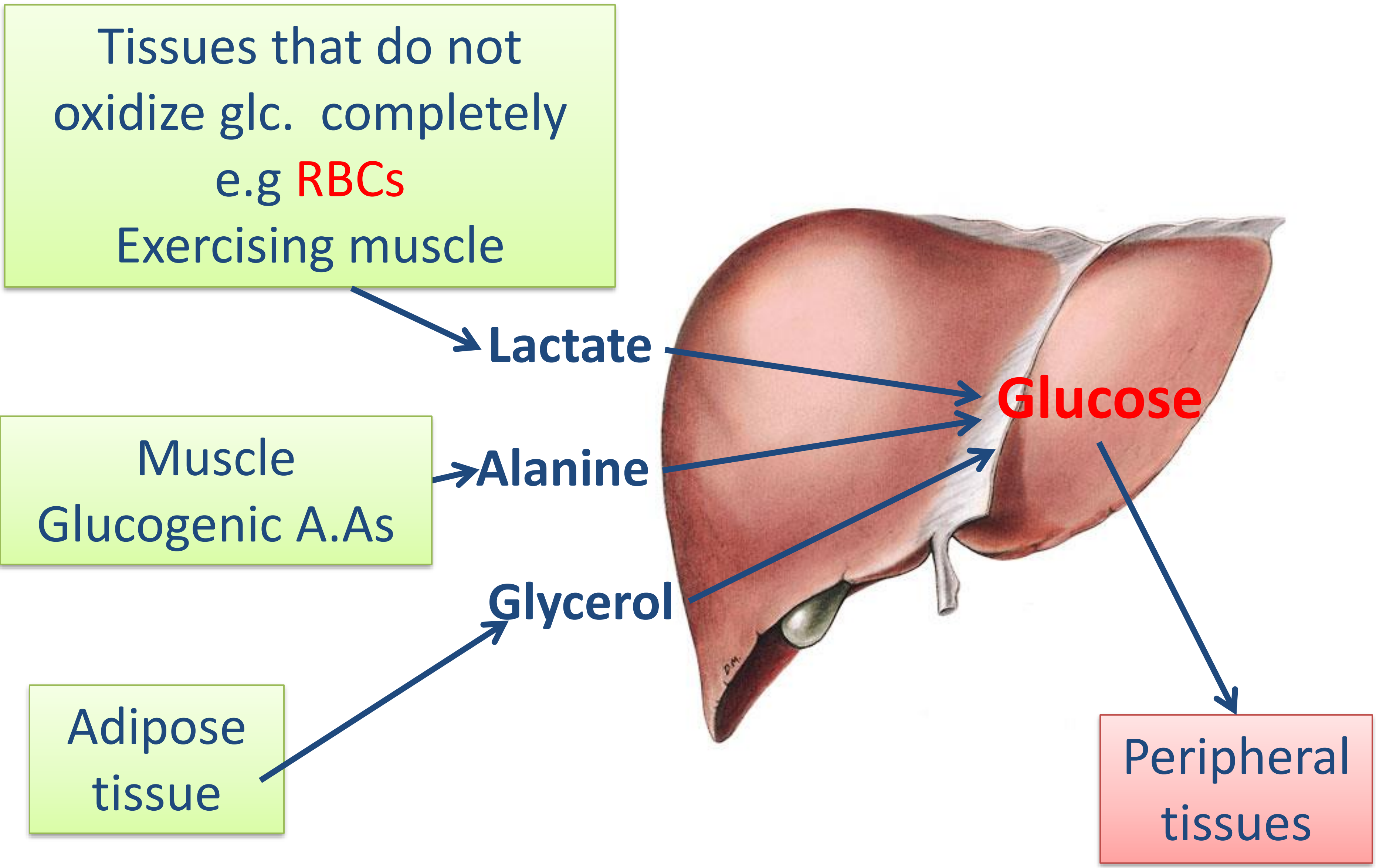
  ≈ 20 g (extra cellular fluid)

  ≈ 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

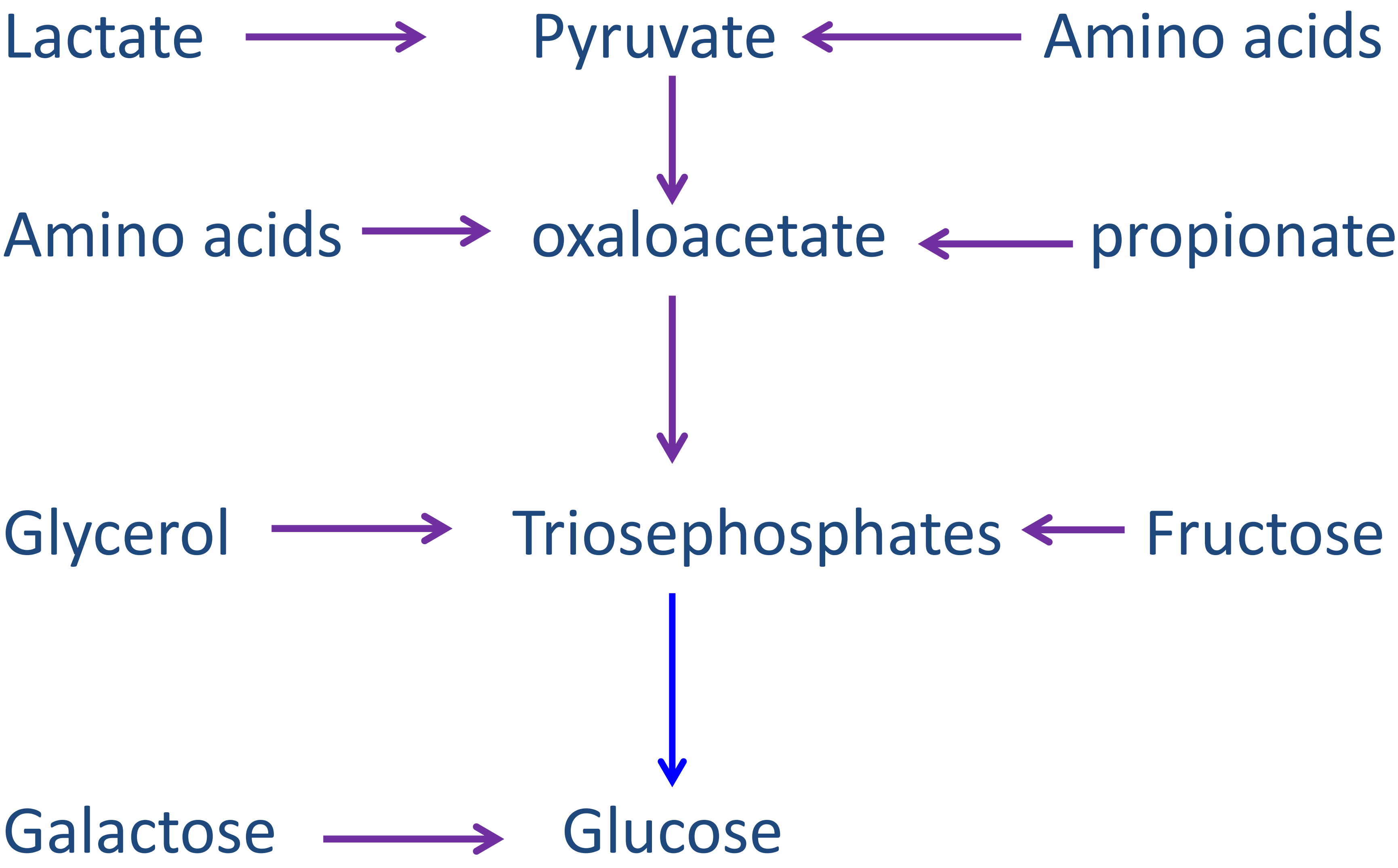


Where and when does gluconeogenesis occur?

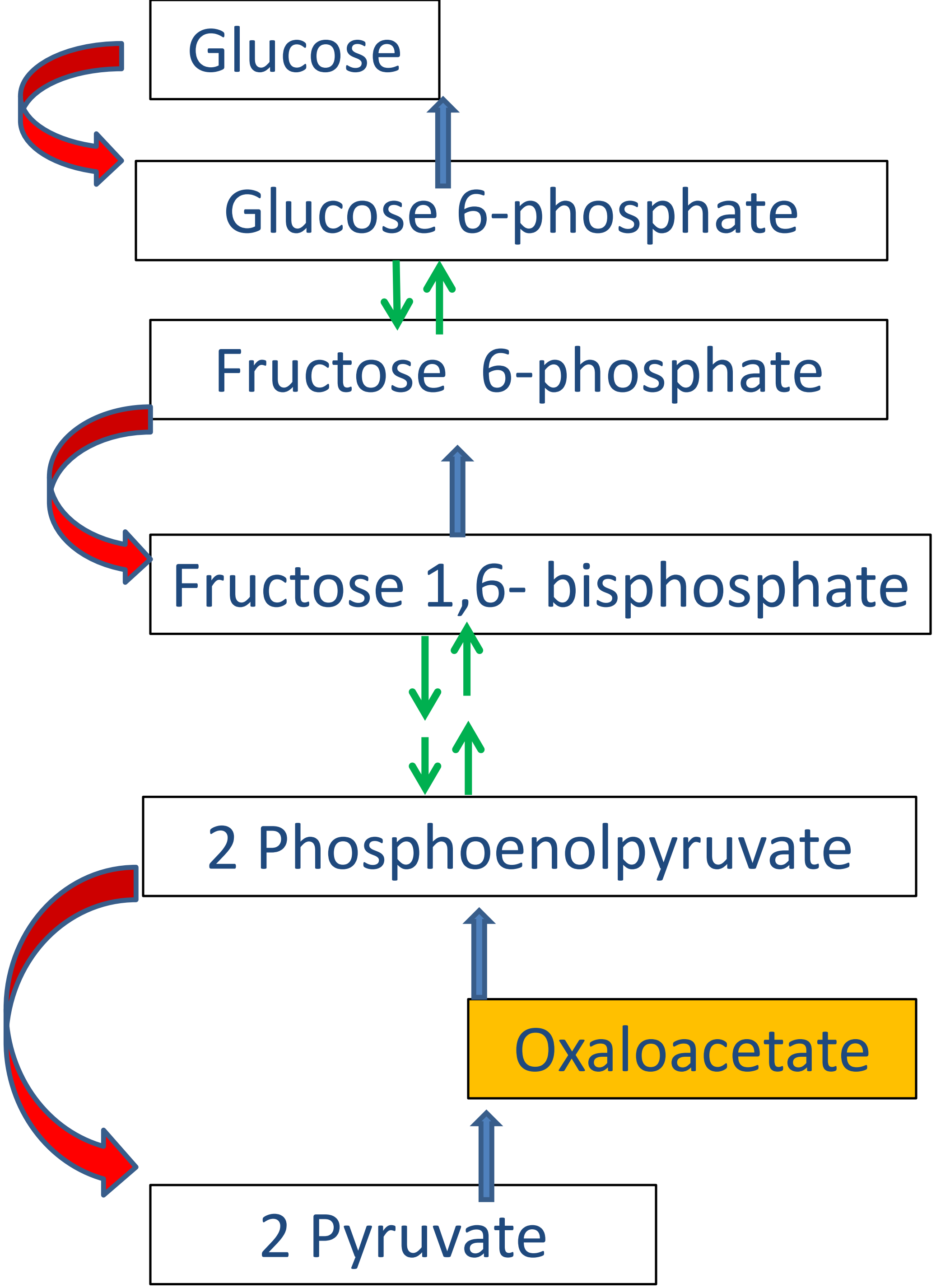
- During an overnight fast, ~ 90% of gluconeogenesis occurs in the liver and 10% by the kidneys

- During prolonged fasting kidneys become major glucose-producing organs (40% of total glucose production)

Entrance of substrates into gluconeogenesis



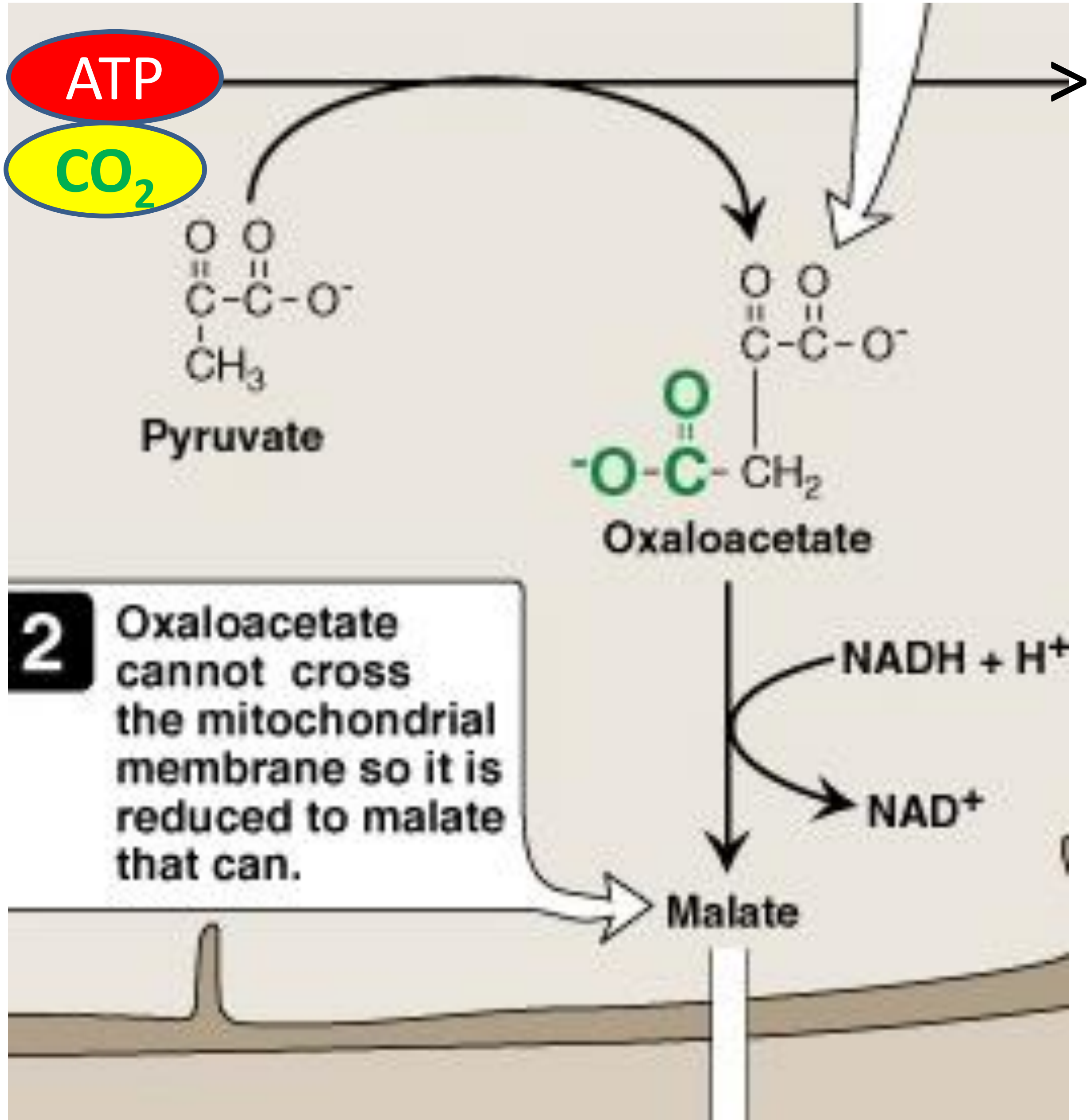
Gluconeogenesis is the opposite of glycolysis BUT



Reversing the irreversible steps

1. From pyruvate to phosphoenolpyruvate (PEP)

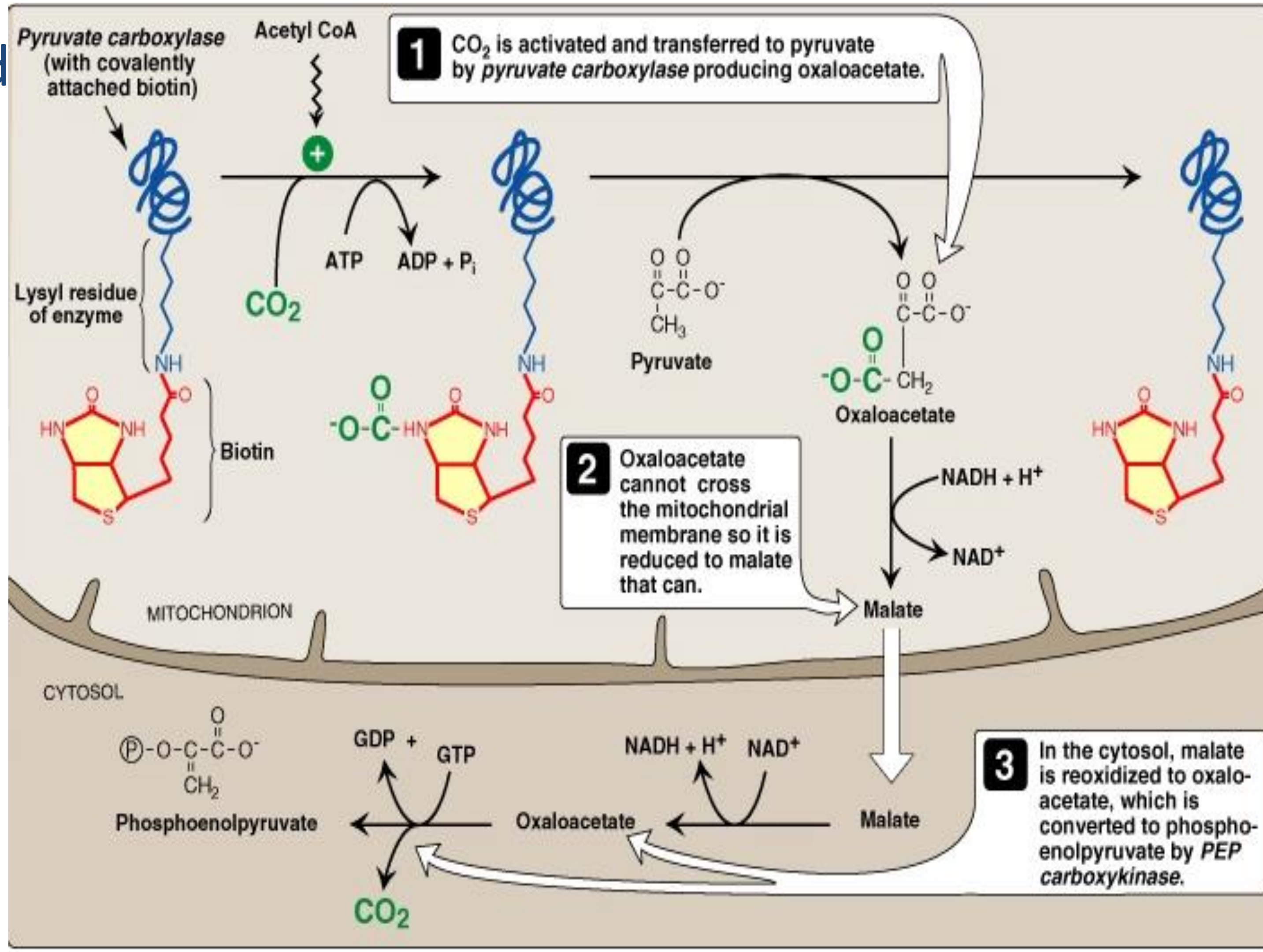
Carboxylation of Pyruvate Produces Oxaloacetate (OAA)



- 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

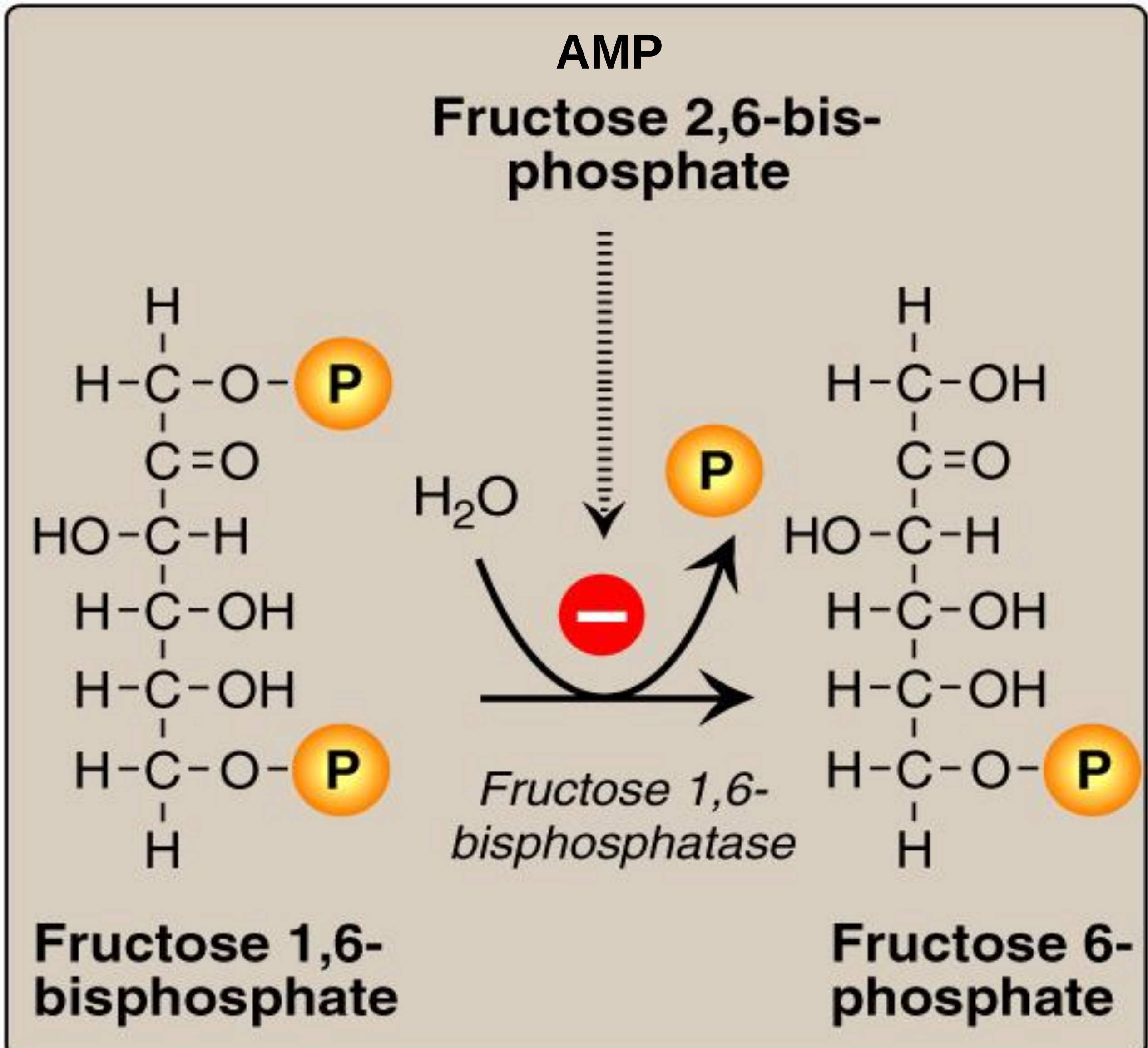


Reversing the irreversible steps

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

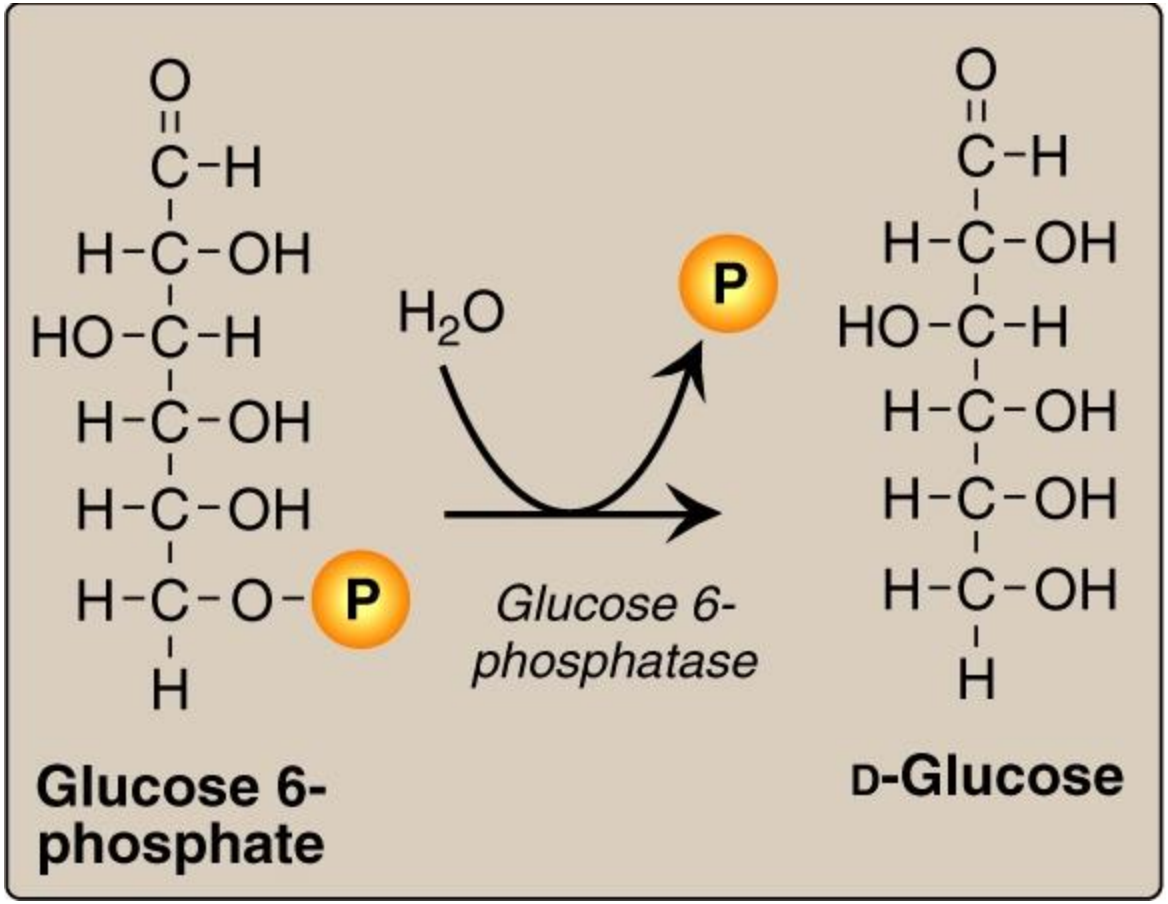
Dephosphorylation of fructose 1,6-bisphosphate

This reaction bypasses the irreversible phosphofructokinase -1 reaction



Reversing the irreversible steps

3. From glucose-6-phosphate to glucose



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

Glc. + Pi $\rightarrow$ Glc. 6-phosphate + H_2O ΔG = +ve

ATP + H_2O $\rightarrow$ ADP + P_i ΔG = -ve

Hexokinase

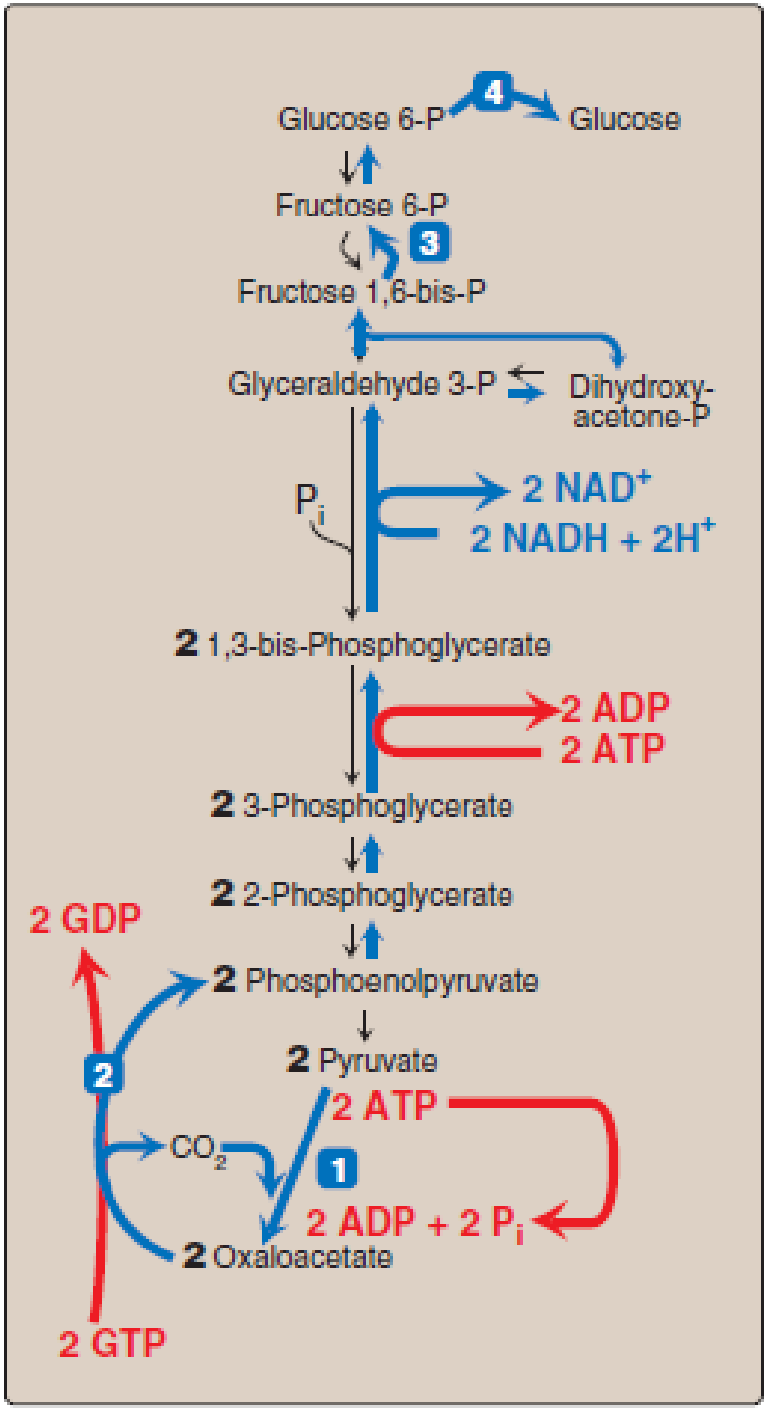
Glc. + ATP $\rightarrow$ Glc. 6-phosphate + ADP ΔG = -ve

- Hydrolysis

Phosphatase

Glc. 6-phosphate + H_2O $\rightarrow$ Glc. + P_i ΔG = -ve

Energy requirements of gluconeogenesis



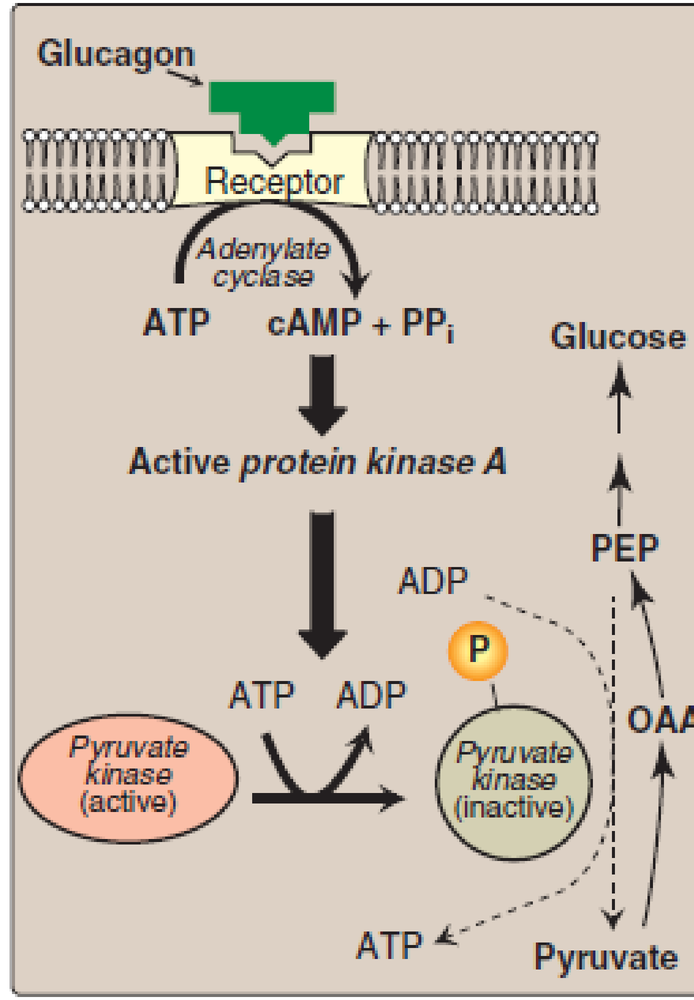
Regulation of gluconeogenesis

- 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