بسم الله الرحمن الرحيم

Glucose Metabolism: Gluconeogenesis

By

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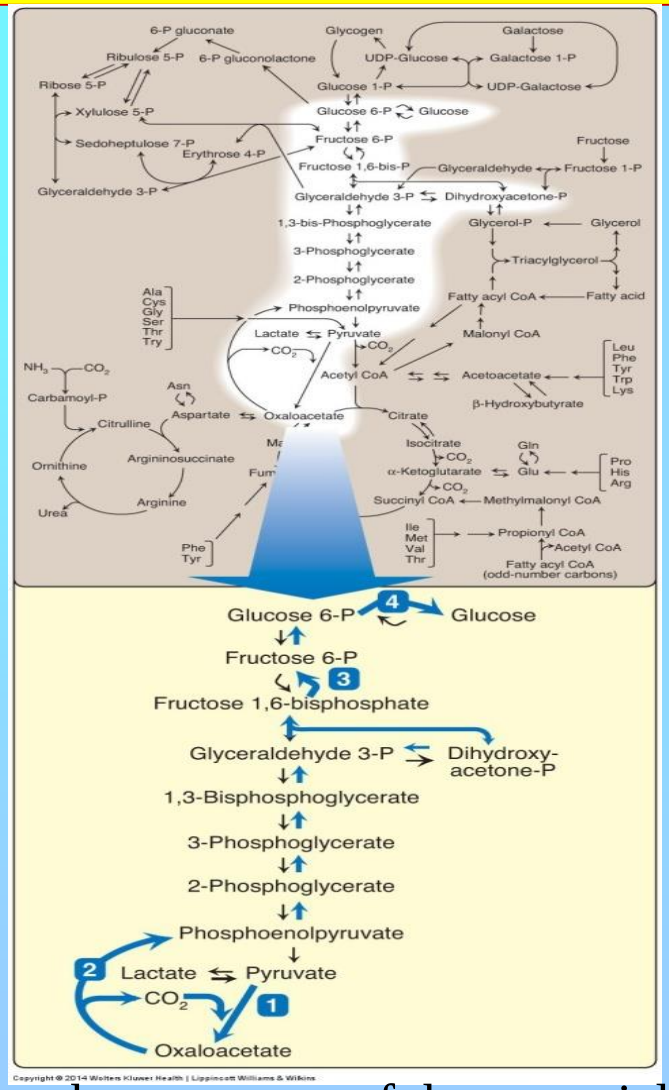
Objectives

- The importance of gluconeogenesis as an important pathway for glucose production
- The main reactions of gluconeogenesis
- The rate-limiting enzymes of gluconeogenesis
- Gluconeogensis 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

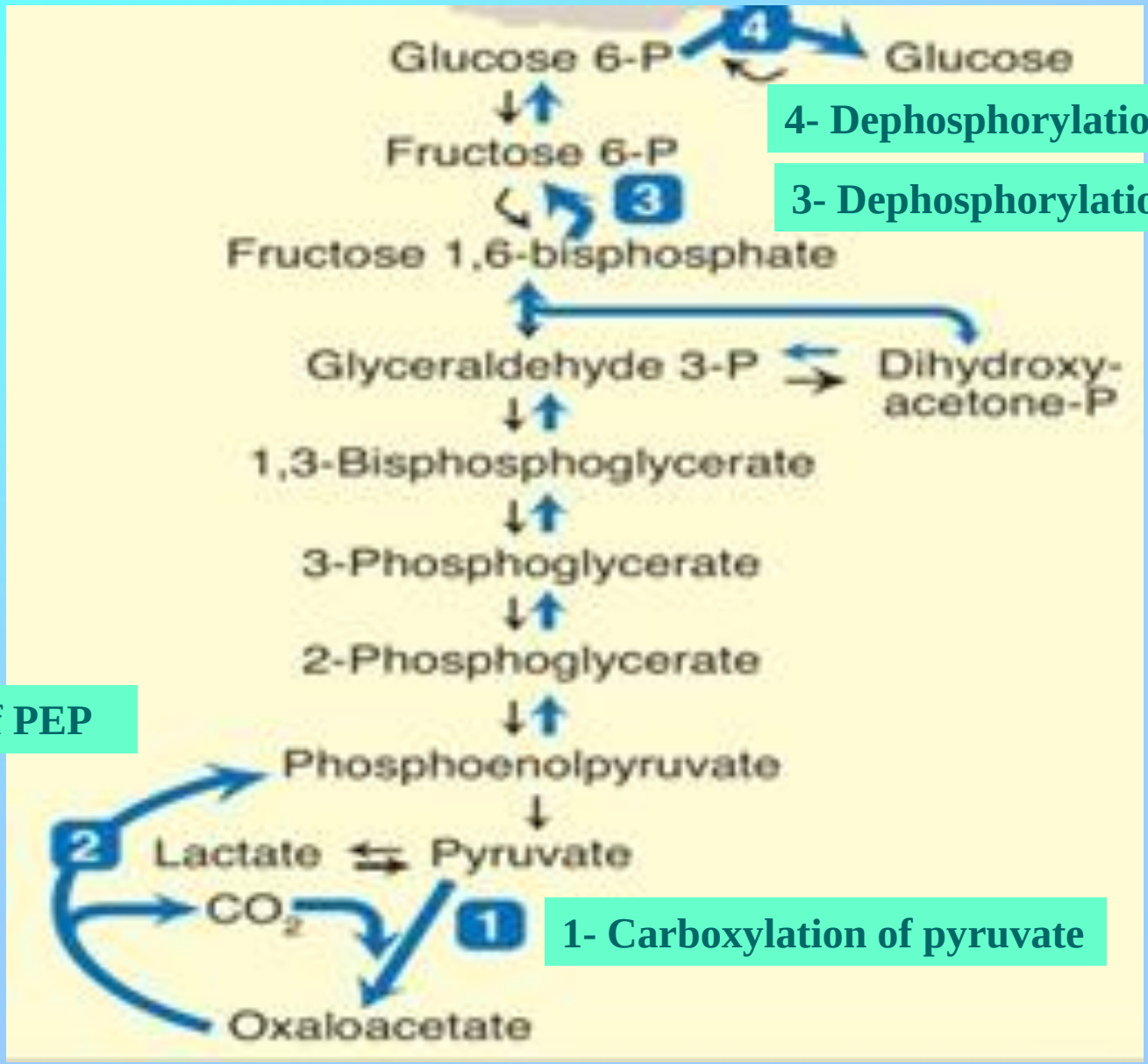
- **Site: Liver (mainly) and Kidneys**
- **Both mitochondria and Cytosol are involved**

  Exception: if the substrate is Glycerol: only cytosol

- **Gluconeogenic substrates:**

  Glycerol
  Lactate and Pyruvate
  Glucogenic amino acids

Gluconeogenesis Pathway



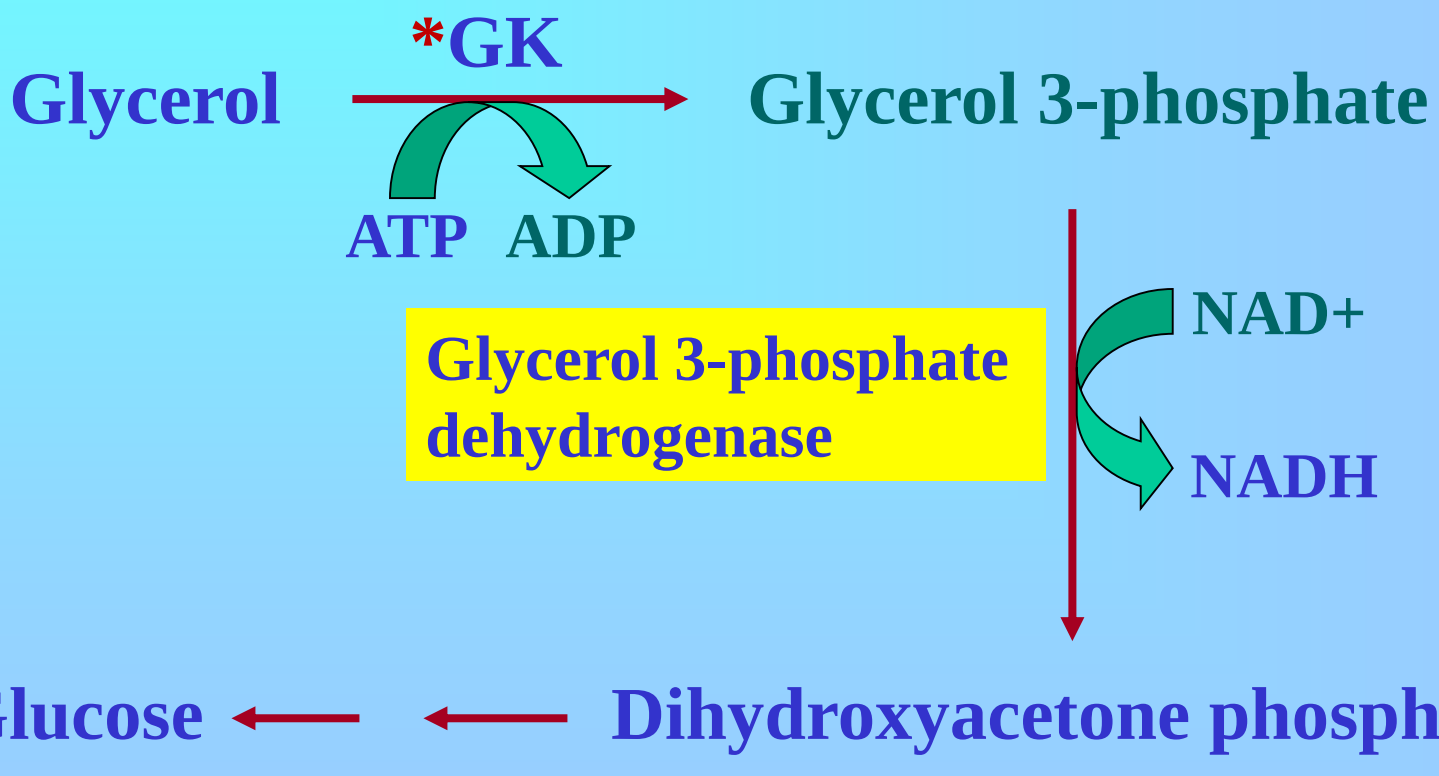
4- Dephosphorylation of G-6-P

3- Dephosphorylation of F 1,6-P

2- Formation of PEP

1- Carboxylation of pyruvate

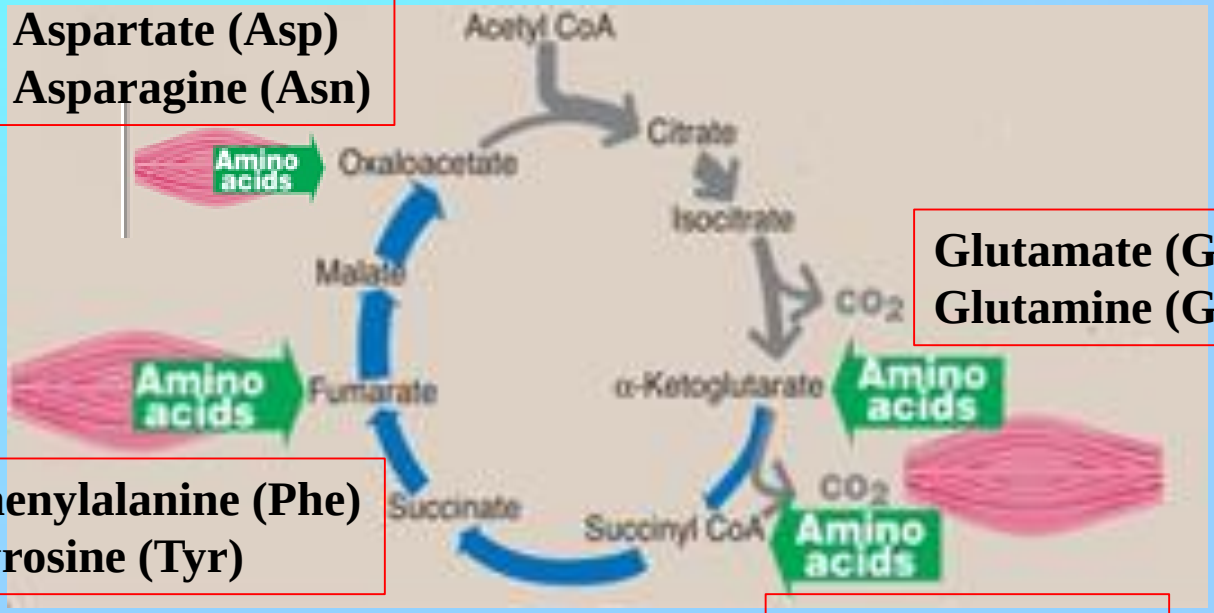
Gluconeogenic Substrates: Glycerol



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

Glucogenic Amino Acids

Aspartate (Asp)
Asparagine (Asn)



Glutamate (Glu)
Glutamine (Gln)

Phenylalanine (Phe)
Tyrosine (Tyr)

Methionine (Met)
Valine (Val)

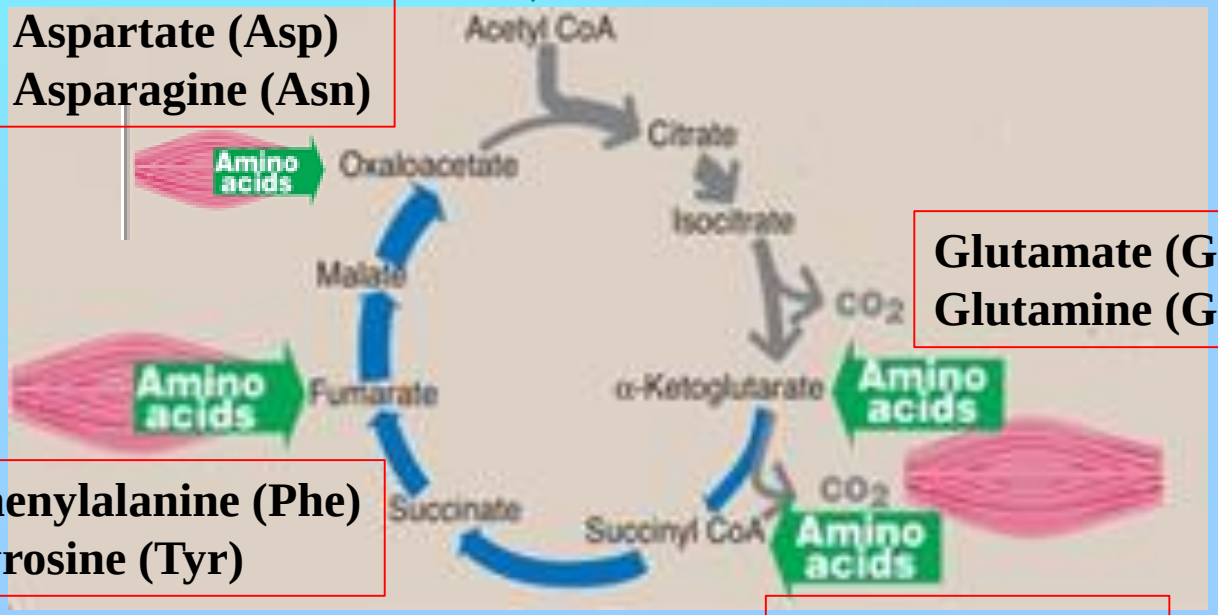
Gluconeogenic Substrates

Lactate

Alanine (Ala)
Glycine (Gly)

Pyruvate

Aspartate (Asp)
Asparagine (Asn)

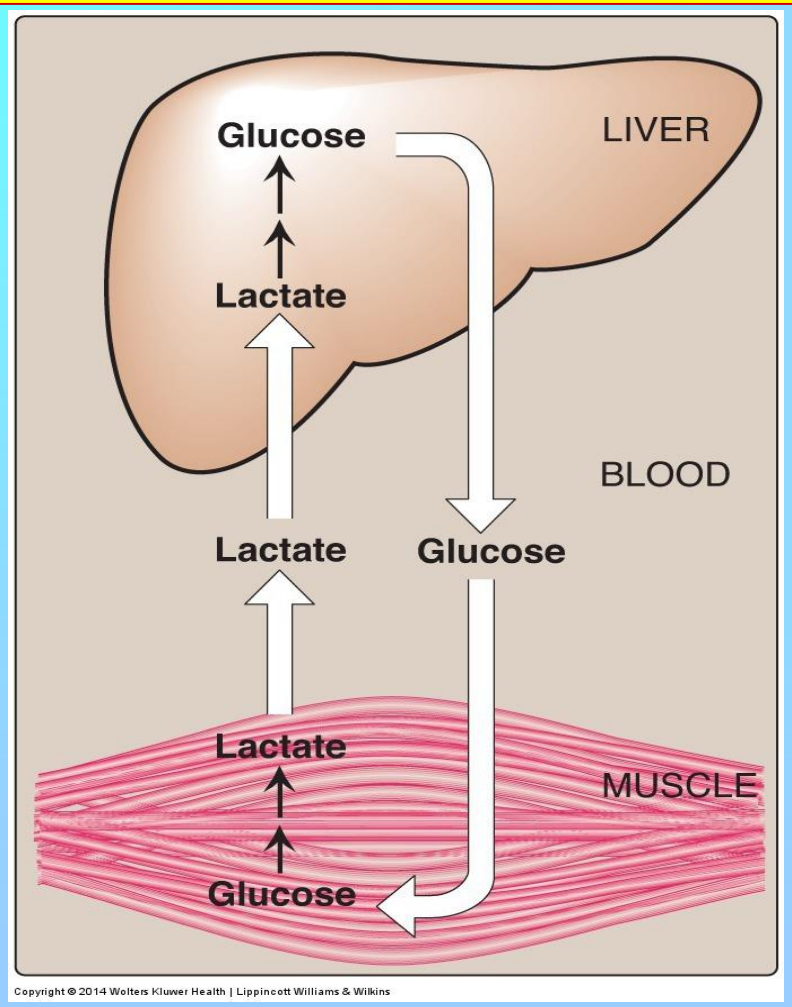


Glutamate (Glu)
Glutamine (Gln)

Phenylalanine (Phe)
Tyrosine (Tyr)

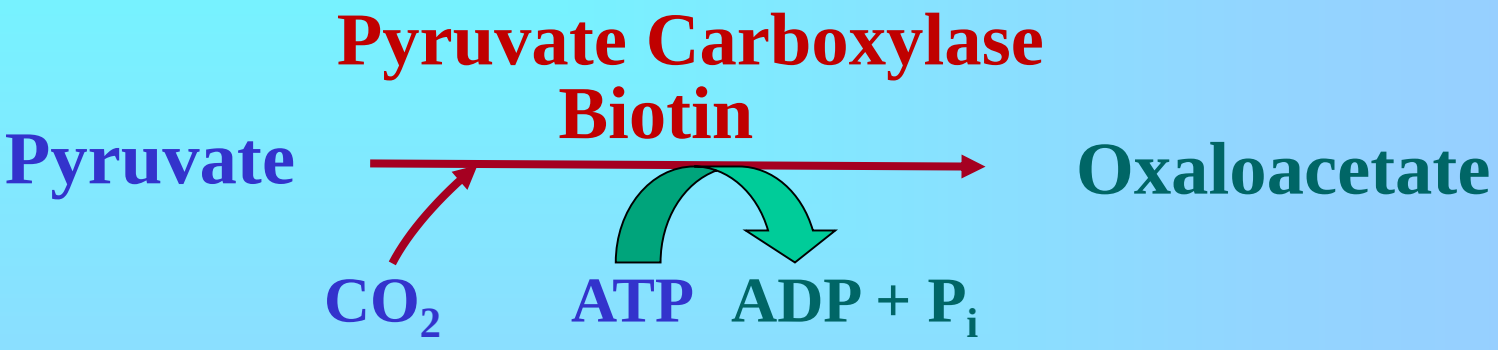
Methionine (Met)
Valine (Val)

Gluconeogenic Substrates: Lactate (Cori Cycle)



The inter-tissue Cori cycle.

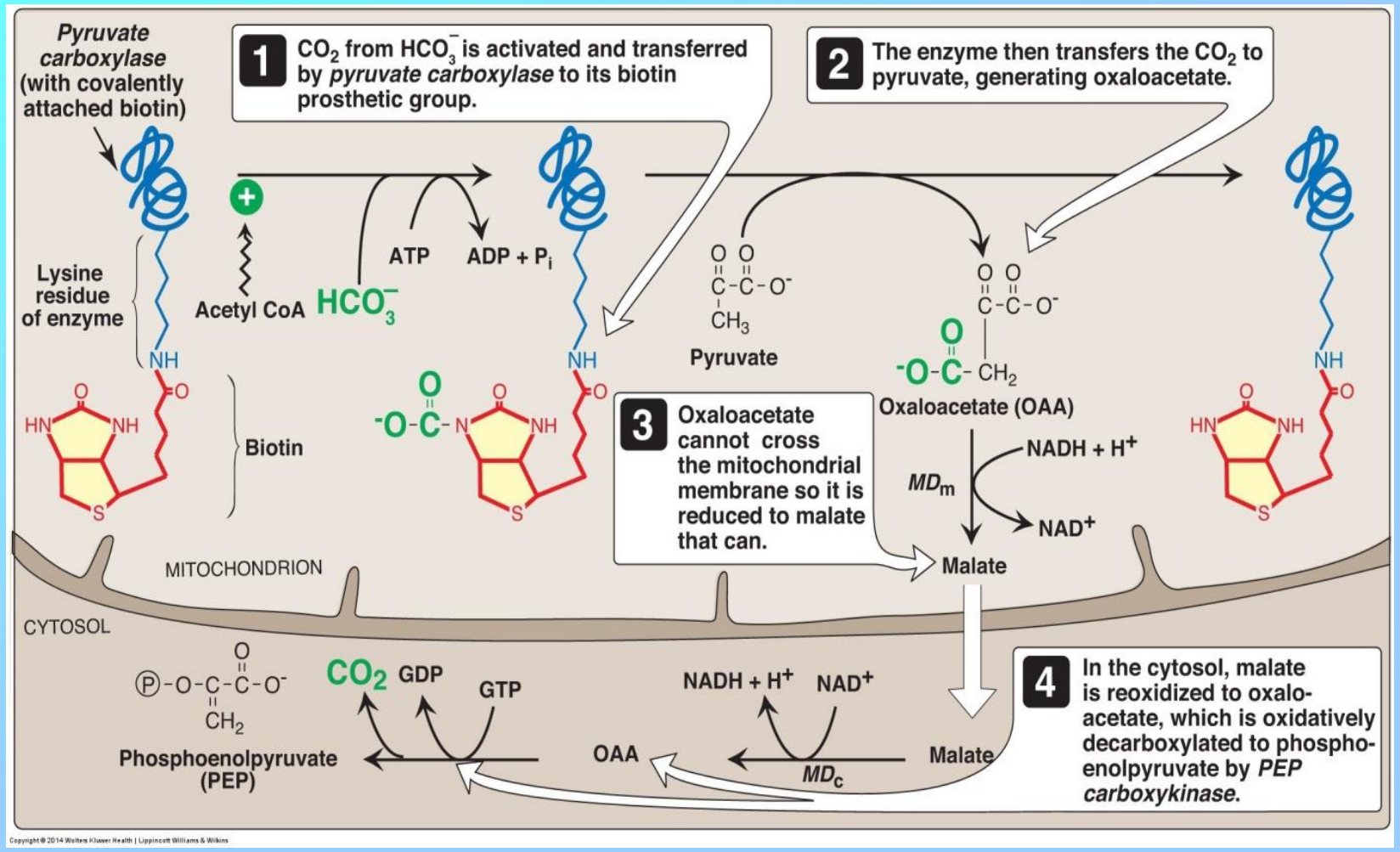
Pyruvate Carboxylation



Pruvate Carboxylase and PEP-CK

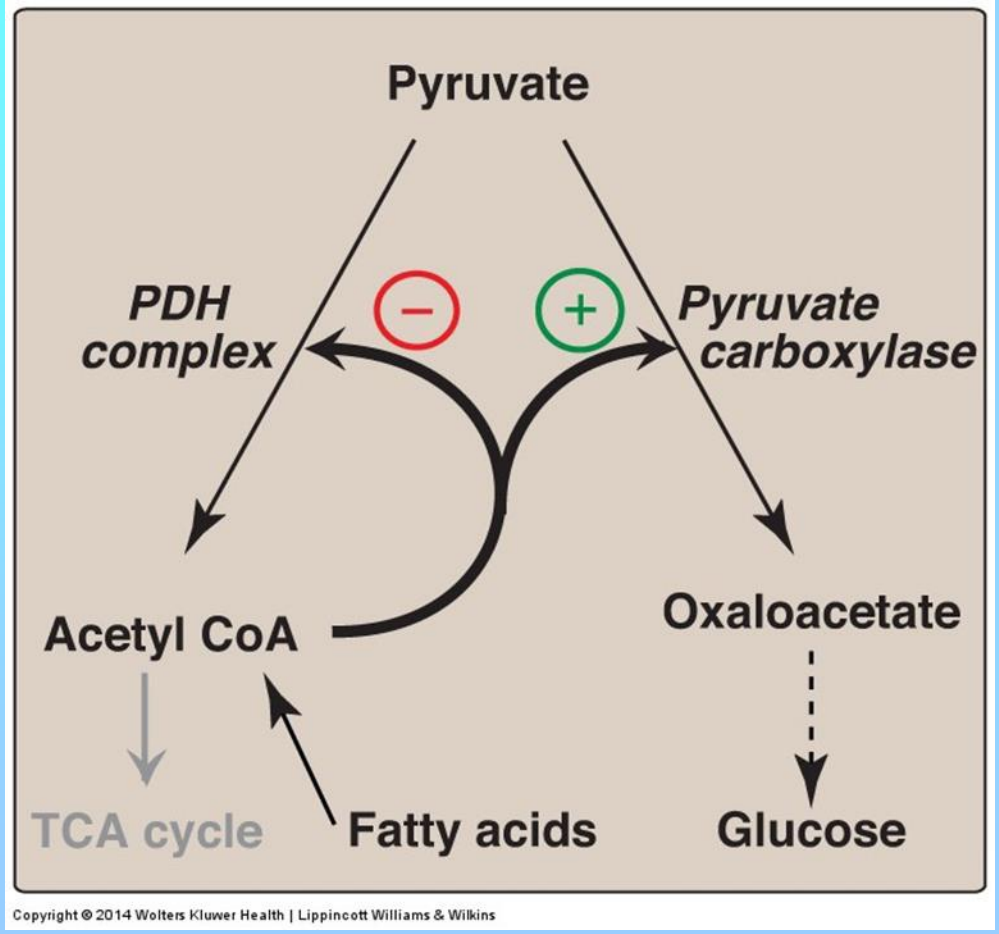
Fasting:
↑ Acetyl CoA (From FAO)*

***Fatty Acid Oxidation**



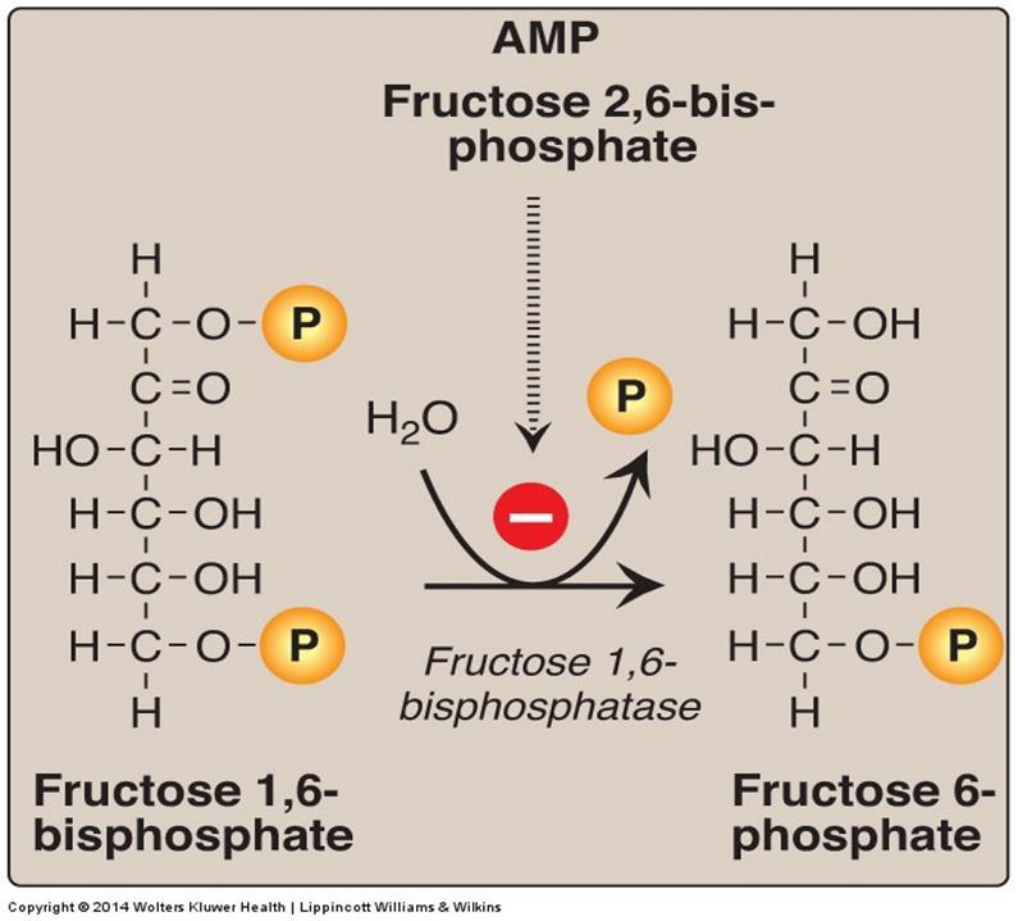
Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Regulation of Pruvate Carboxylase reaction



Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis

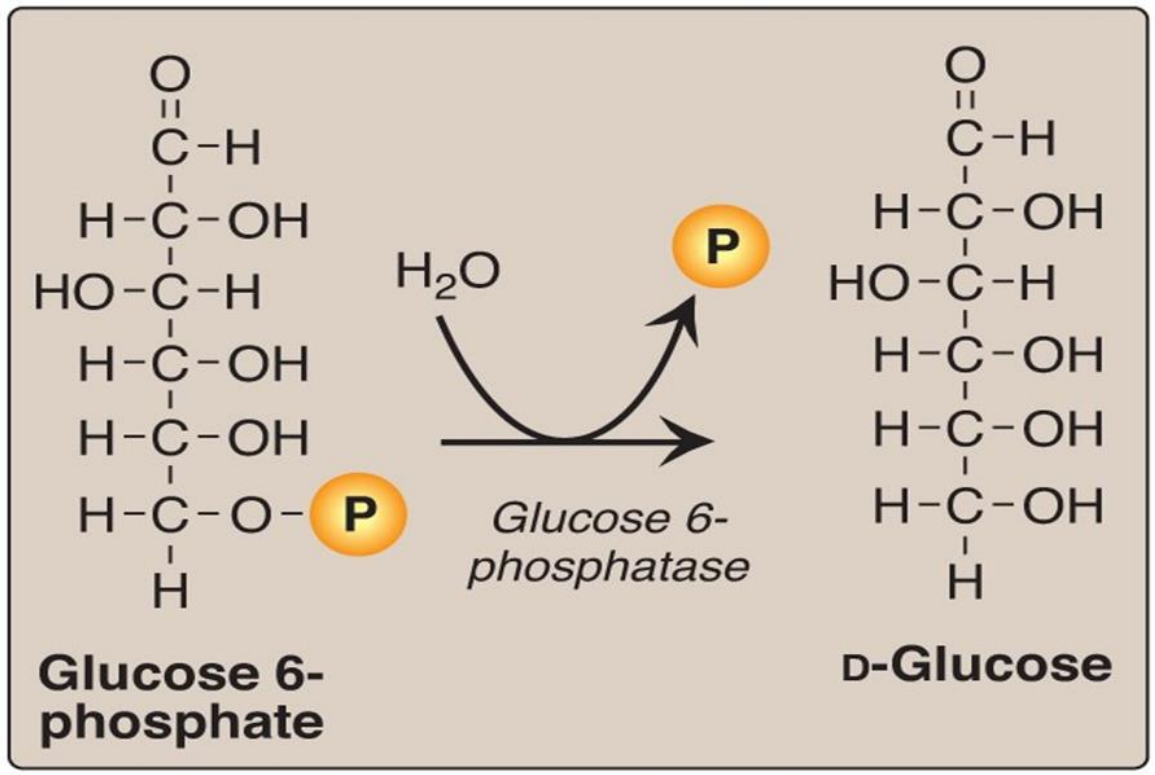
Fructose 1,6-Bisphosphatase



Dephosphorylation of fructose 1,6-bisphosphate.

Fructose 1,6-bisphosphatase ≠ PFK-1

Glucose 6-Phosphatase

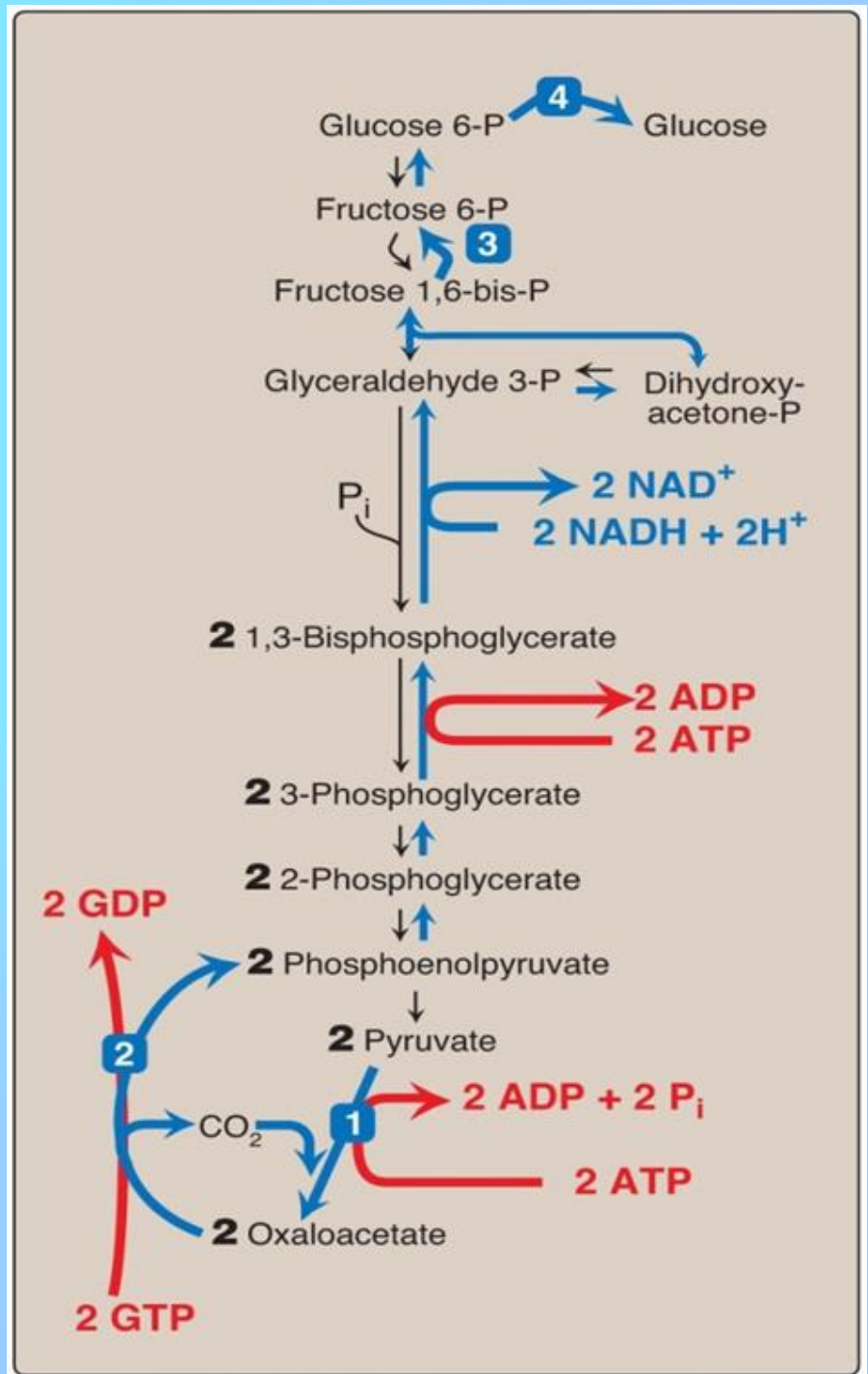


Dephosphorylation of glucose 6-phosphate allows release of free glucose from the liver and kidney into blood

Glucose 6-phosphatase ≠ Glucokinase

Gluconeogensis:
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 Message

- **Gluconeogenesis:**
  Synthesis of glucose from noncarbohydrates
  Anabolic
  Energy-consuming
- **4 Unique enzymes are required for reversal of the 3 irreversible reactions of glycolysis**
- **Both gluconeogenesis & glycolysis are reciprocally-regulated**