Chapter 3-II:

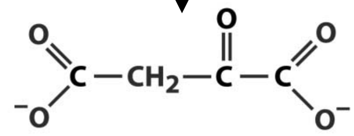
Glycogen Metabolism and Gluconeogenesis

Gluconeogenesis

Glucose synthesis form Lactate, pyruvate, citric acid cycle intermediates, carbon skeletons of amino acids, but not from acetyl-CoA
In liver (lesser in kidney cortex)

Amino acids

↓



Oxaloacetate

↓

glucose

Liver glycogen depletion during fasting

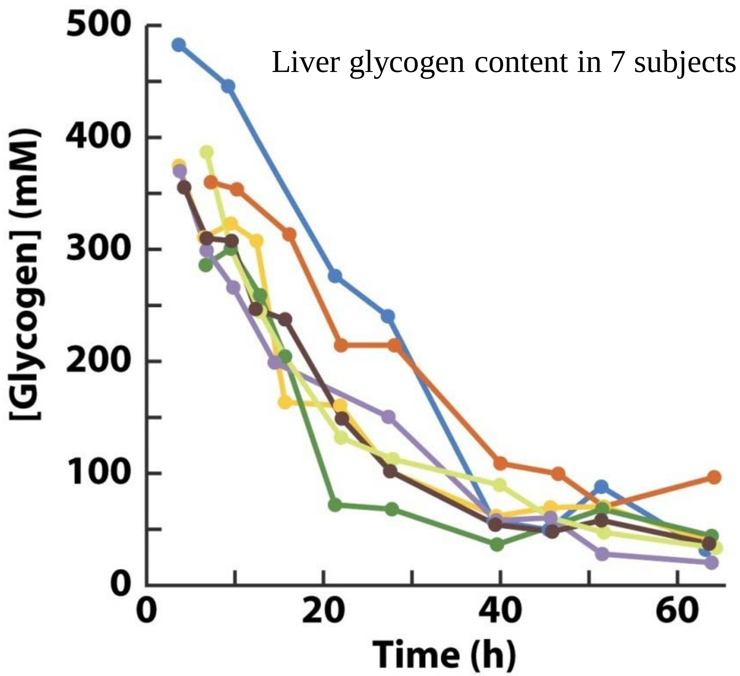


Figure 21-26 Fundamentals of Biochemistry, 2/e

Far-equilibrium steps of glycolysis are bypassed

↑ Glucose-6-phosphatase
Fructose bisphosphatase
Phosphoenol pyruvate carboxykinase (PEPCK)
Pyruvate carboxylase

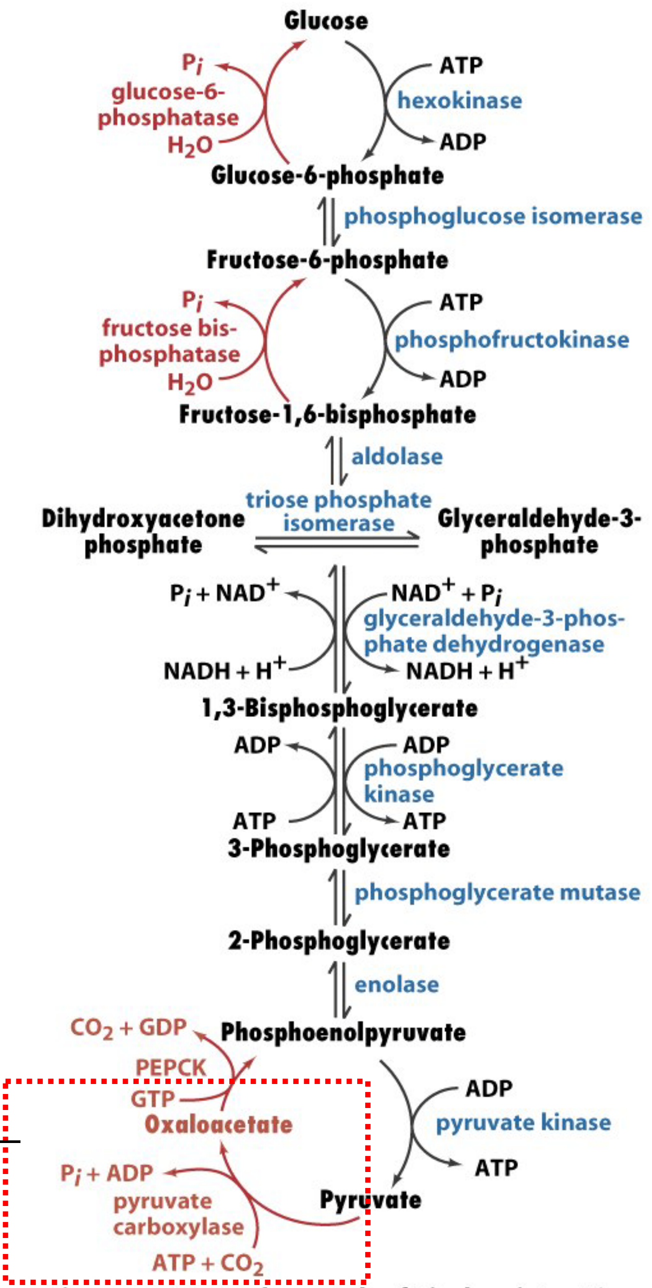
Occur in mitochondria & cytosol

Table 14-1 **$\Delta G^{\circ\prime}$ and ΔG for the Reactions of Glycolysis in Heart Muscle**[a]

Reaction	Enzyme	$\Delta G^{\circ\prime}$ ($kJ \cdot mol^{-1}$)	ΔG ($kJ \cdot mol^{-1}$)
1	Hexokinase	−20.9	−27.2
2	PGI	+2.2	−1.4
3	PFK	−17.2	−25.9
4	Aldolase	+22.8	−5.9
5	TIM	+7.9	~0
6 + 7	GAPDH + PGK	−16.7	−1.1
8	PGM	+4.7	−0.6
9	Enolase	−3.2	−2.4
10	PK	−23.0	−13.9

[a]Calculated from data in Newsholme, E.A. and Start, C., *Regulation in Metabolism*, p. 97, Wiley (1973).

Table 14-1 Fundamentals of Biochemistry, 2/e



mitochondria ←

Figure 15-23 Fundamentals of Biochemistry, 2/e

Pyruvate carboxylase

mitochondrial enzyme, tetramer of ~1160 a.a. subunits
dehydration of bicarbonate to transfer CO_2 to pyruvate
oxaloacetate is a kind of activated pyruvate at the expense of ATP

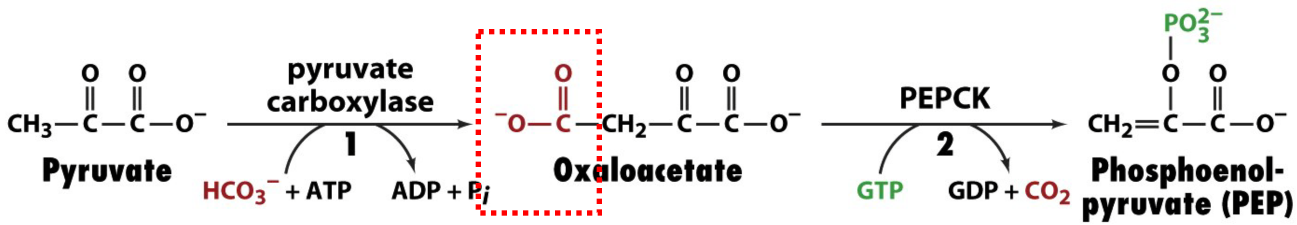


Figure 15-24 Fundamentals of Biochemistry, 2/e

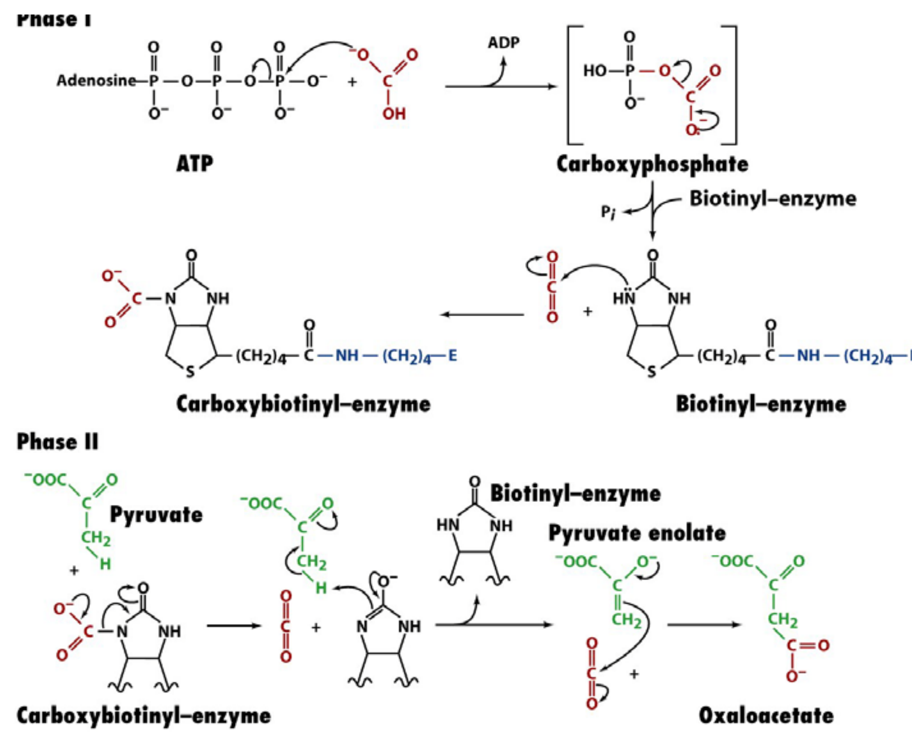


Figure 15-26 Fundamentals of Biochemistry, 2/e

Biotin prosthetic group

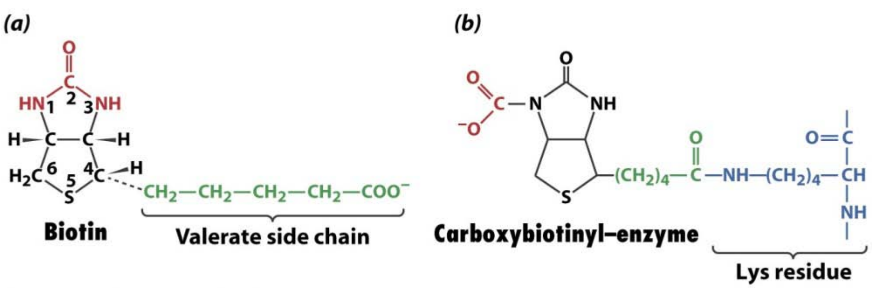


Figure 15-25 Fundamentals of Biochemistry, 2/e

PEPCK
Monomer of ~610 residues
Variable in location (mito or cytosol): equal distribution in human
GTP requiring decarboxylation/phosphorylation of oxaloacetate

PEPCK-C mouse

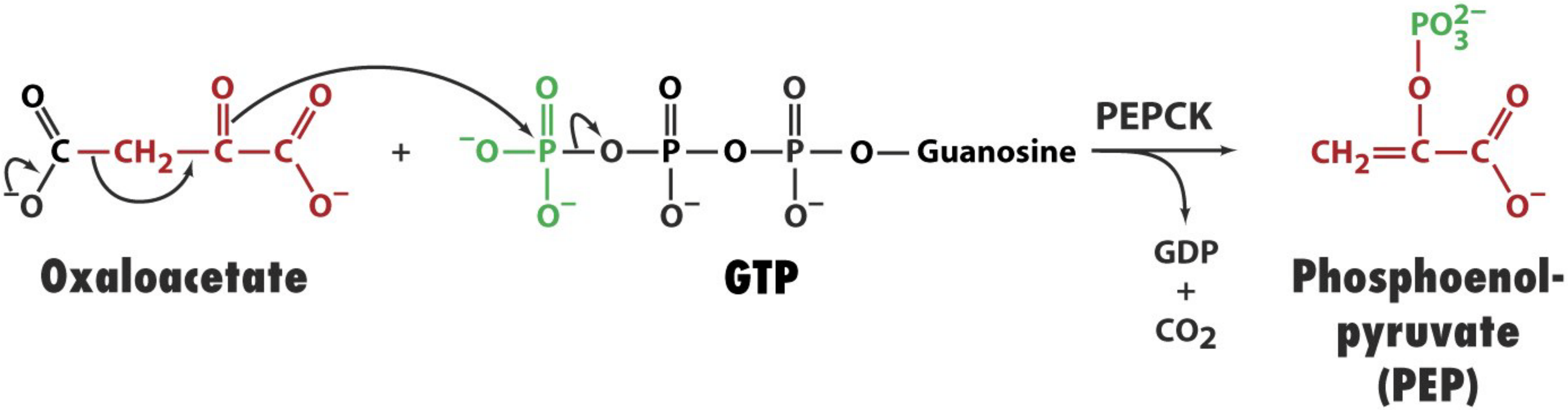


Figure 15-27 Fundamentals of Biochemistry, 2/e

<u>Metabolite transport between mitochondria and cytosol</u>

- PEP through transport proteins
- Oxaloacetate transport (cytosolic PEPCK species): malate-asparate shuttle
  - asparate aminotransferase route (route 1)
  - malate route (route 2): involve the transport of NADH reducing equivalents
  - Both pathways are freely reversible:
    - NADH for gluconeogenesis in cytosol
    - NADH for ETC in mitochondria

Deamination via urea cycle in liver

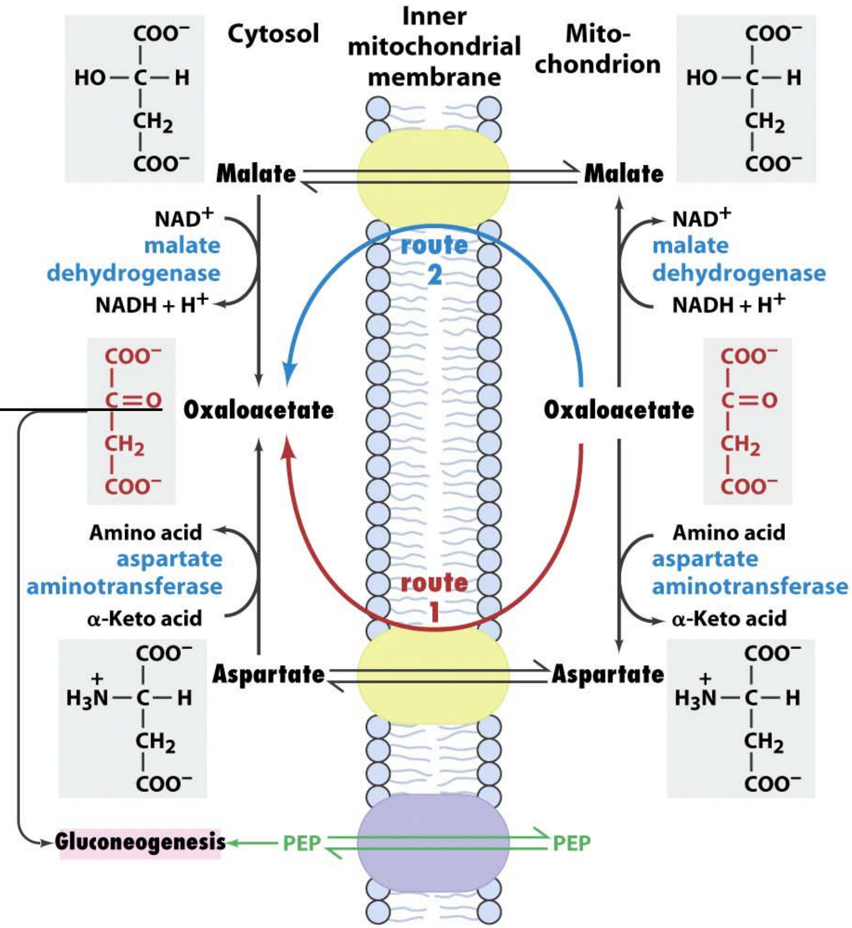


Figure 15-28 Fundamentals of Biochemistry, 2/e

Hydrolytic reactions

Glucose-6-phosphatase
Fructose bisphosphatase

The net energetic cost of gluconeogenesis

6 ATP equivalents: try calculation

3 substrate cycles

Regulation of gluconeogenesis

Reciprocal regulation of glycolysis and gluconeogenesis
3 potential points for regulation →

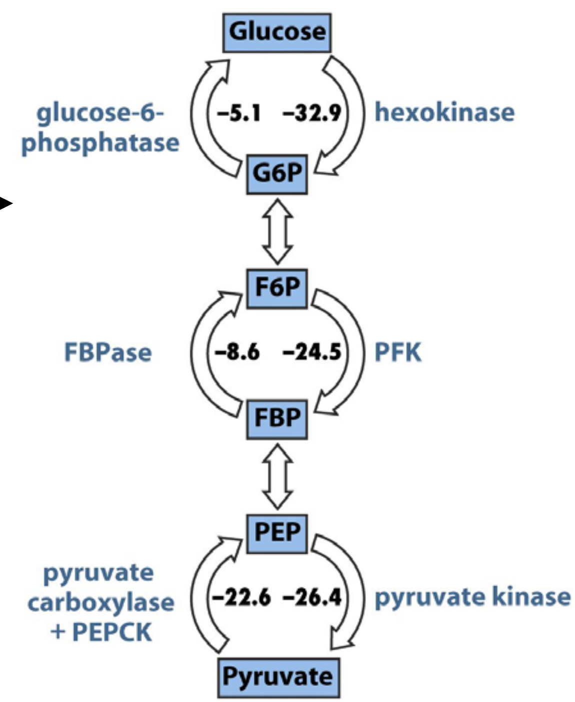


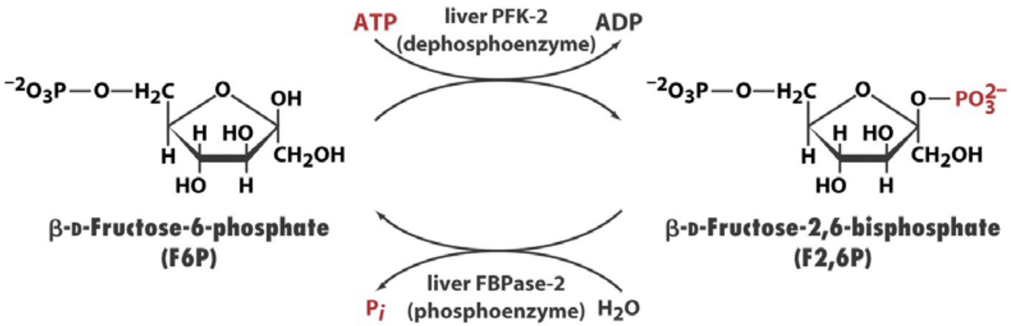
Figure 15-29 Fundamentals of Biochemistry, 2/e

Fructose-2,6-bisphosphate

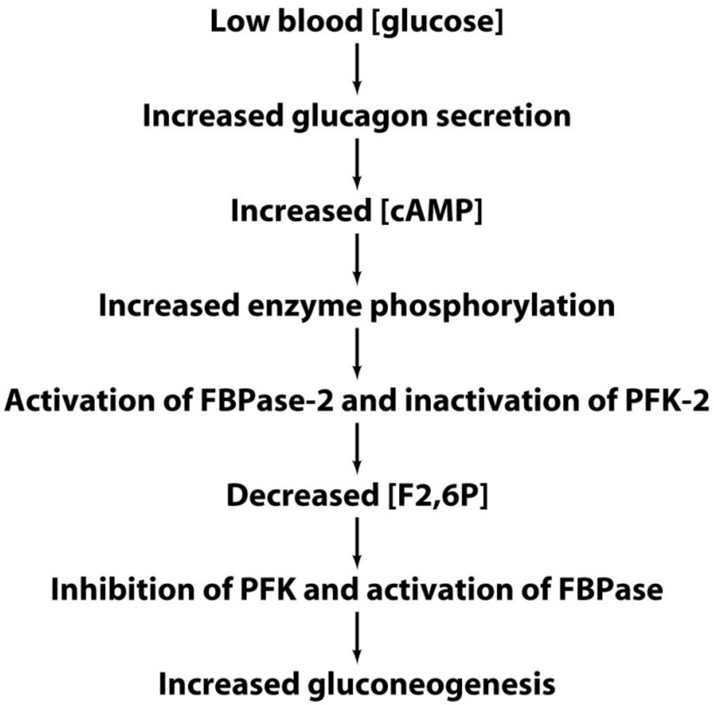
Extremely potent allosteric effector
Activate PFK, inhibits FBPase

Synthesis and degradation by a bifunctional two domain protein
PFK-2/FBPase-2

A variety of effectors
Covalent modification by PKA & phosphoprotein phosphatase



In liver



In muscle (not a gluconeogenic tissue)
Different PFK-2/FBPase-2 isozymes
Ex. Heart & skeletal muscle

Other allosteric effectors influence gluconeogenic flux

- Pyruvate carboxylase: activated by Acetyl-CoA
- PEPCK: no known allosteric effector
- Pyruvate kinase: allosteric inhibition in liver by alanine
  - inactivation by phosphorylation
- Hexokinase
- Glucose-6-phosphatase

Transamination of alanine (a major gluconeogenic precursor)