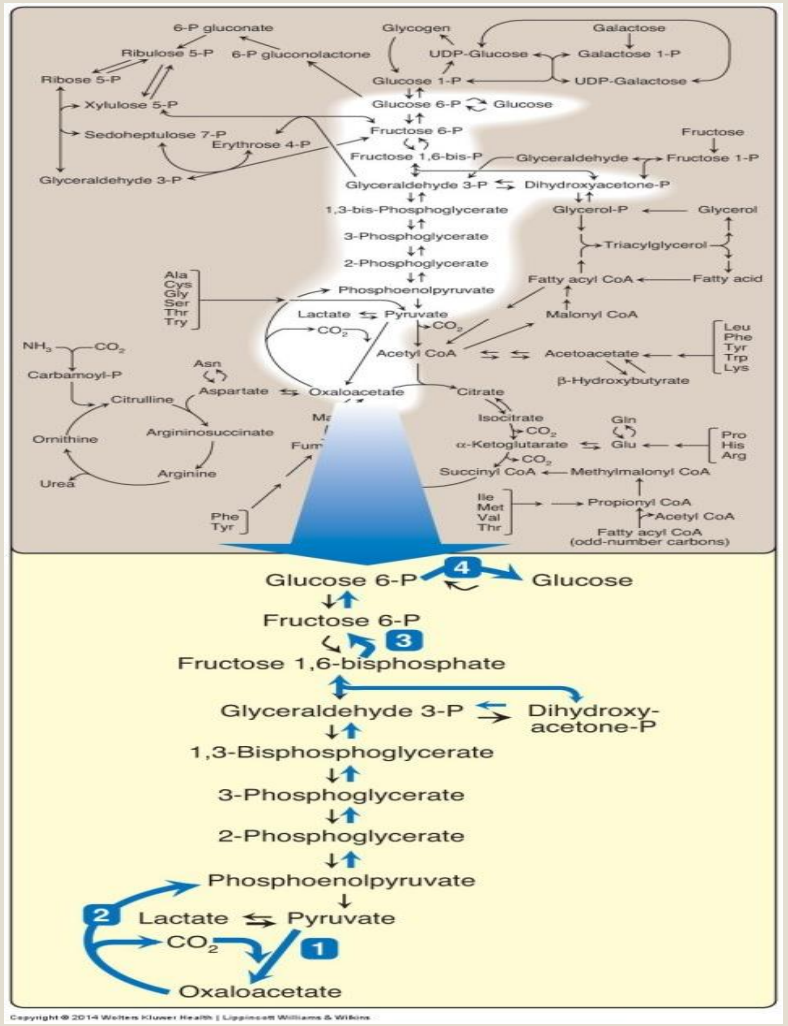
Glucose Metabolism (Gluconeogenesis)

Objectives

- The importance of gluconeogenesis as an important pathway for glucose production
- The main reactions of gluconeogenesis
- The rate-limiting enzymes of gluconeogenesis
- Gluconeogenesis is an energy-consuming, anabolic pathway

Gluconeogenesis in general metabolism

The gluconeogenesis pathway shown as one of the essential pathways of energy metabolism.

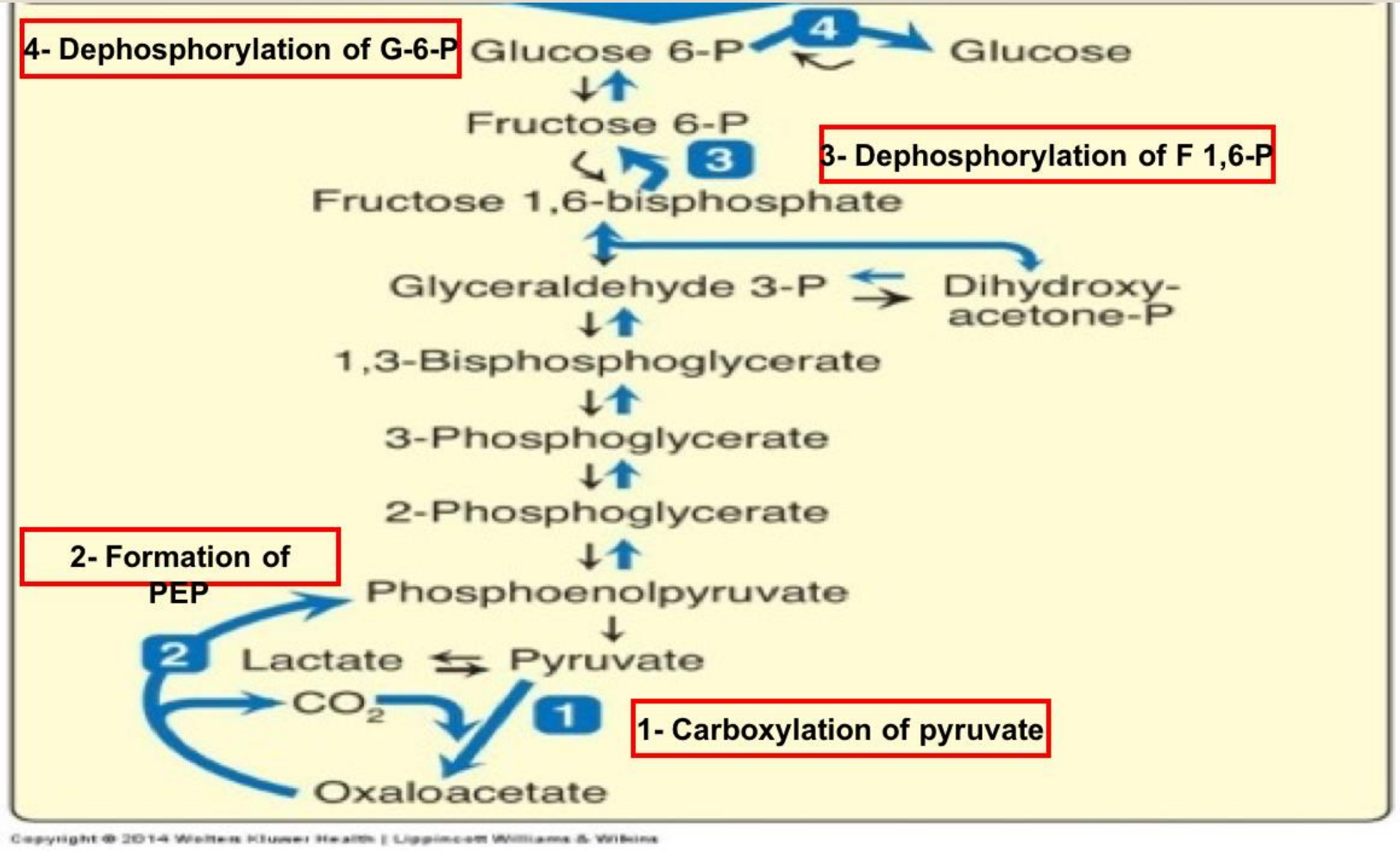


Gluconeogenesis: An Overview

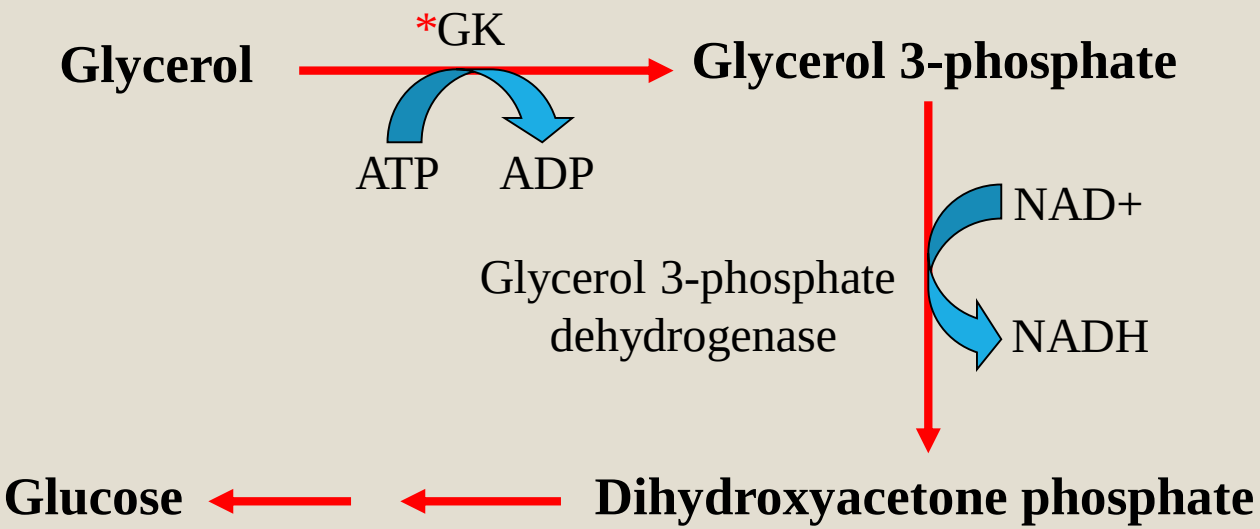
- Site: Liver (mainly) and Kidneys
- Both mitochondria and Cytosol are involved
- Exception: if the substrate is Glycerol: only cytosol
- Gluconeogenic substrates:

  Glycerol
  Lactate and Pyruvate
  Glucogenic amino acids

Gluconeogenesis Pathway

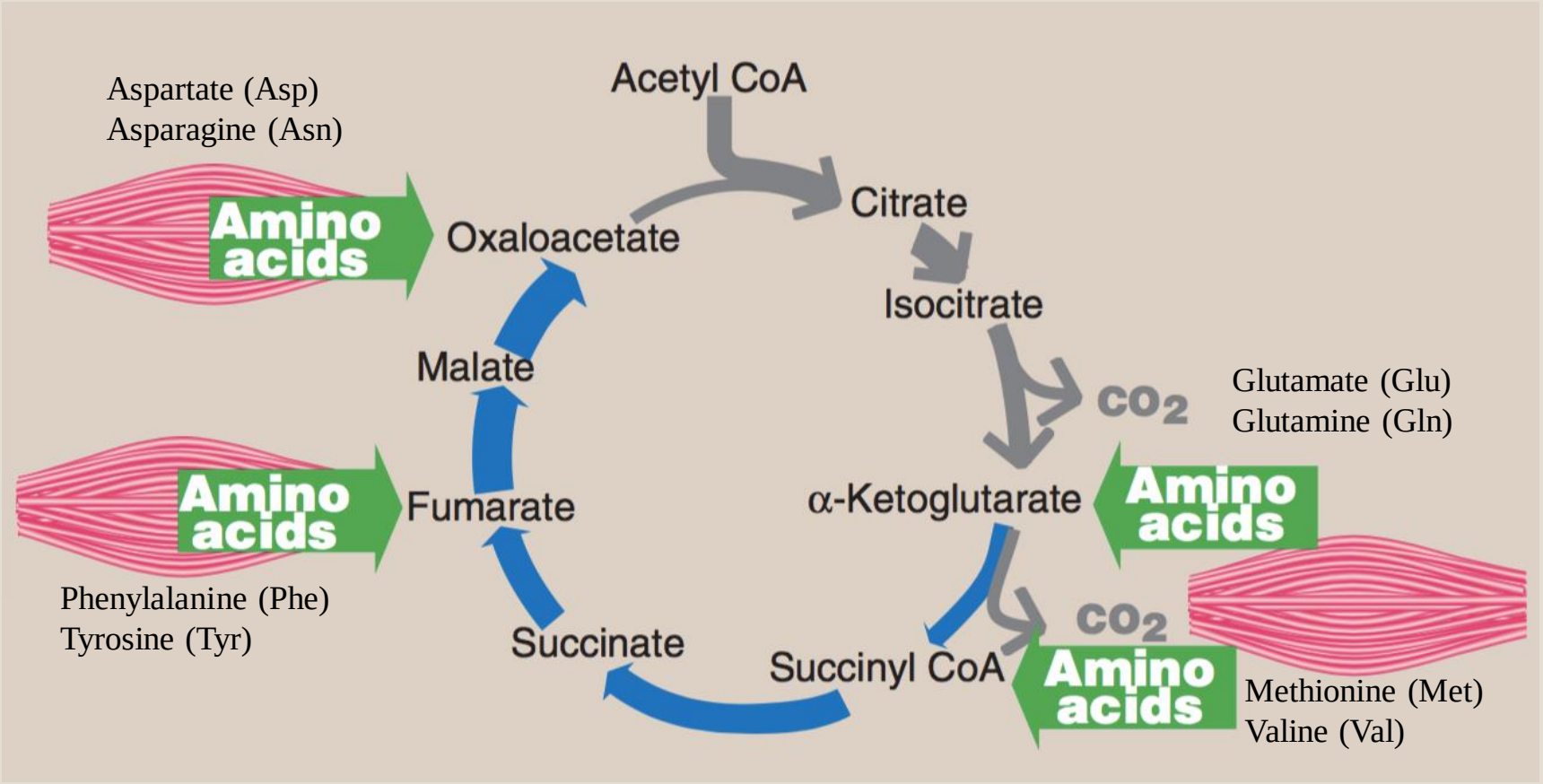


Gluconeogenic Substrates: Glycerol

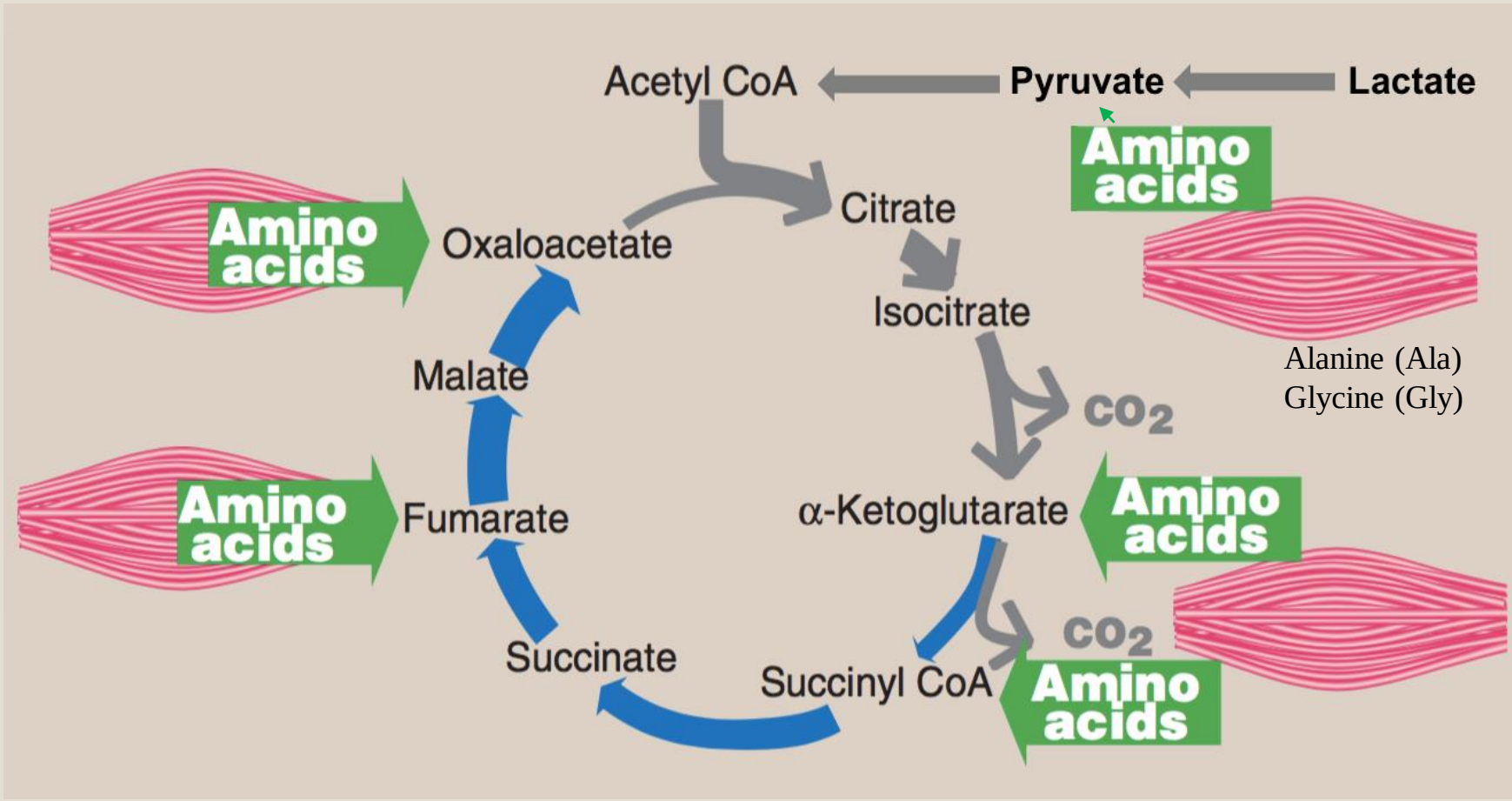


**GK: Glycerol kinase (present only in liver & kidneys)*

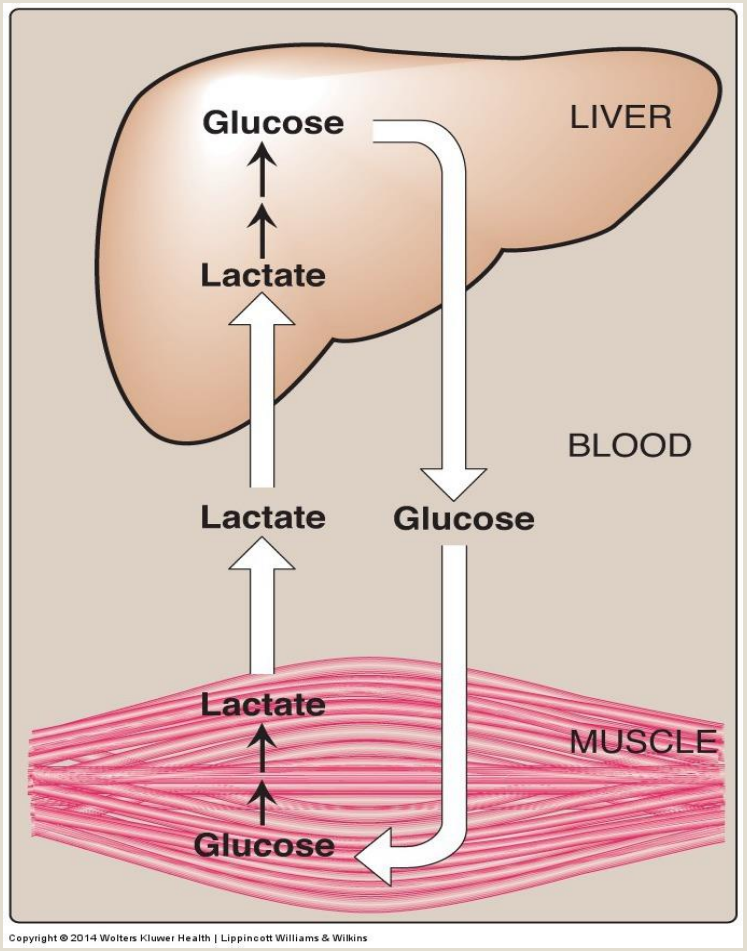
Glucogenic Amino Acids



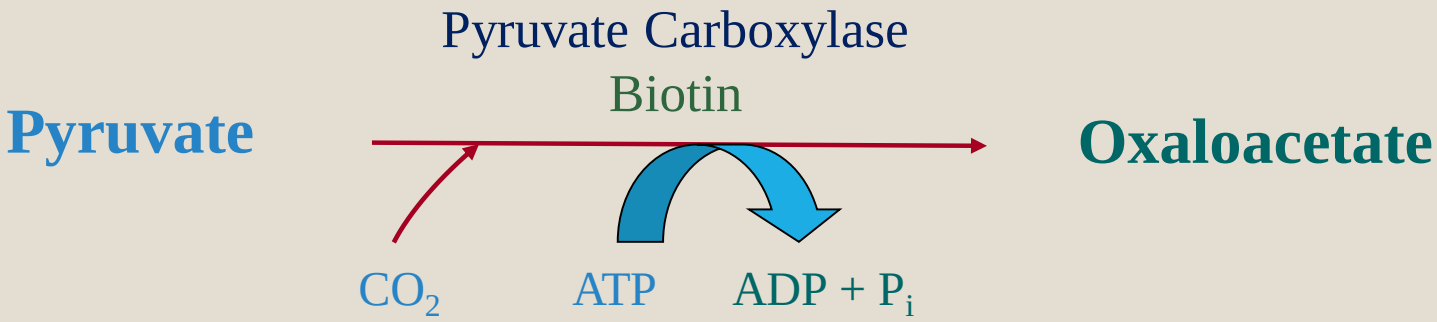
Gluconeogenic Substrates



Gluconeogenic Substrates: Lactate (Cori Cycle)



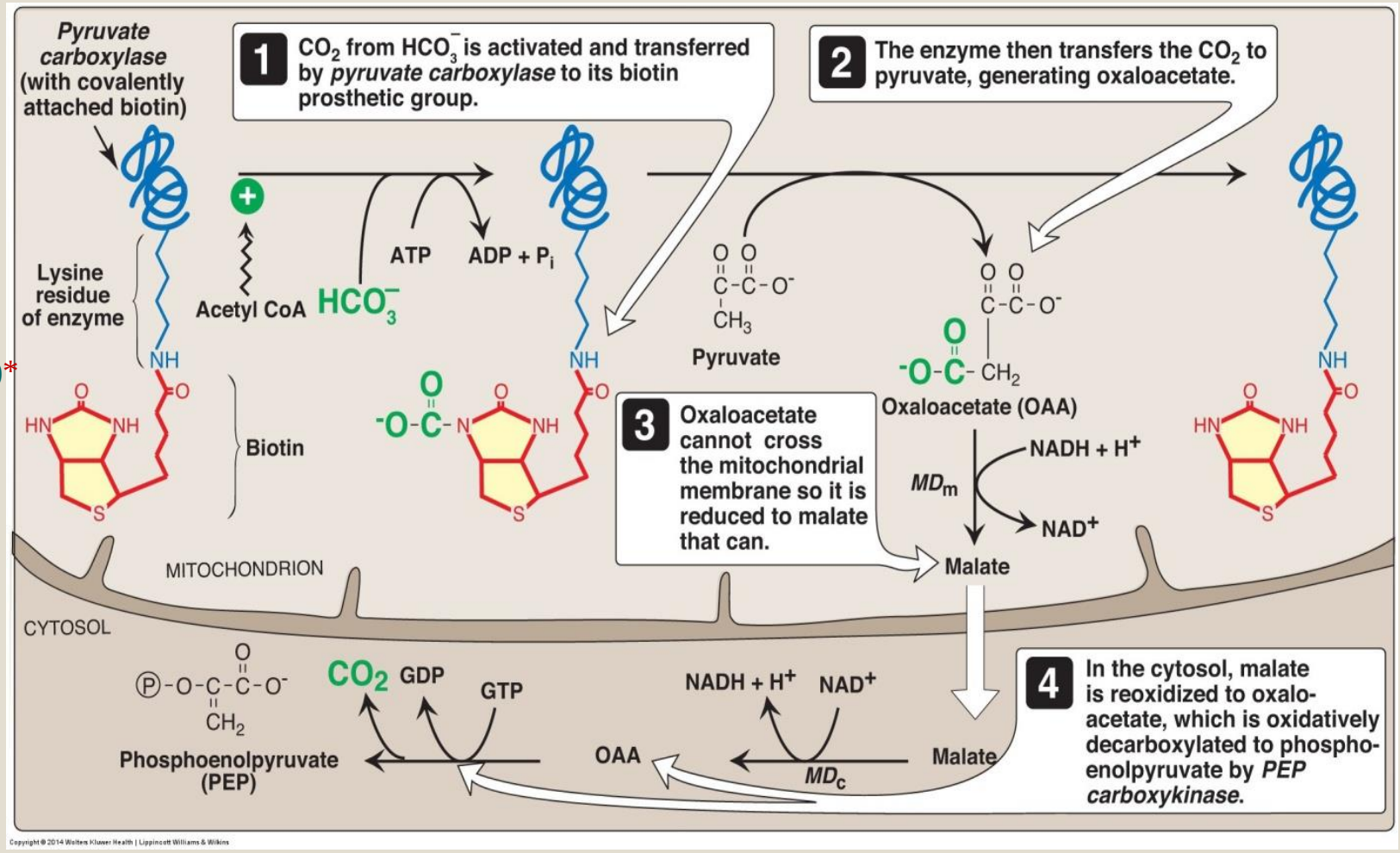
Pyruvate Carboxylation



Pyruvate Carboxylase and PEP-CK

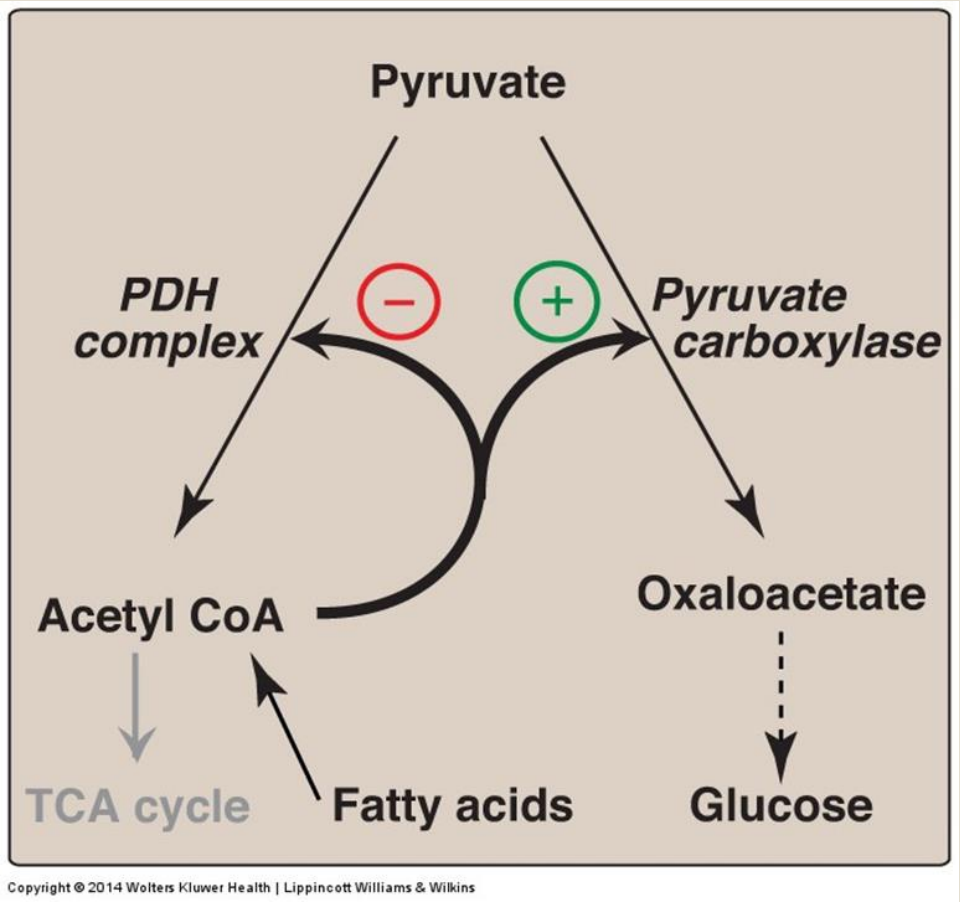
↑ Fasting: Acetyl CoA (From FAO)*

*Fatty Acid Oxidation



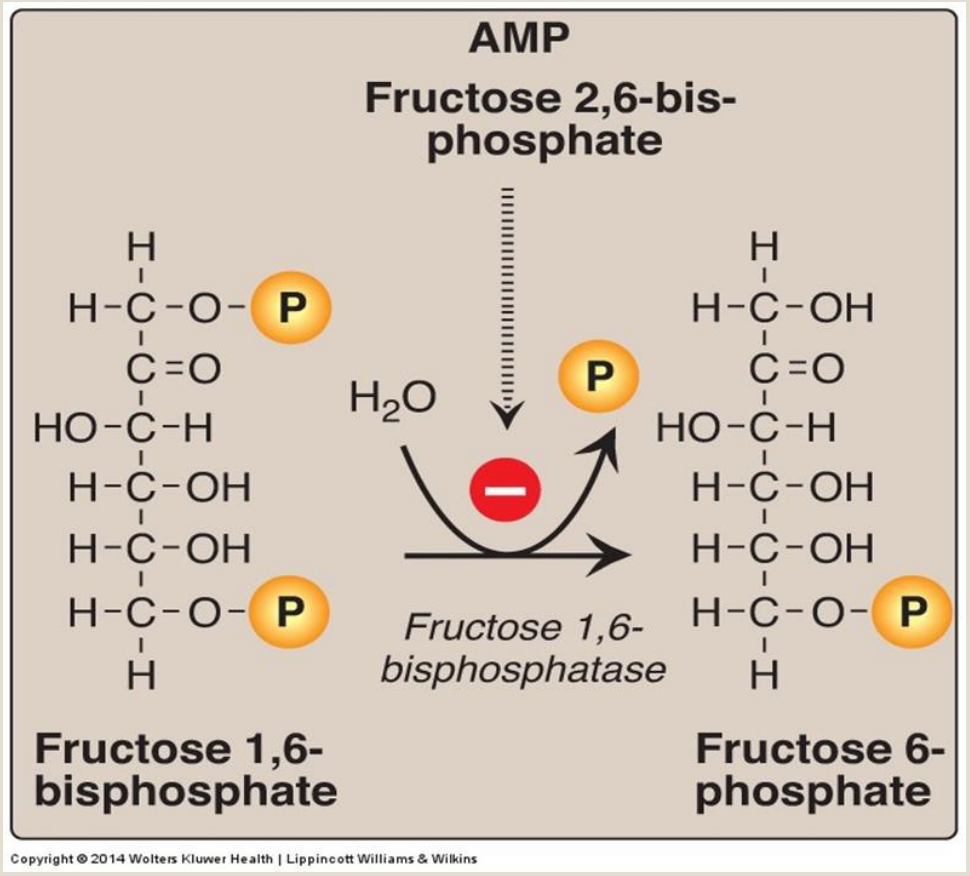
Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Regulation of Pyruvate Carboxylase reaction



Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis

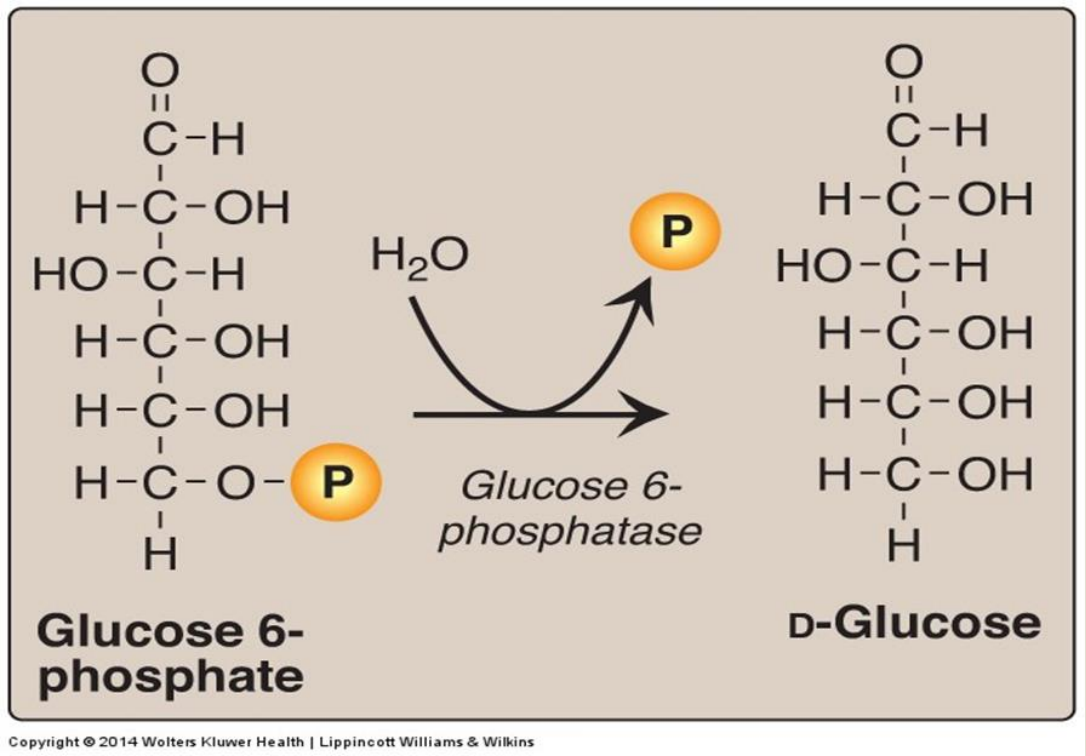
Fructose 1,6-Bisphosphatase



Dephosphorylation of fructose 1,6-bisphosphate

Fructose 1,6-bisphosphatase ≠ PFK-1

Glucose 6-Phosphatase

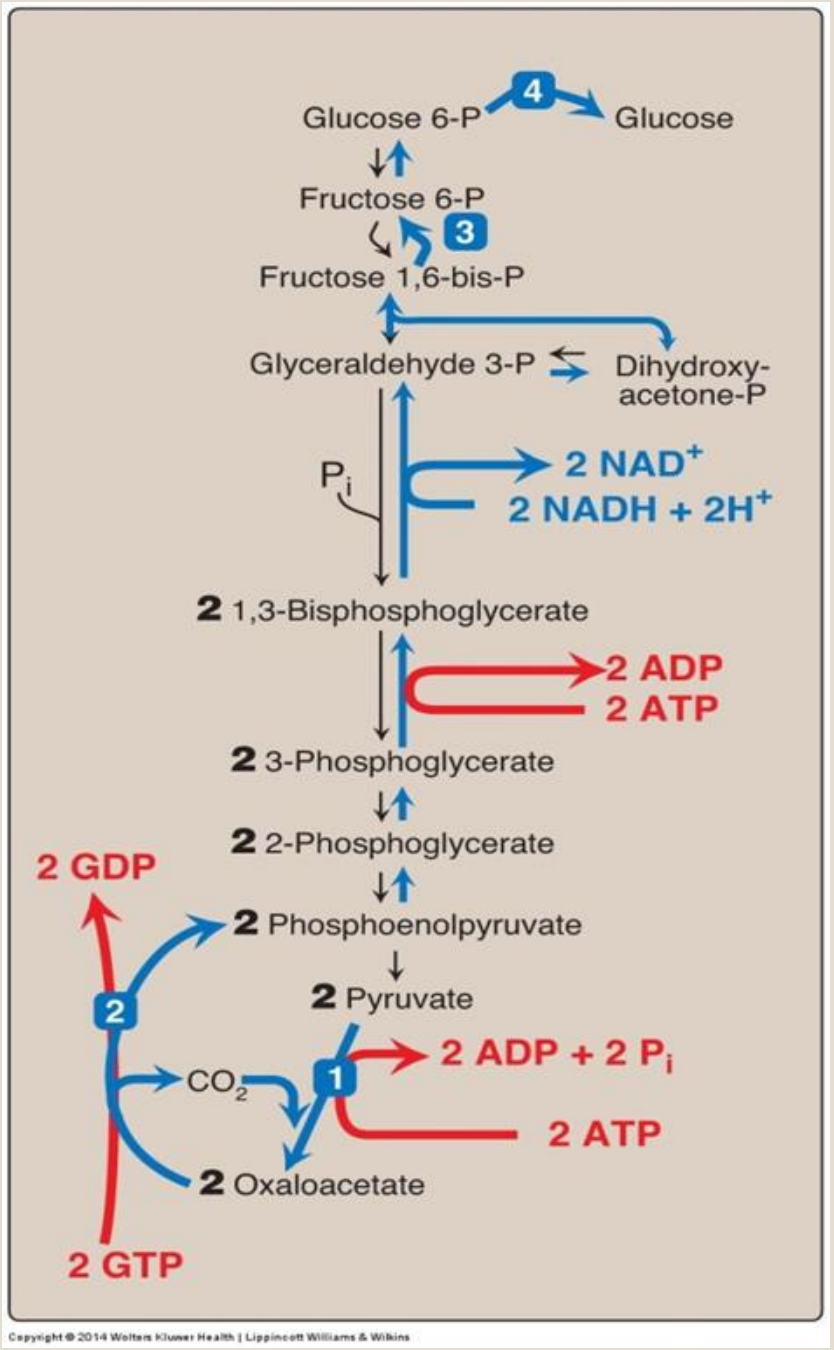


Dephosphorylation of glucose 6-phosphate allows release of free glucose from the liver and kidney into blood

Glucose 6-phosphatase ≠ Glucokinase

Gluconeogenesis: Energy- Consumed

Six High-Energy Phosphate Bonds From Pyruvate to Glucose



Gluconeogenesis: Regulation

- **Reciprocal control**

  Gluconeogenesis & Glycolysis

- **Allosteric:**

  Acetyl CoA ⊕ (Pyruvate carboxylase)

  AMP ⊖ or ATP ⊕
  F 2,6-Bisphosphate ⊖
  } F 1,6-bisphosphatase

- **↑Glucagon (↓I/G ratio) stimulates gluconeogenesis**

  - Allosteric (↓ F 2,6-Bisphosphate)
  - Induction (PEP-CK)

Take Home Messages

- Gluconeogenesis is an important pathway for glucose production from non-carbohydrate sources during prolonged fasting.
- Lactate, glycerol and glucogenic amino acids are the major gluconeogenic substrates.
- Gluconeogenesis is not a simple reversal of glycolysis. In fact, gluconeogenesis requires 4 unique reactions to circumvent the 3 irreversible reactions of glycolysis.
- Gluconeogenesis and glycolysis are reciprocally controlled, allowing efficient glucose metabolism.
- It is mainly anabolic pathway that consumes ATP for the synthesis of glucose.

Reference

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014, Unit 2, Chapter 10, Pages 117-124.