بسم الله الرحمن الرحيم

Glucose Metabolism: Gluconeogenesis

By

Amr S. Moustafa, *MD, PhD*

Assistant Prof. & Consultant, Medical Biochemistry Unit,
Pathology Dept., College of Medicine, KSU
amrsm@ksu.edu.sa

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: An Overview

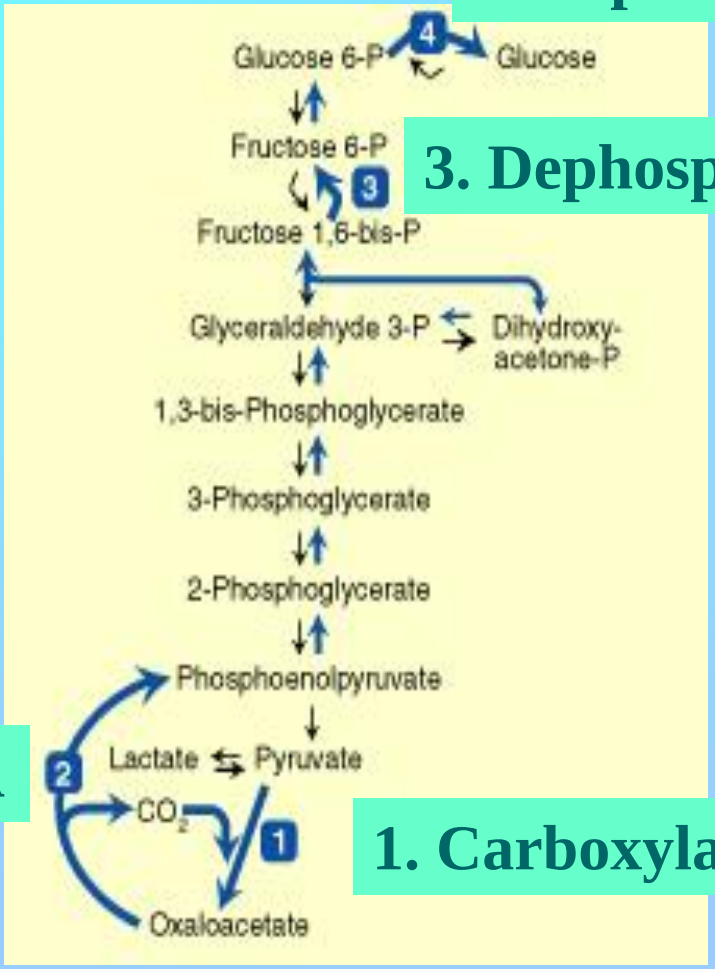
- Liver (mainly) and Kidneys
- Both mitochondria and Cytosol

  Exception: Glycerol, only cytosol
- Gluconeogenic substrates:

  Glycerol
  Lactate and Pyruvate
  Glucogenic amino acids

Gluconeogenic Pathway

4. Dephosphorylation of G6P

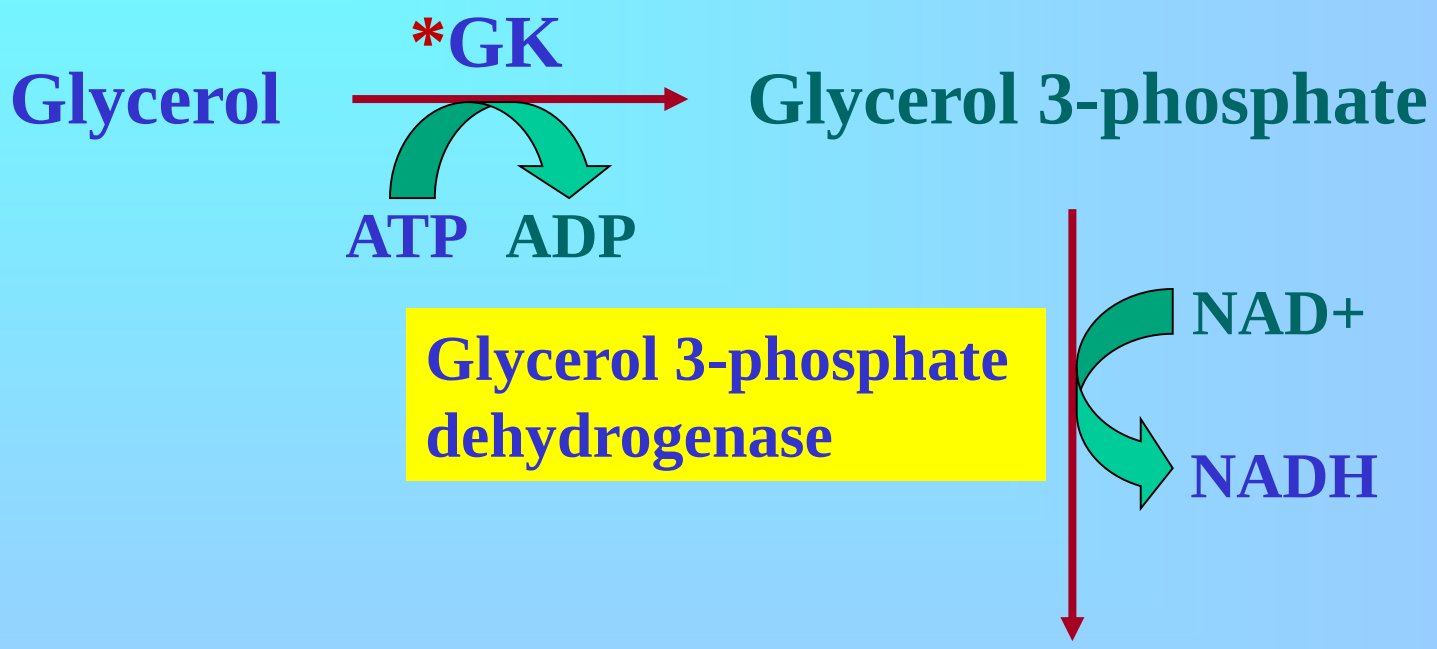


3. Dephosphorylation of F1,6P

2. Transport of OA

1. Carboxylation of pyruvate

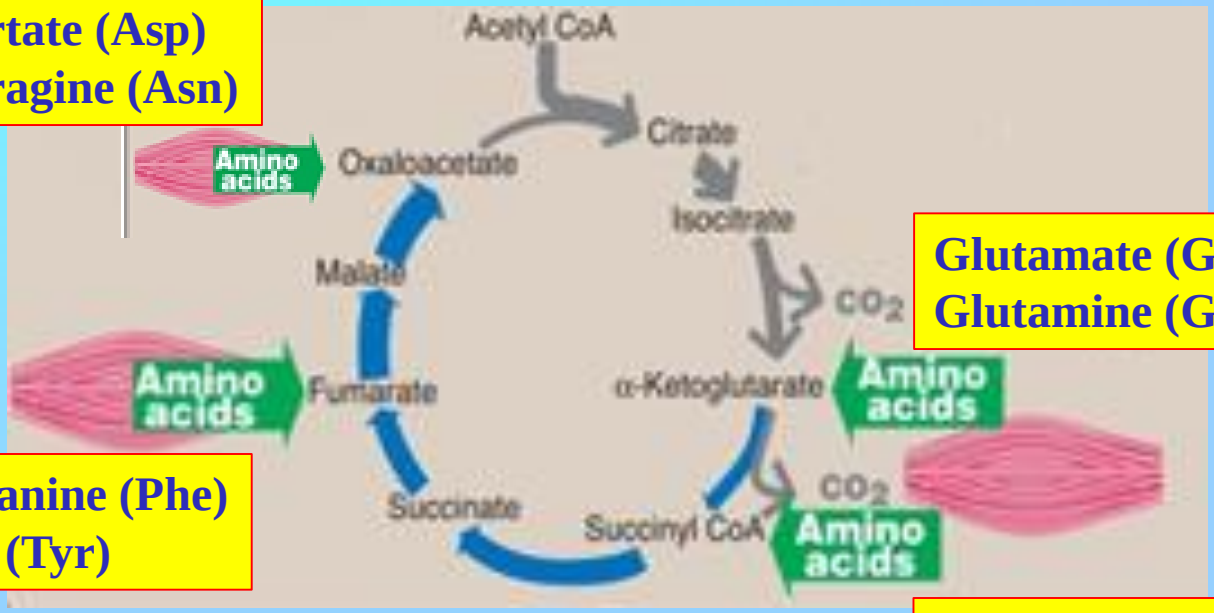
Gluconeogenic Substrates: Glycerol



*GK: Glycerol kinase 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

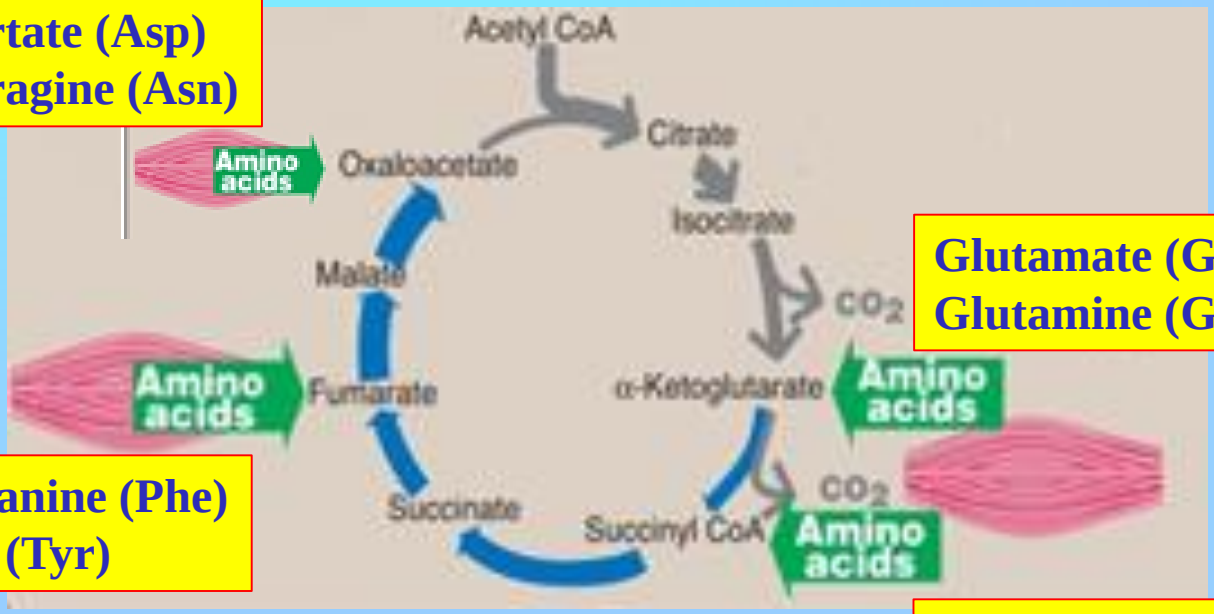
Lactate

Pyruvate

Amino acids

Alanine (Ala)
Glycine (Gly)

Aspartate (Asp)
Asparagine (Asn)

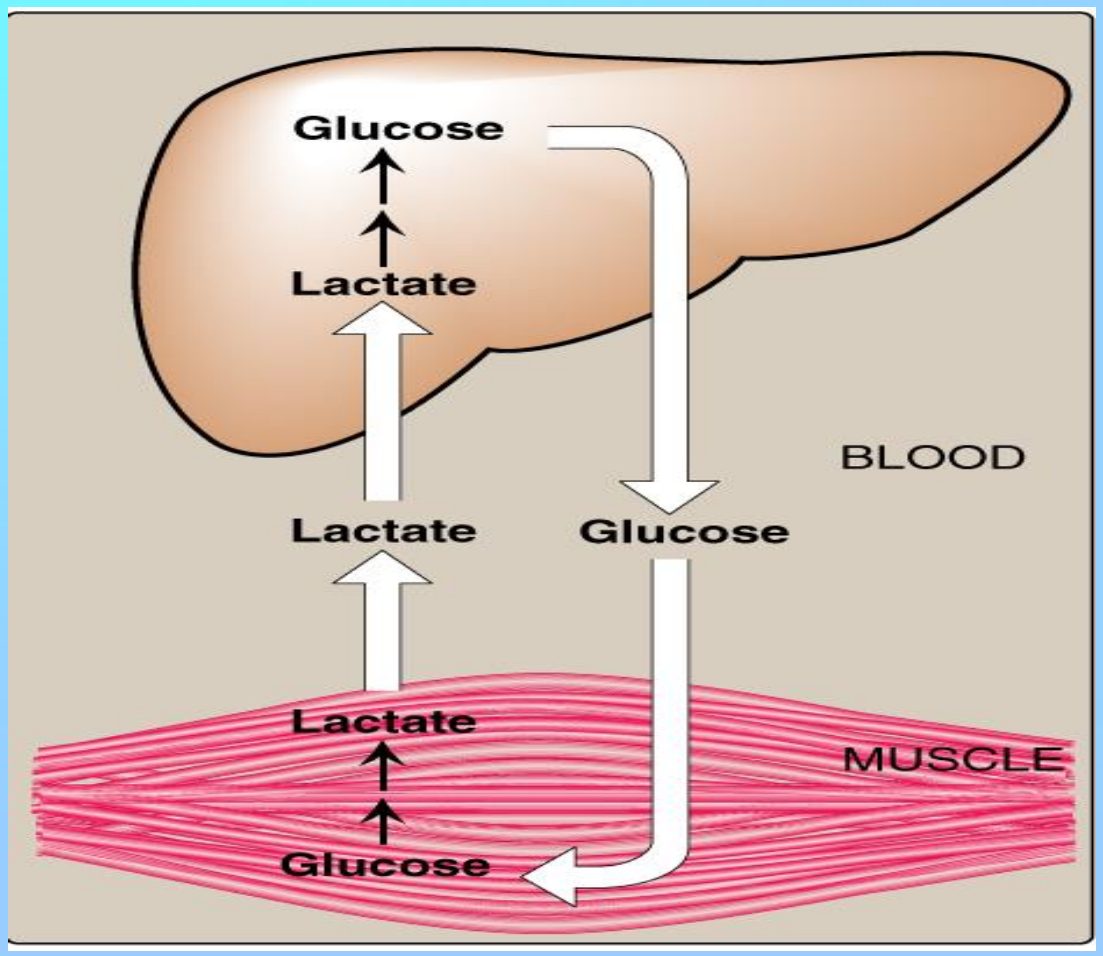


Glutamate (Glu)
Glutamine (Gln)

Phenylalanine (Phe)
Tyrosine (Tyr)

Methionine (Met)
Valine (Val)

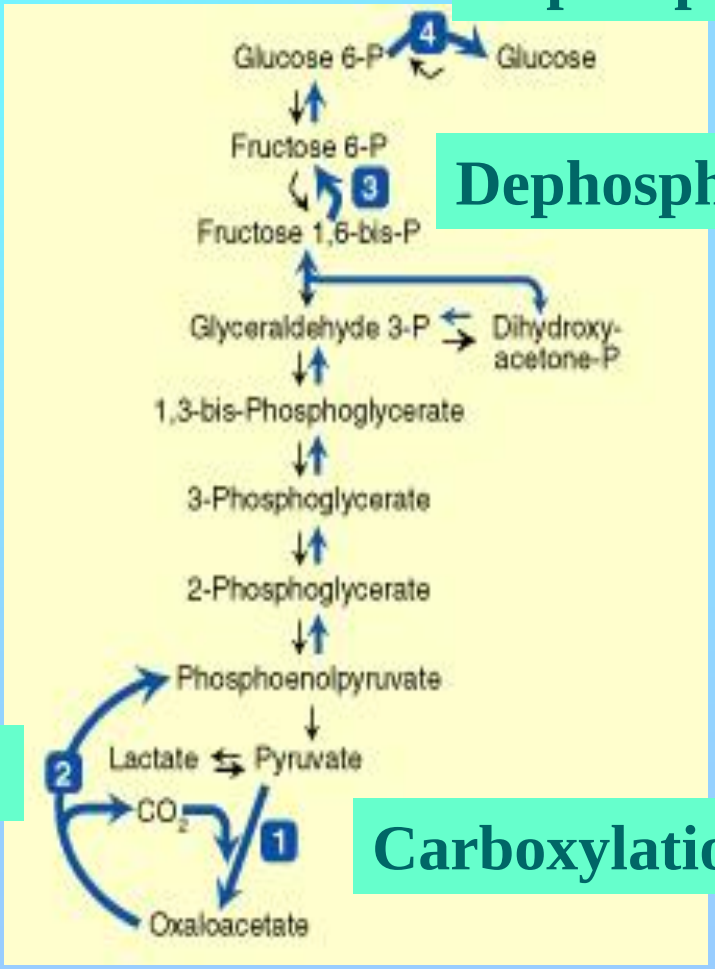
Gluconeogenic Substrates: Lactate (Cori Cycle)



Gluconeogenic Pathway

Dephosphorylation of G-6-P

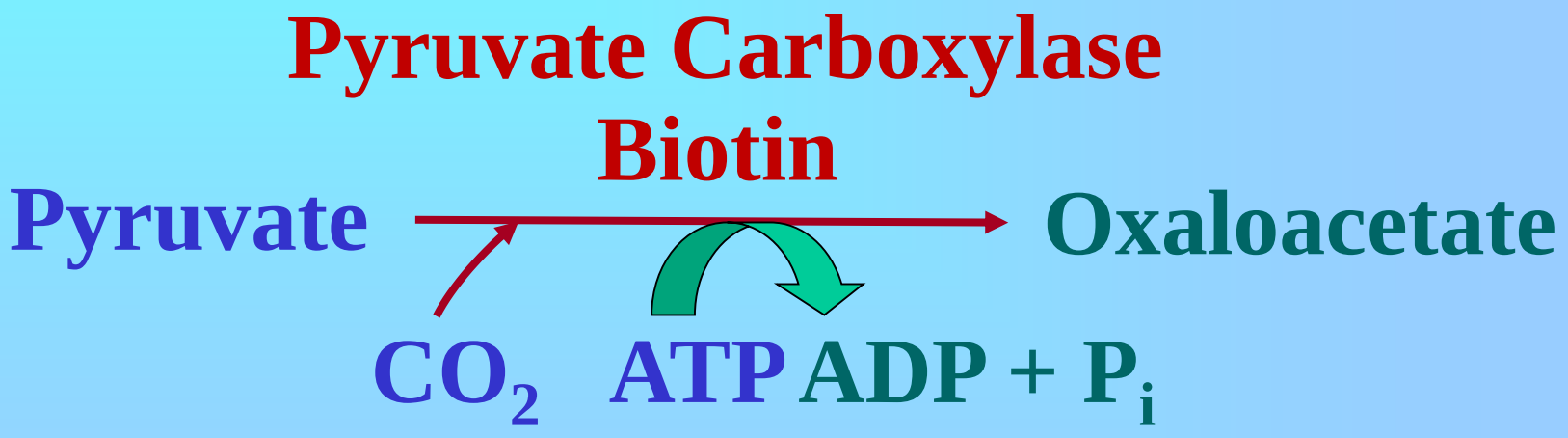
Dephosphorylation of F 1,6-P



Transport of OAA

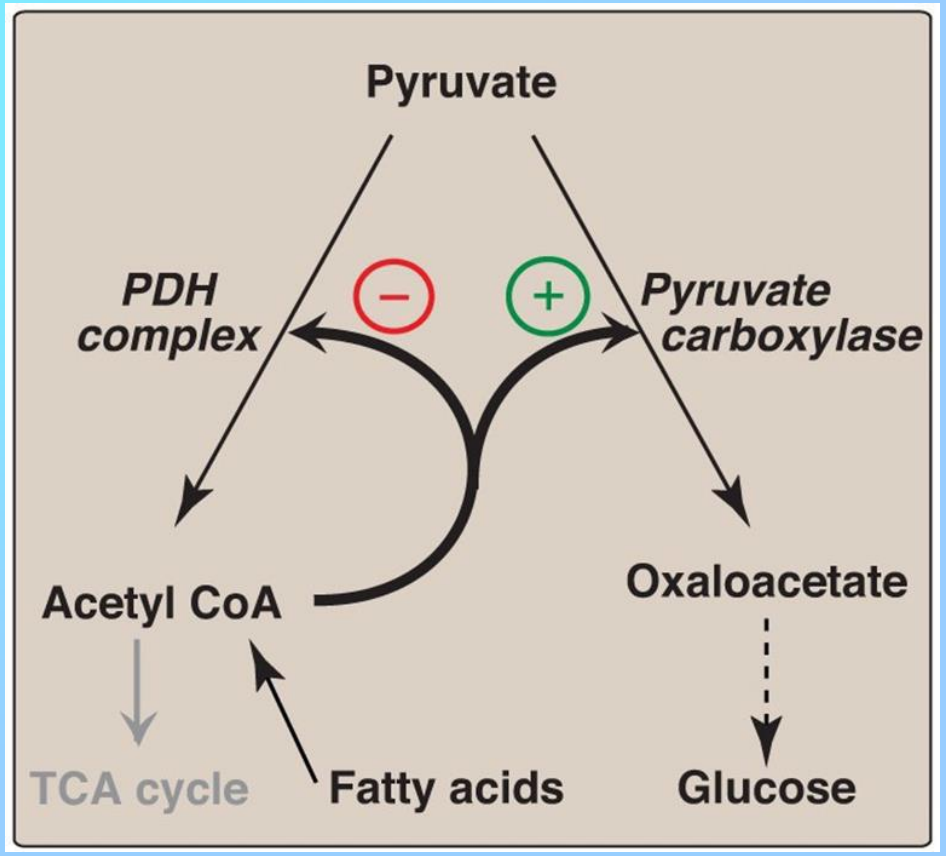
Carboxylation of pyruvate

Carboxylation of Pyruvate in the Mitochondria



Regulation of Pyruvate Carboxylase

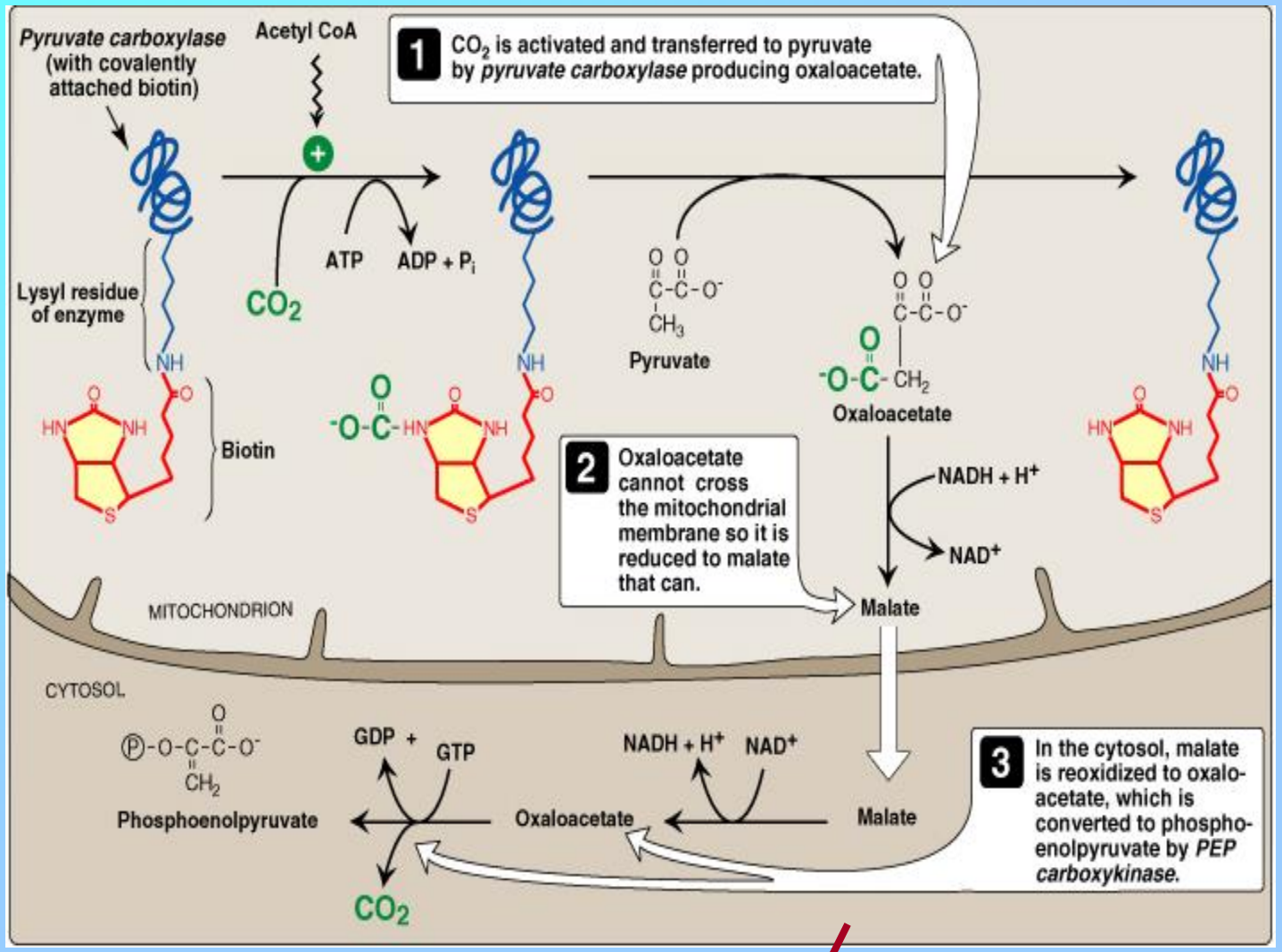
Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis



Pruvate Carboxylase and PEP-CK

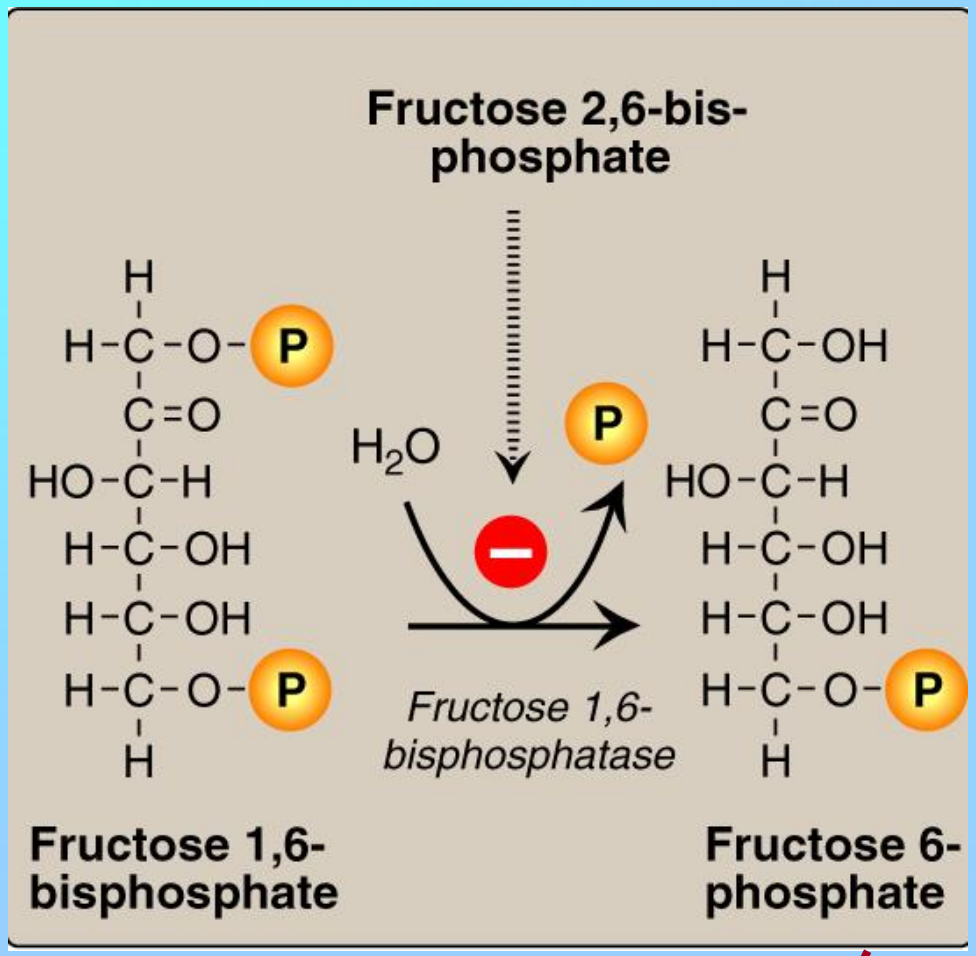
Fasting:
↑ Acetyl CoA
(From FAO)*

***Fatty Acid Oxidation**



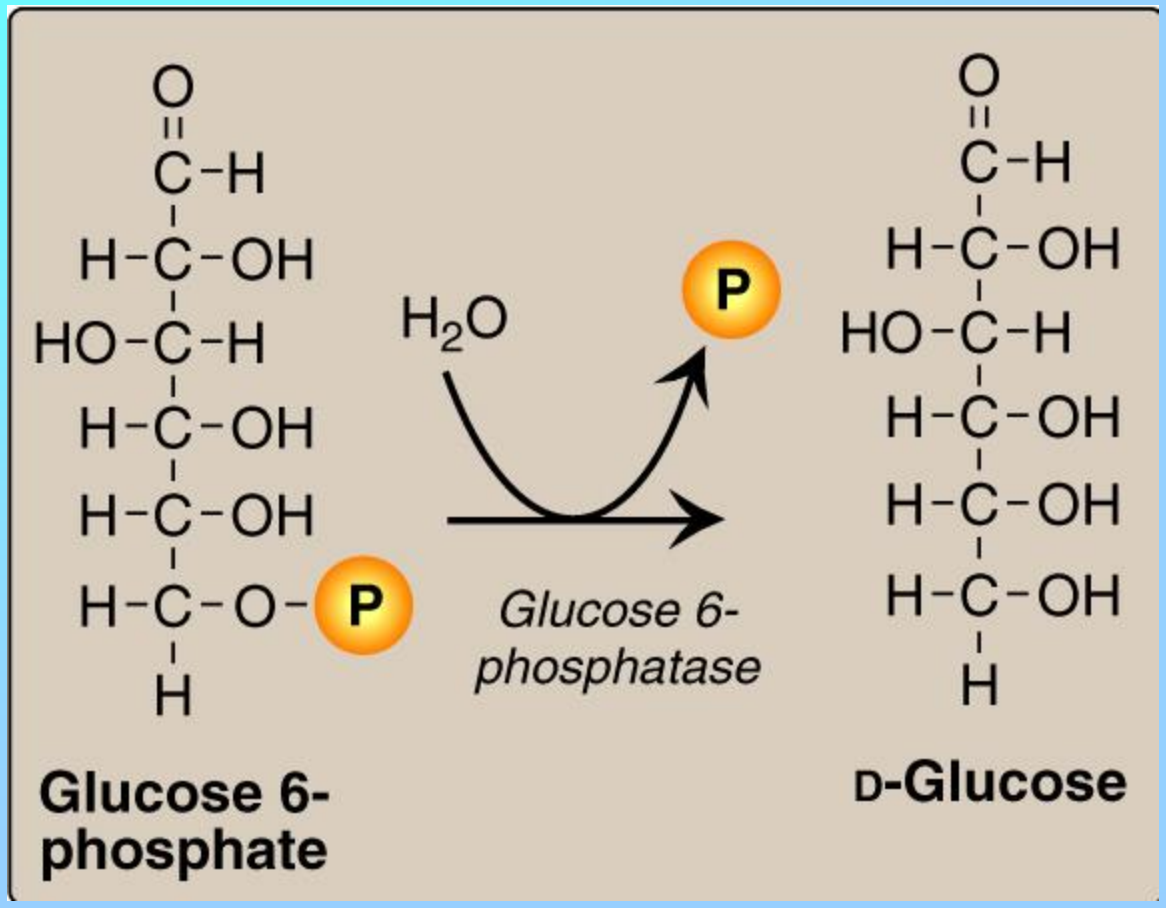
Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Fructose 1,6-Bisphosphatase



Fructose 1,6-bisphosphatase ≠ PFK-1

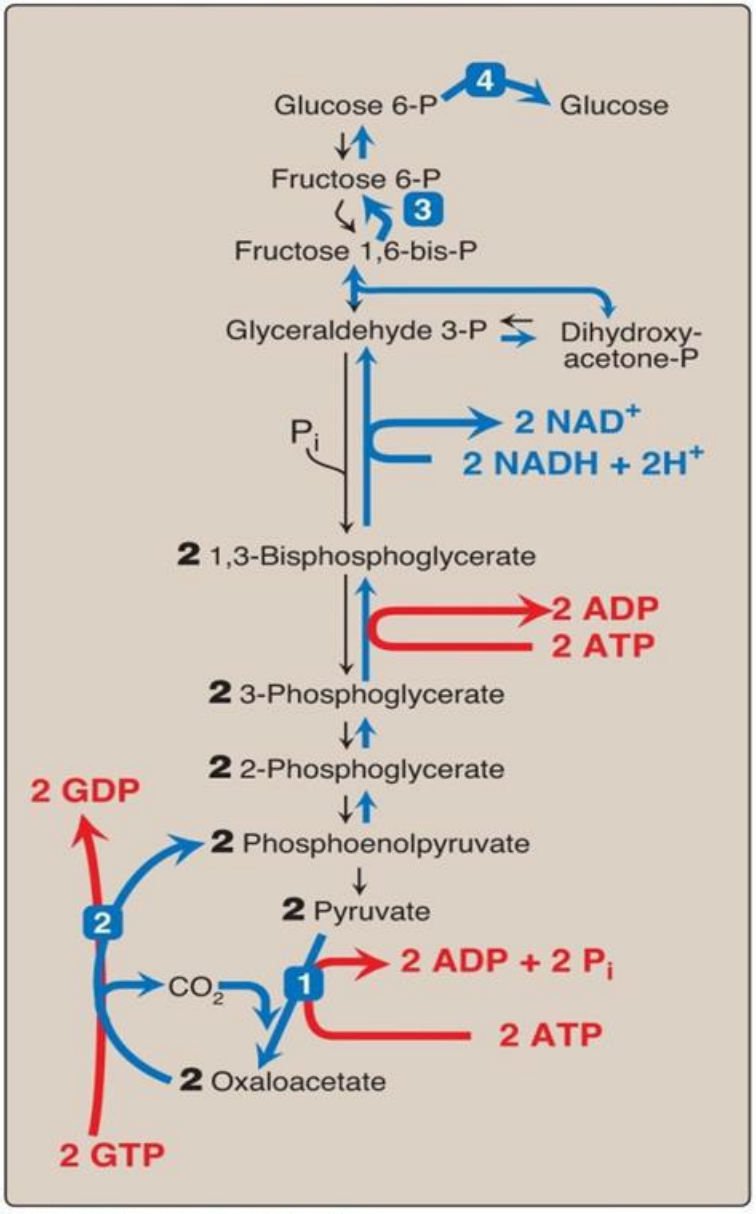
Glucose 6-Phosphatase



Glucose 6-phosphatase ≠ Glucokinase

Gluconeogensis: E- Consumed

Six High-Energy Phosphate Bonds Are Consumed for the Conversion of Pyruvate to Glucose



Gluconeogenesis: Regulation

- **Reciprocal control of**
  Gluconeogenesis & Glycolysis
- **Allosteric regulation:**
  Acetyl CoA (+) Pyruvate carboxylase

  AMP (-) or (+) ATP
  F 2,6-Bisphosphate (-) } **F 1,6-bisphosphatase**

- **↑ Glucagon (↓ I/G ratio)**
  Allosteric (↓ F 2,6-Bisphosphate)
  Induction (PEP-CK)

Take Home Message

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