

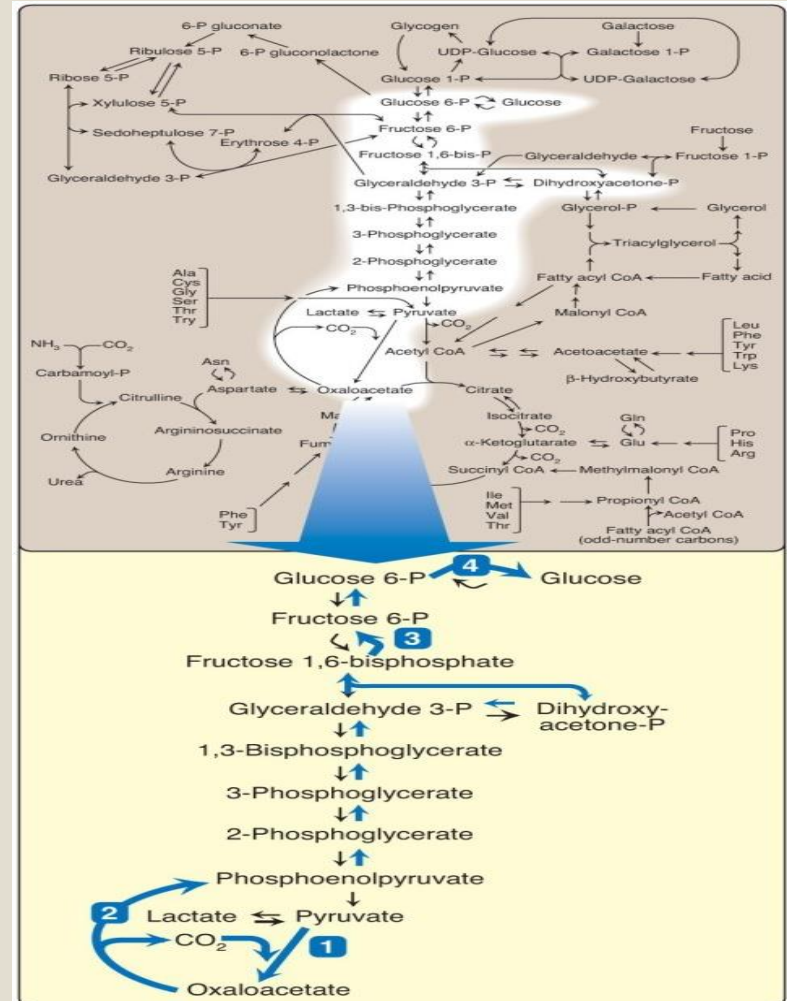
Glucose Metabolism (Gluconeogenesis)

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

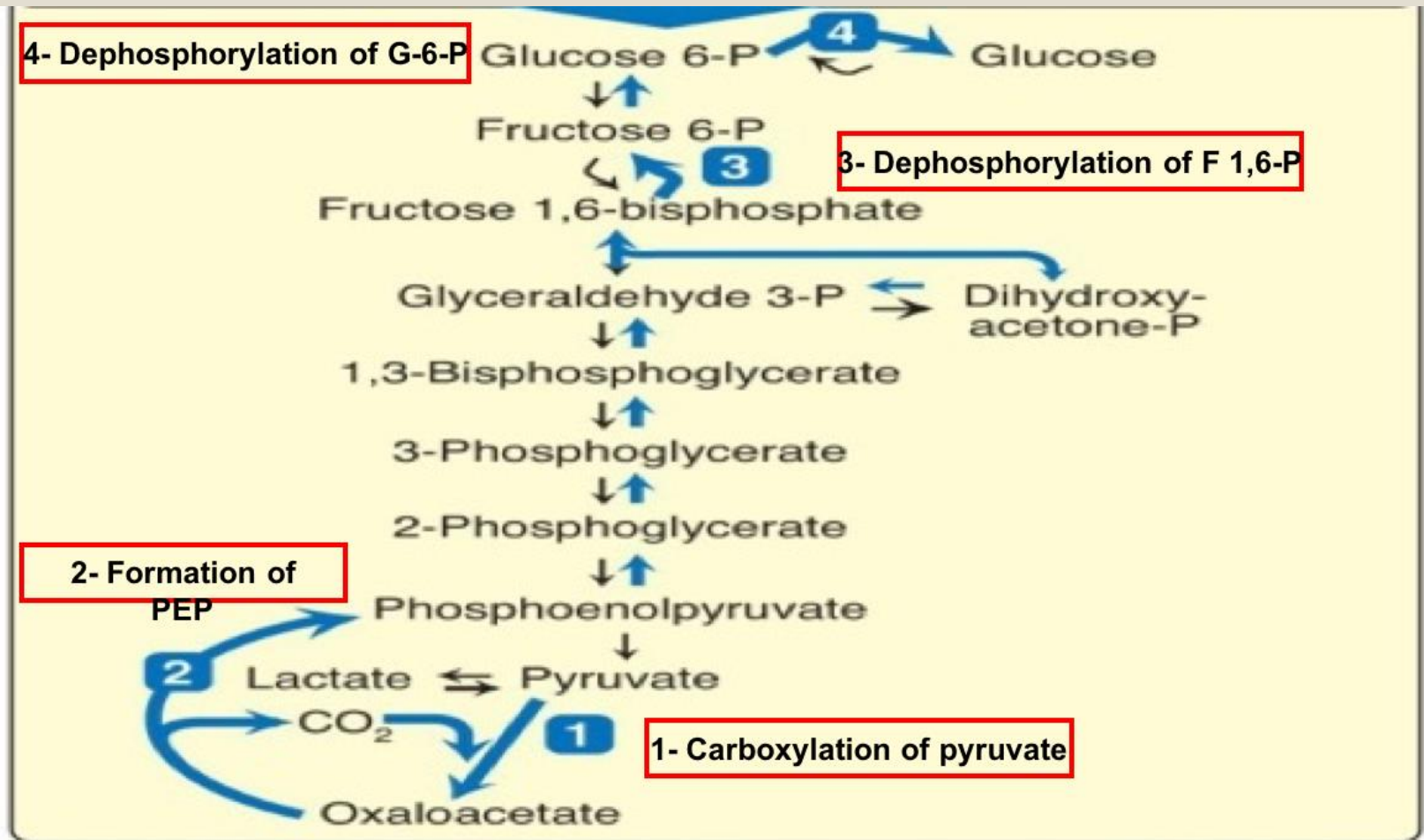
- Site: Liver (mainly) and Kidneys
- Both mitochondria and Cytosol are involved
- Exception: if the substrate is **Glycerol: only cytosol**
- Gluconeogenic substrates:

Glycerol

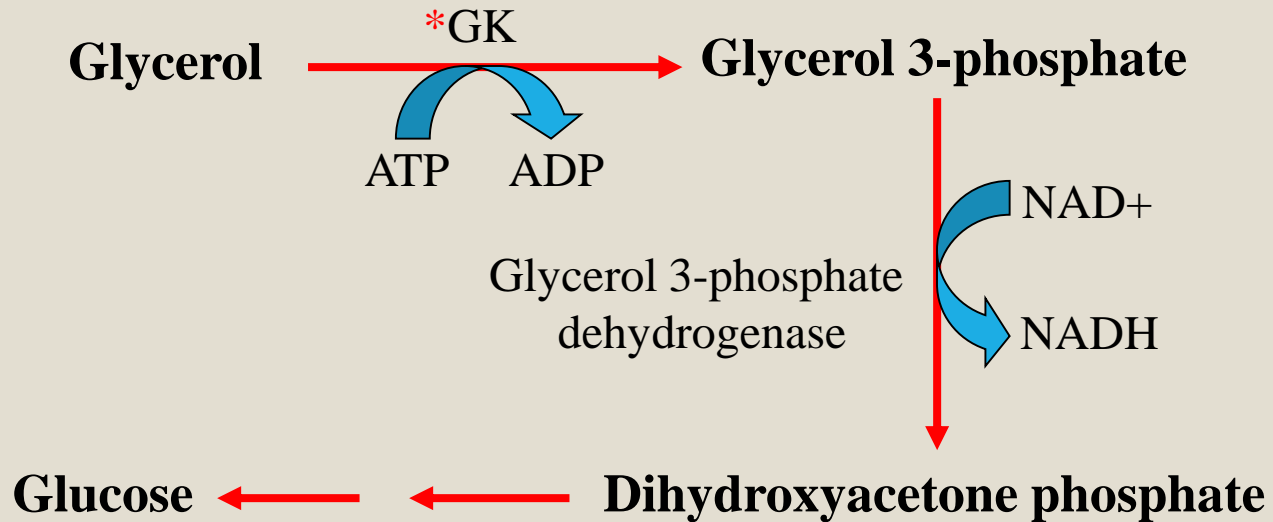
Lactate and Pyruvate

Glucogenic amino acids

Gluconeogenesis Pathway

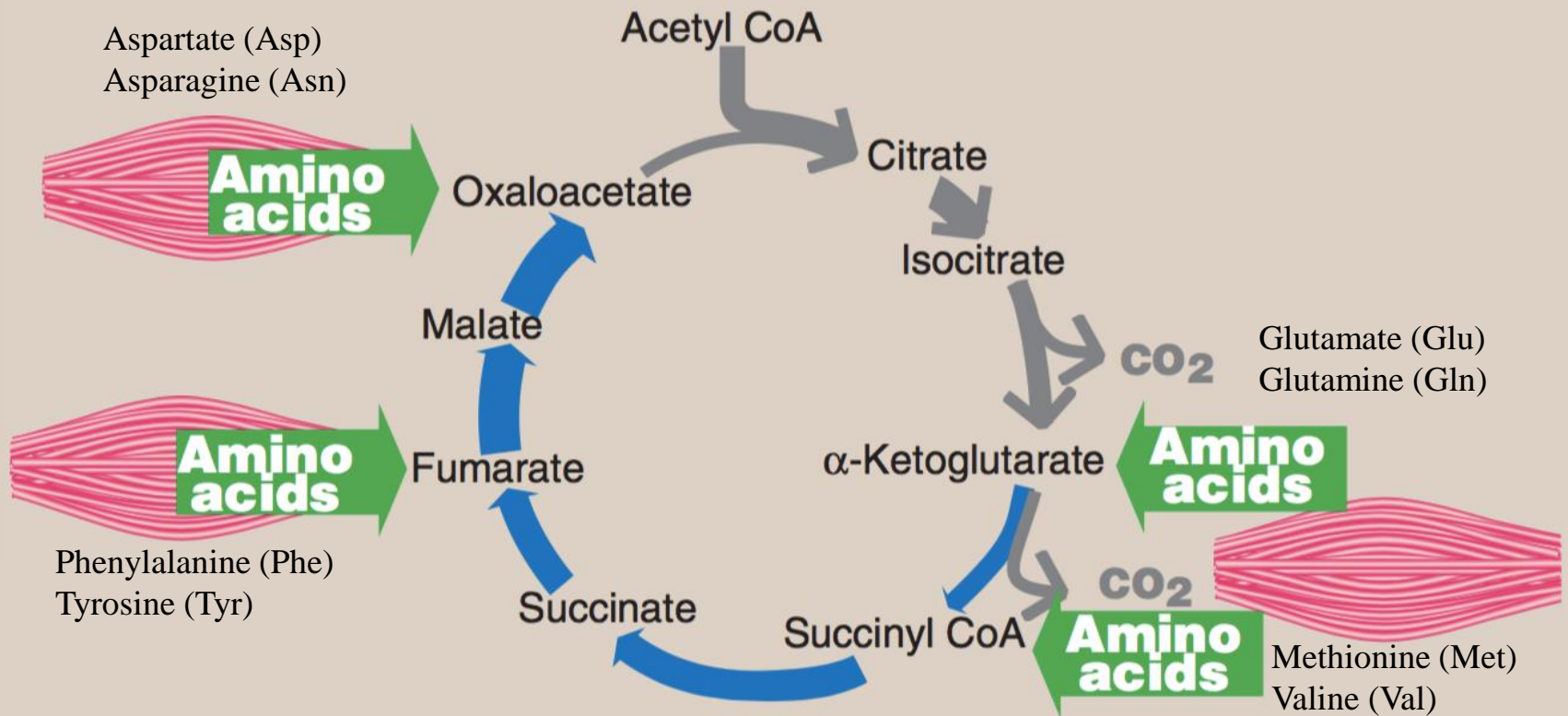


Gluconeogenic Substrates: Glycerol

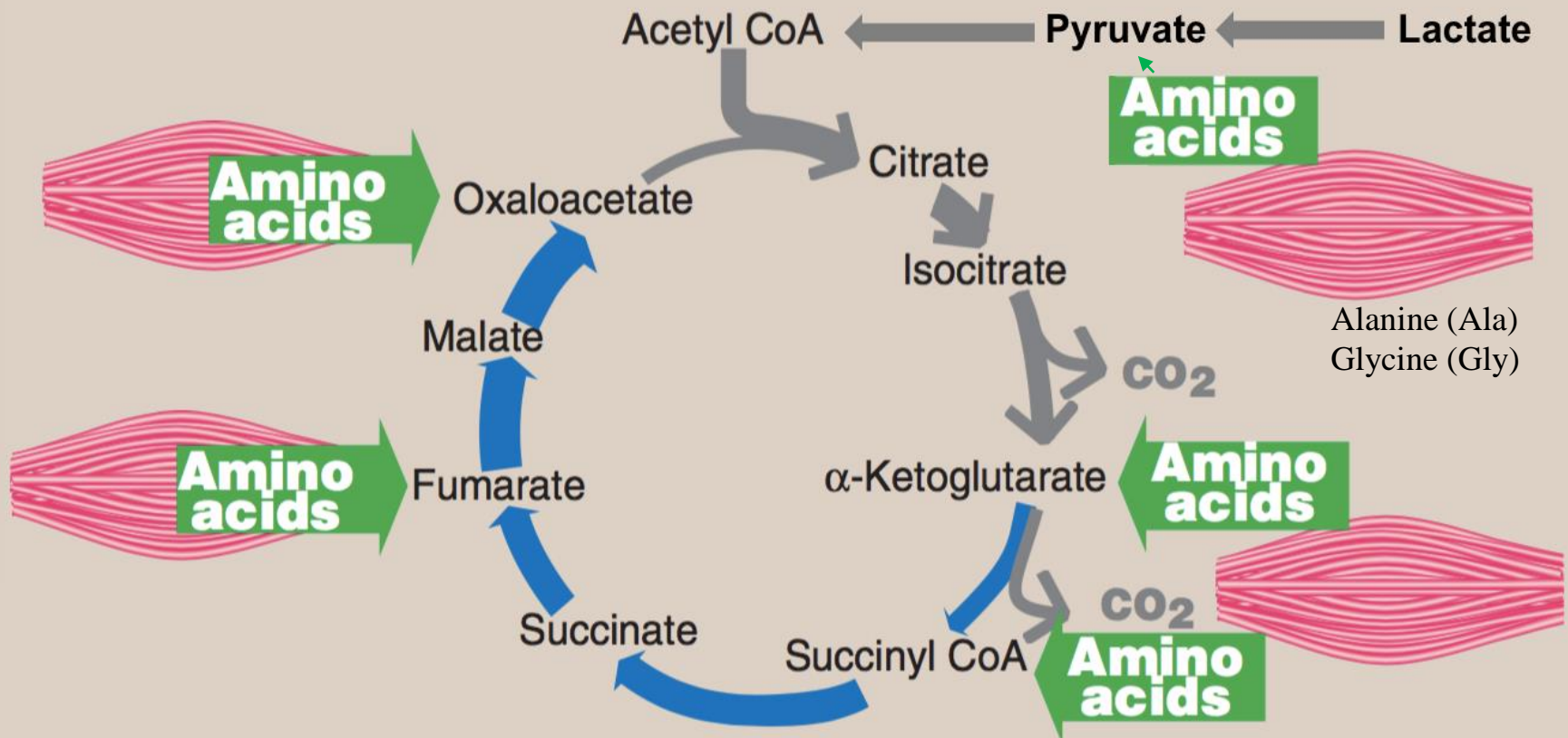


**GK: Glycerol kinase (present only in liver & kidneys)*

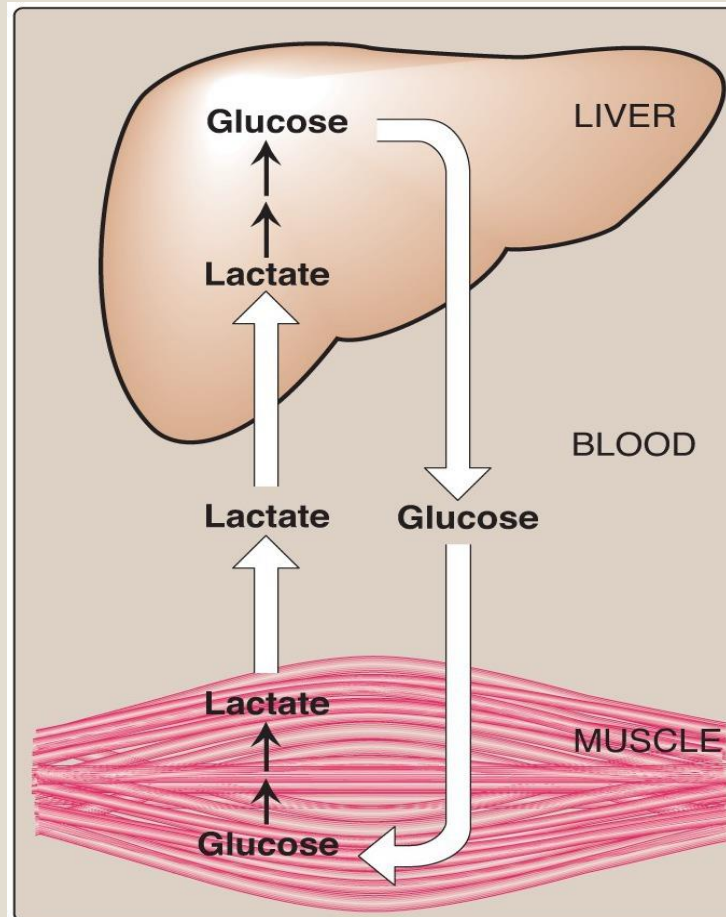
Glucogenic Amino Acids



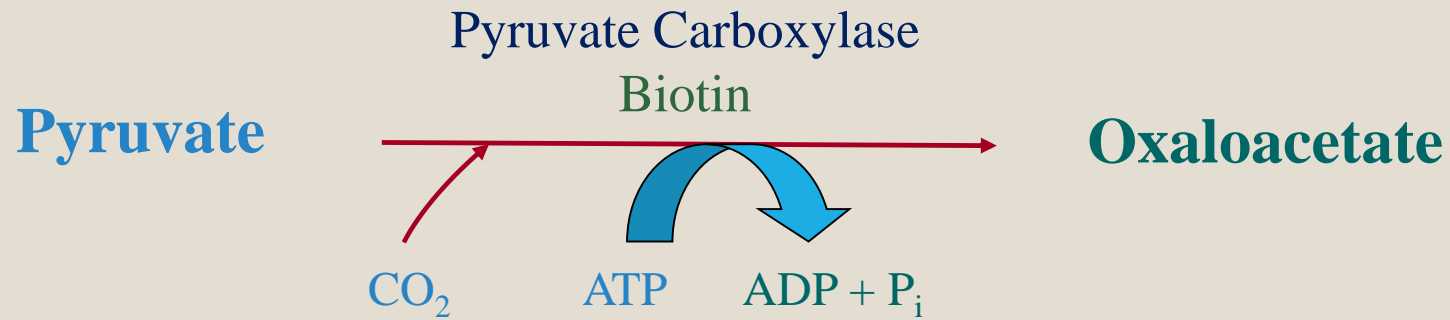
Gluconeogenic Substrates



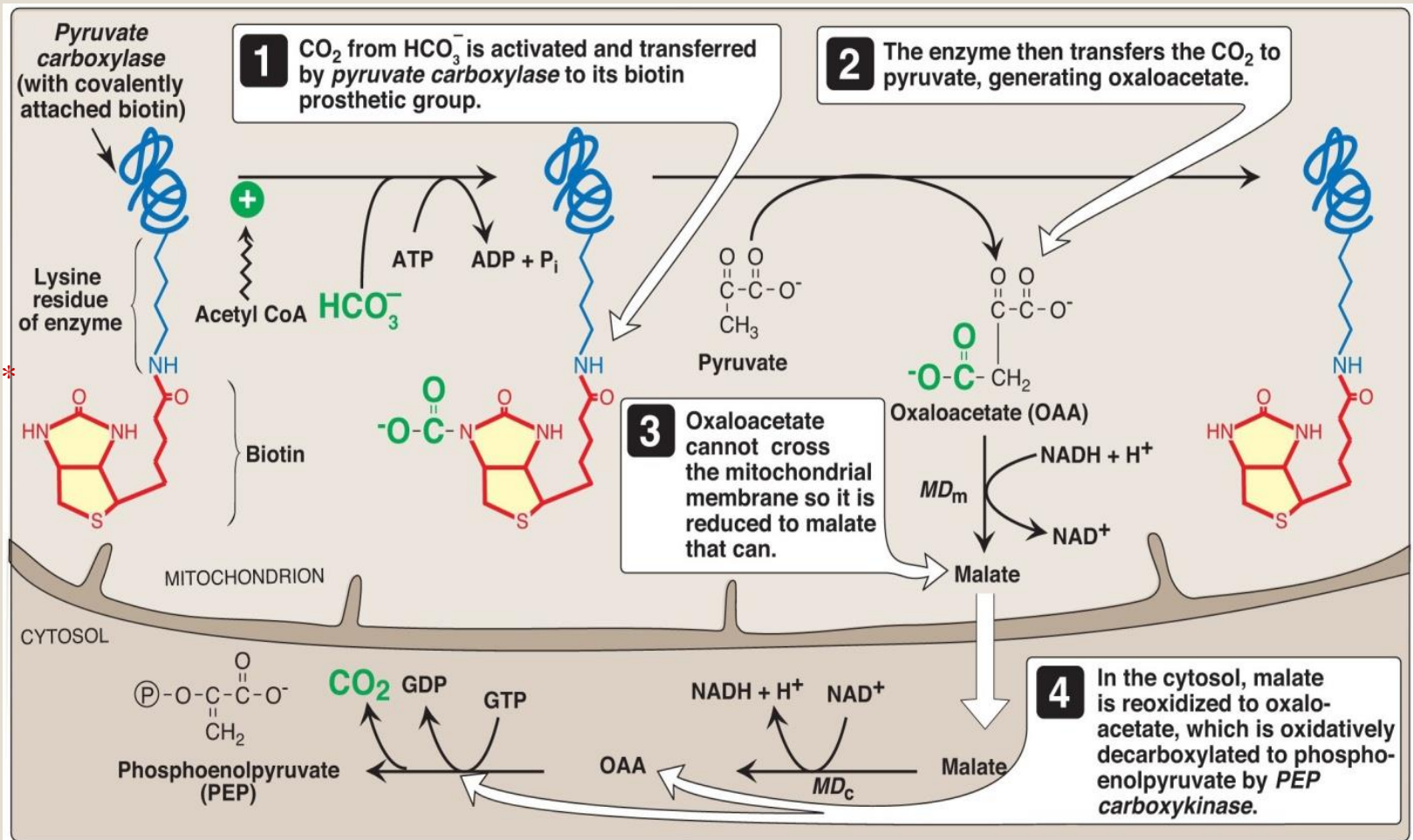
Gluconeogenic Substrates: Lactate (Cori Cycle)



Pyruvate Carboxylation



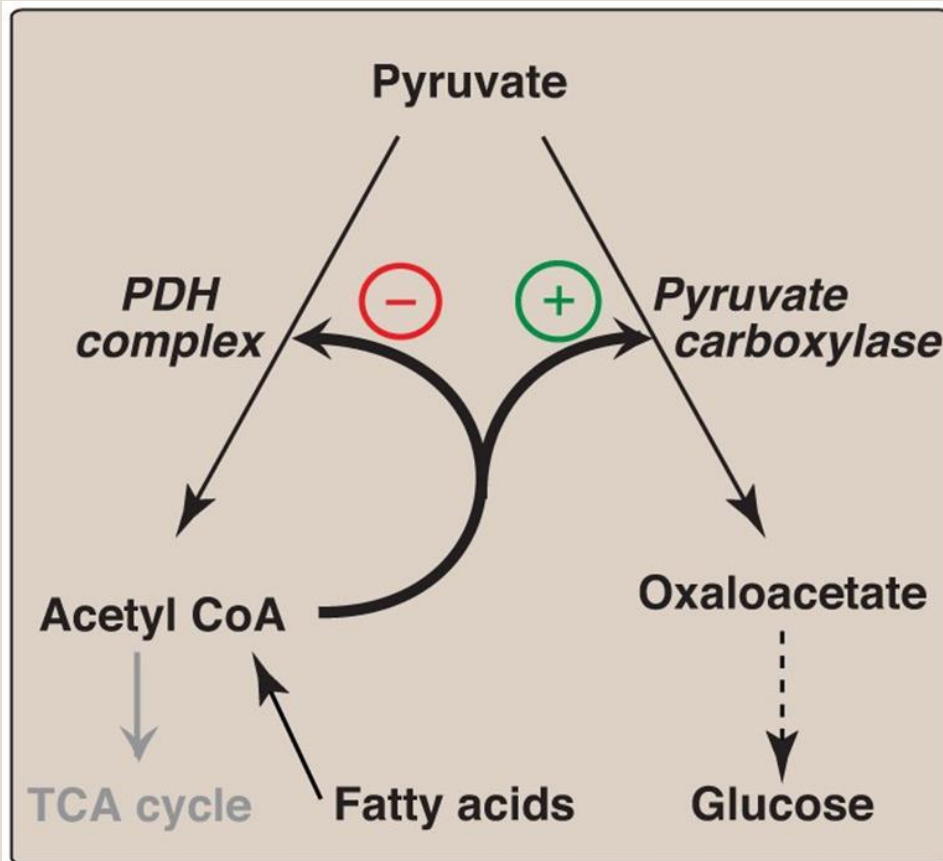
Pyruvate Carboxylase and PEP-CK



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Pyruvate carboxylase + PEP-CK \neq Pyruvate kinase

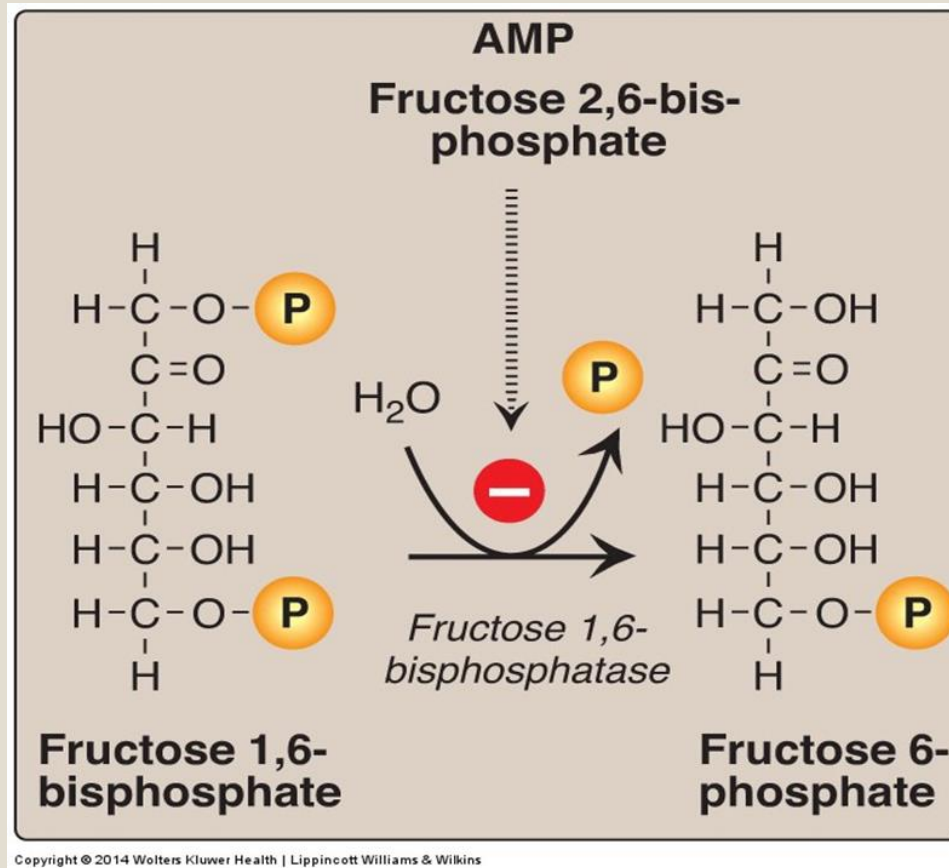
Regulation of Pyruvate Carboxylase reaction



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Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis

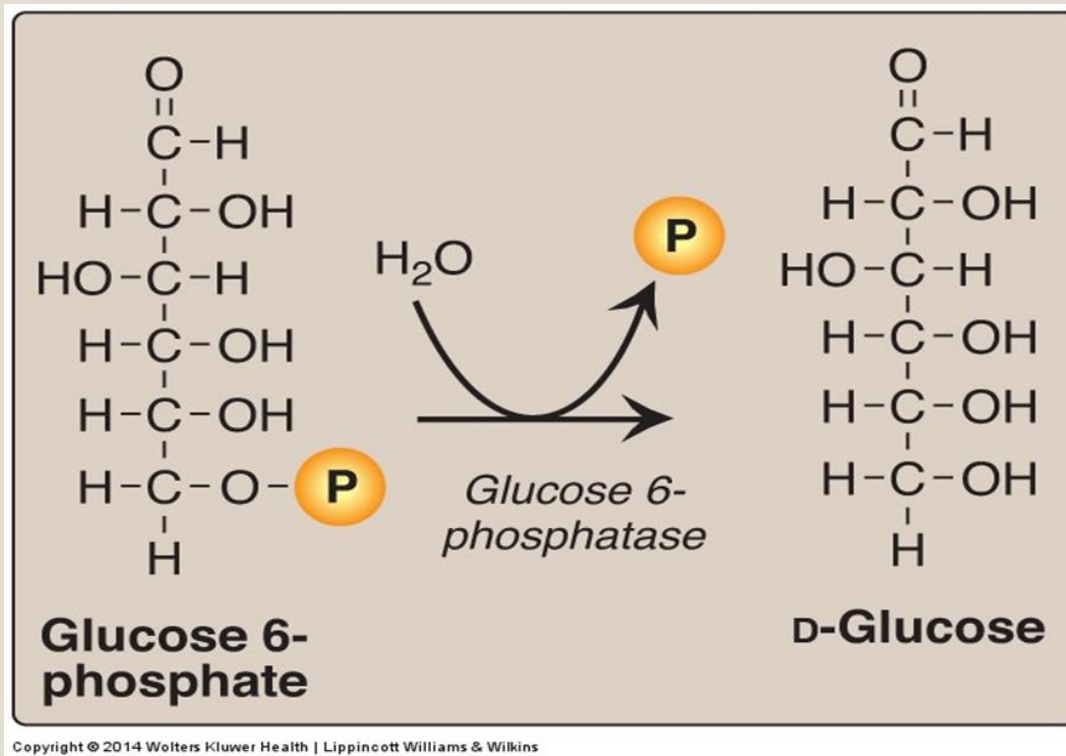
Fructose 1,6-Bisphosphatase



Dephosphorylation of fructose 1,6-bisphosphate

Fructose 1,6-bisphosphatase ~~≠~~ PFK-1

Glucose 6-Phosphatase

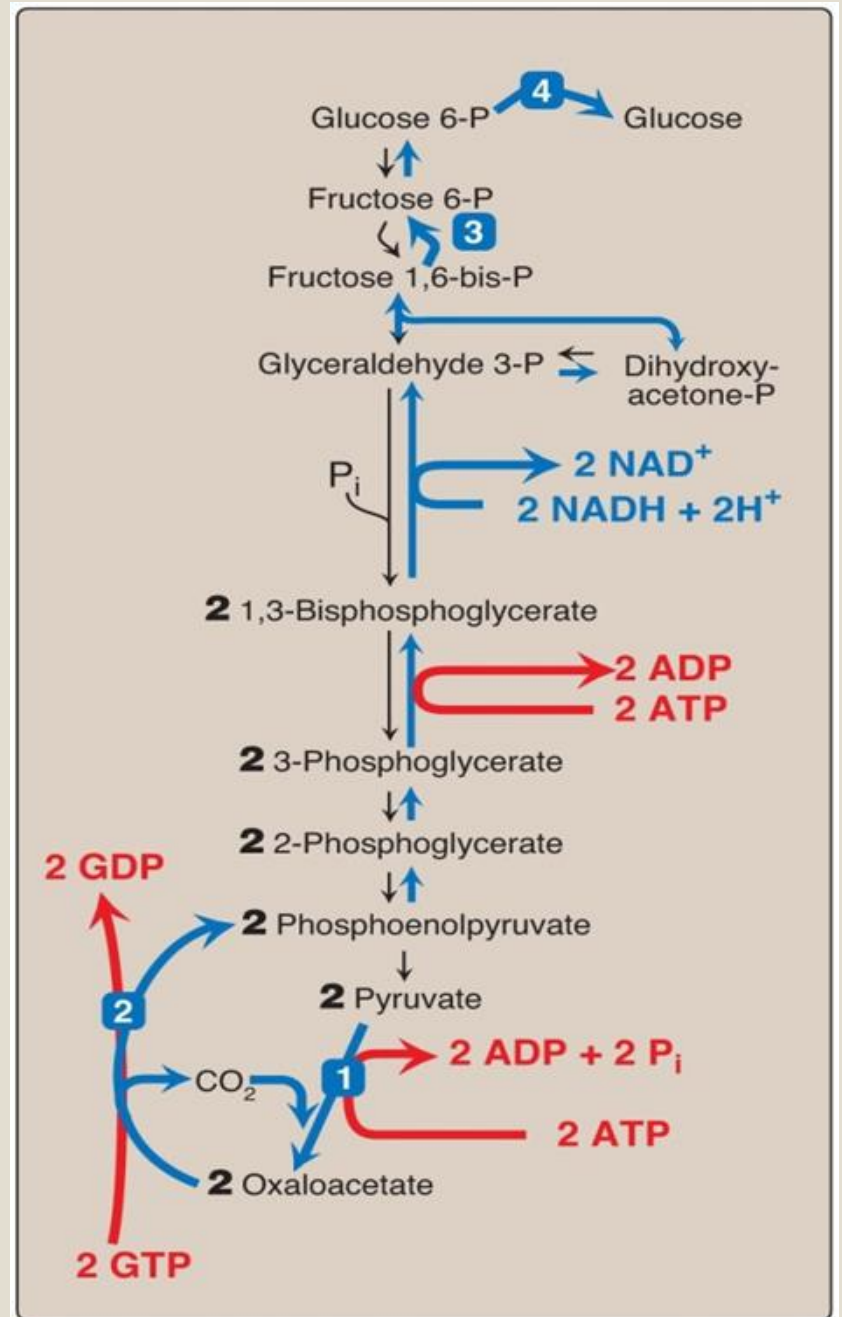


Dephosphorylation of glucose 6-phosphate allows release of free glucose from the liver and kidney into blood

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 \oplus (Pyruvate carboxylase)

AMP \ominus or ATP \oplus } F 1,6-bisphosphatase
F 2,6-Bisphosphate \ominus }

- **\uparrow Glucagon (\downarrow I/G ratio) stimulates gluconeogenesis**

- Allosteric (\downarrow 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.