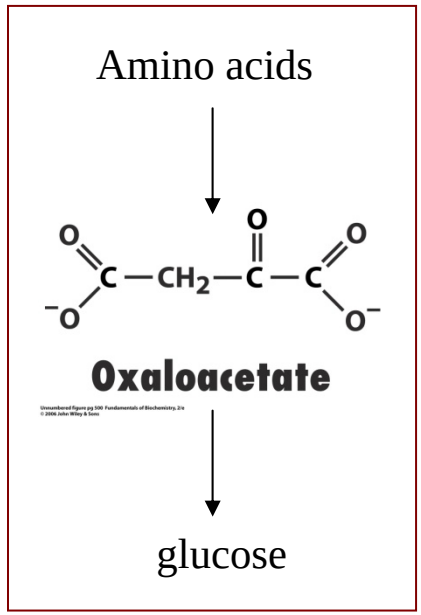
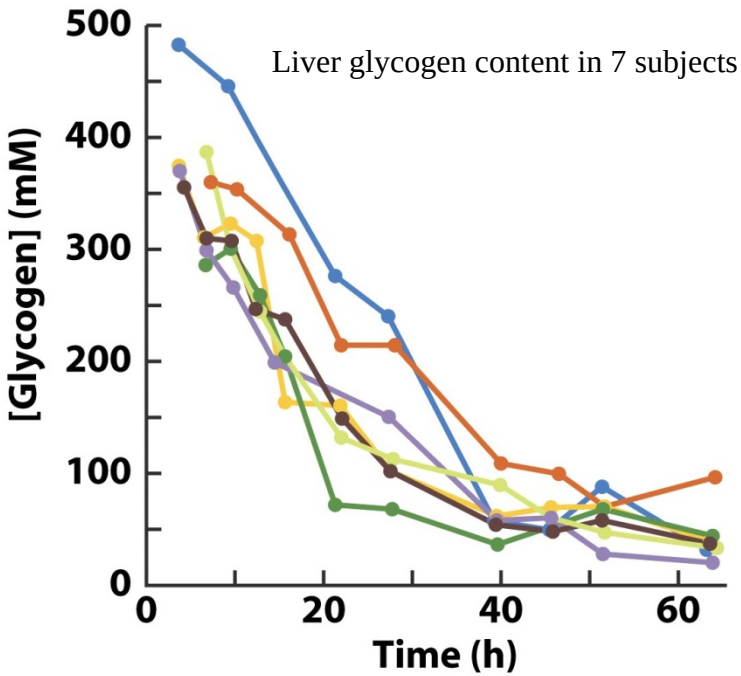
Gluconeogenesis

Glucose synthesis form Lactate, pyruvate, citric acid cycle intermediates, carbon skeletons of amino acids, but not from acetyl-CoA

In liver (lesser in kidney)



Liver glycogen depletion during fasting



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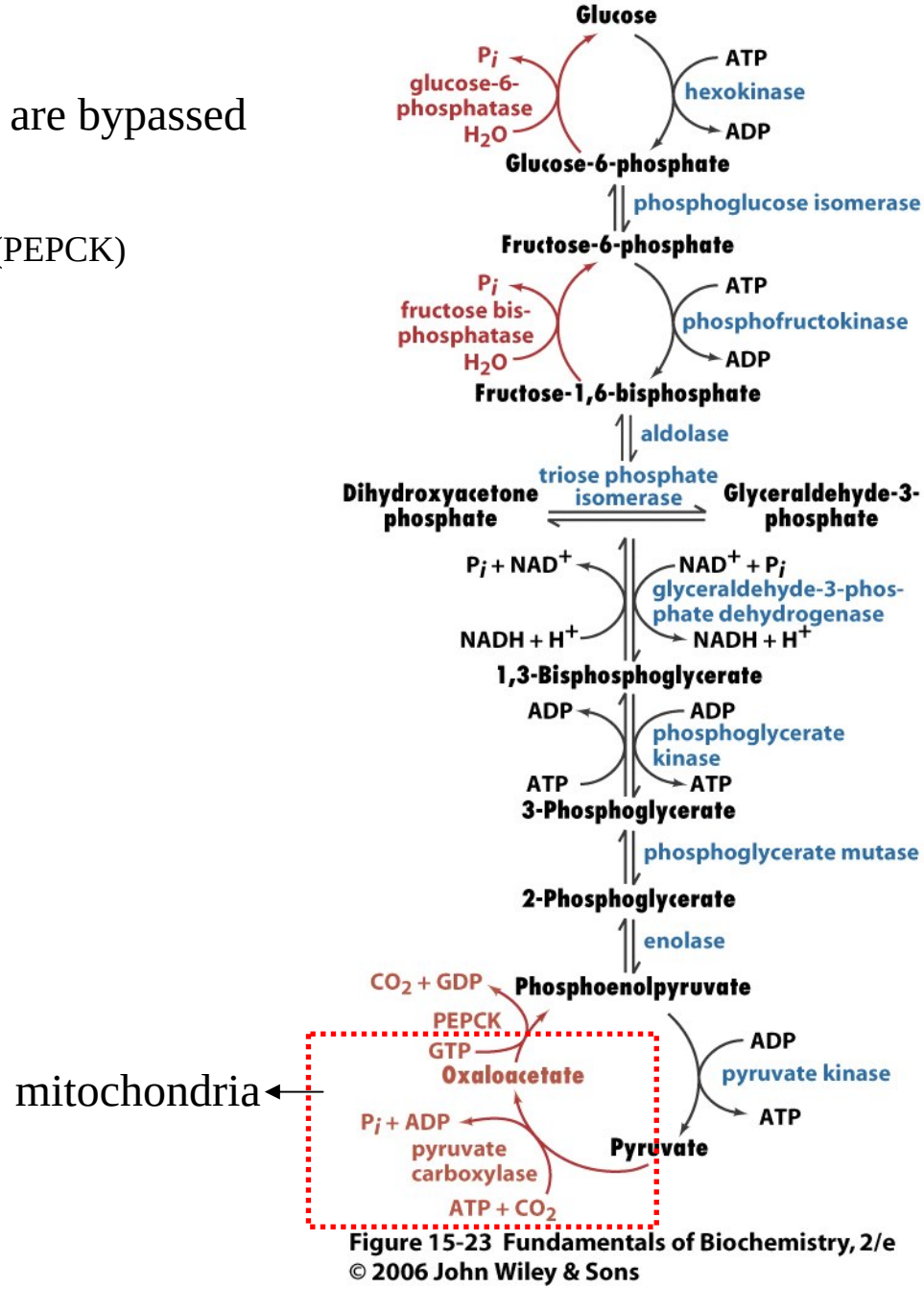
Far-equilibrium steps of glycolysis are bypassed

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

Occur in mitochondria & cytosol



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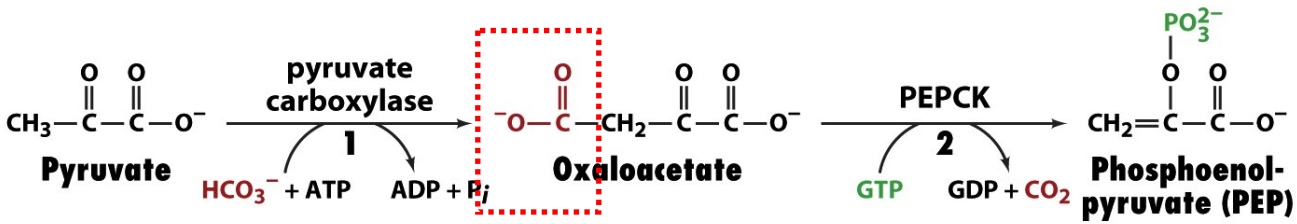
Pyruvate carboxylase

mitochondrial enzyme, tetramer of ~1160 a.a. subunits
dehydration of bicarbonate to transfer CO2 to pyruvate
oxaloacetate is a kind of activated pyruvate at the expense of ATP



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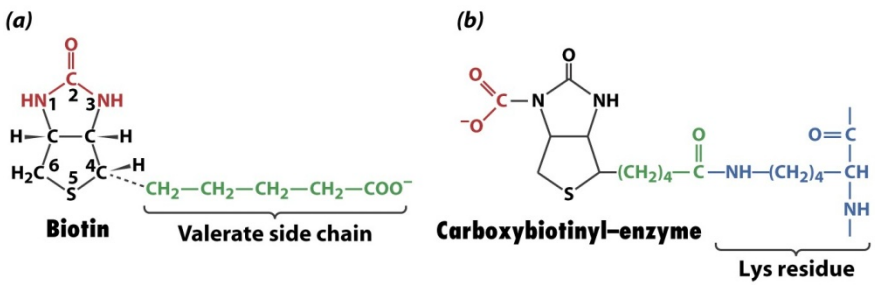
Biotin prosthetic group



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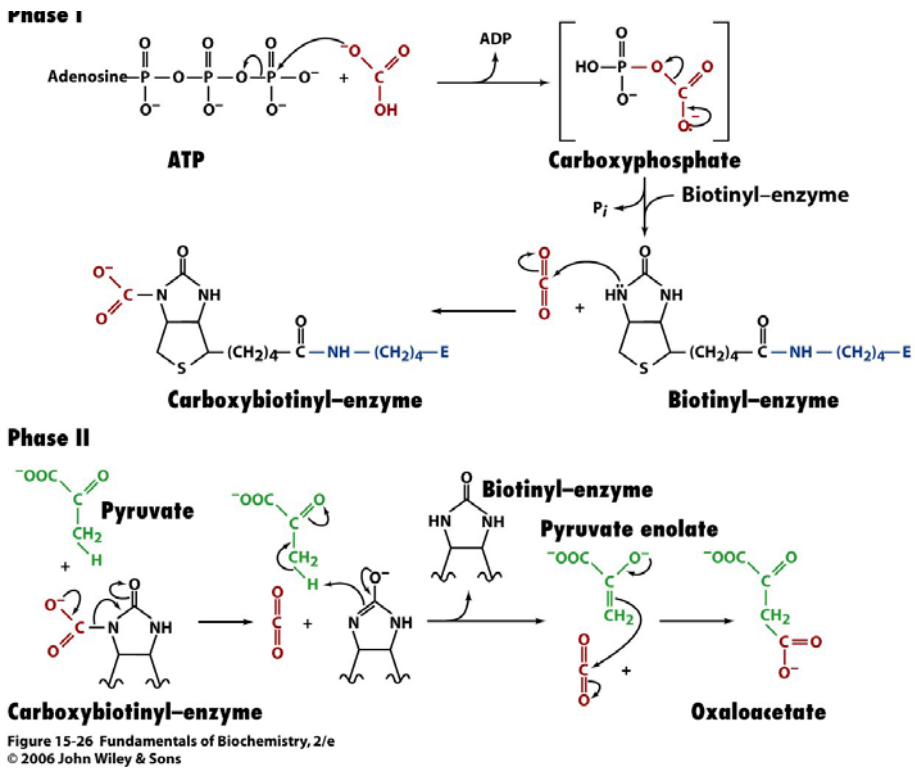

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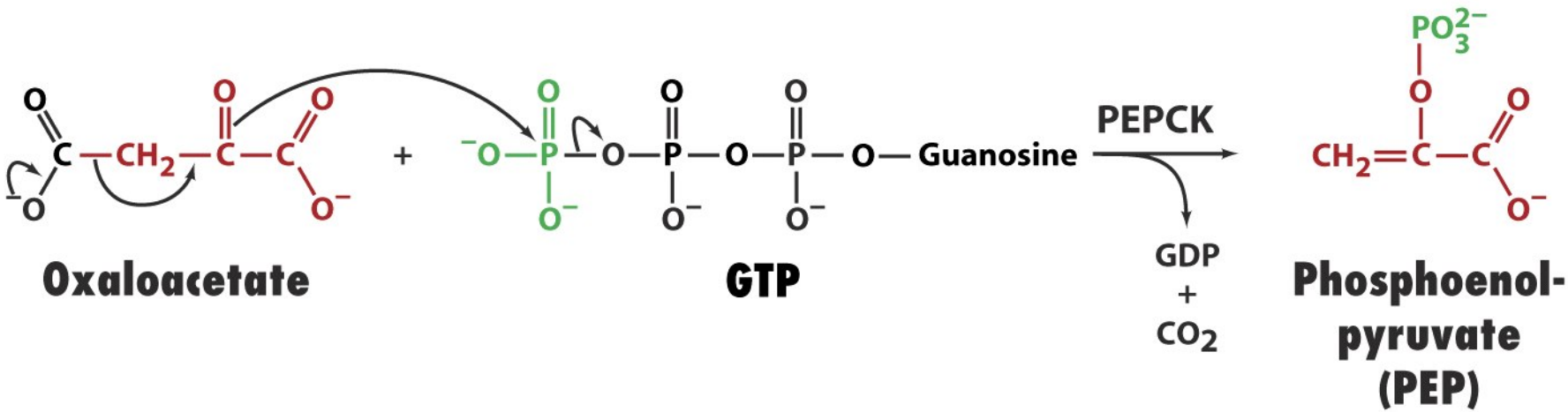
PEPCK
Monomer of ~610 residues
Variable in location (mito or cytosol): equal distribution in human
GTP requiring decarboxylation/phosphorylation of oxaloacetate

PEPCK-C mouse



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Metabolite transport between mitochondria and cytosol

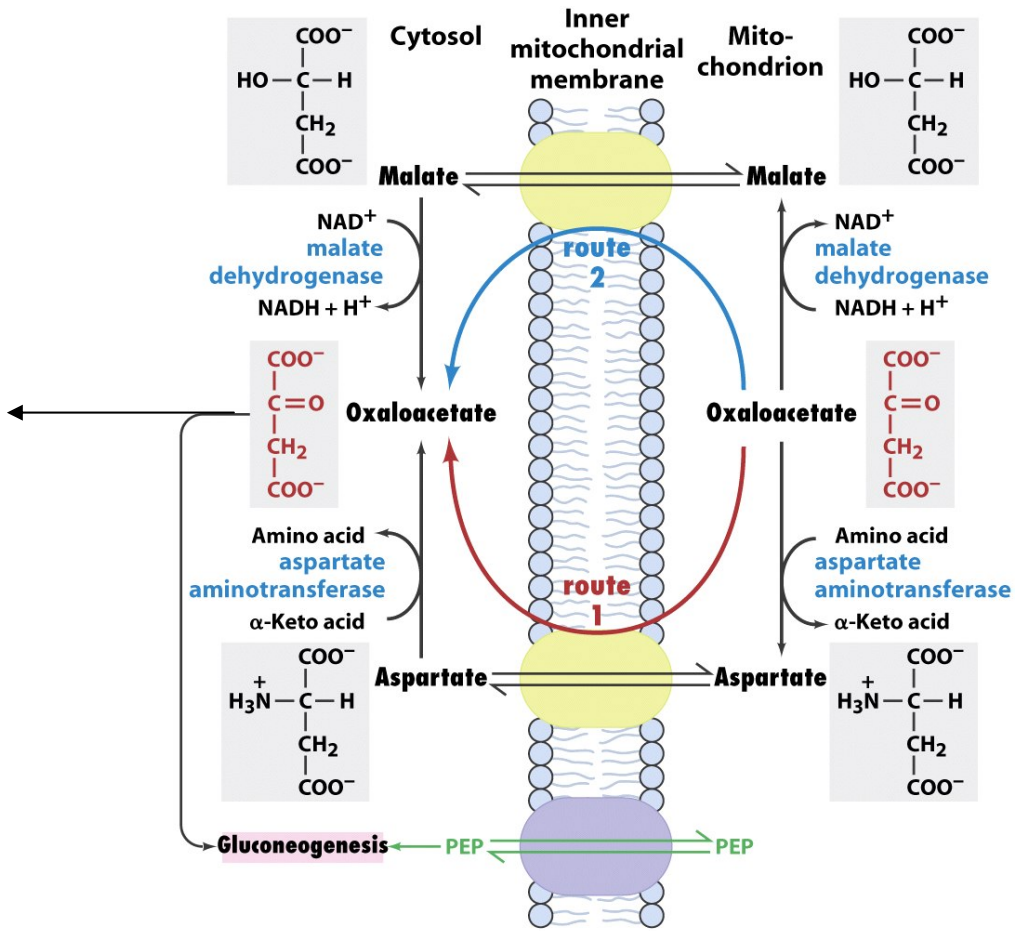
PEP through transport proteins

Oxaloacetate transport (cytosolic PEPCK species): malate-asparate shuttle

asparate aminotransferase route (route 1)

malate route (route 2): involve the transport of NADH reducing equivalents

Deamination via urea cycle in liver



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Hydrolytic reactions

Glucose-6-phosphatase
Fructose bisphosphatase

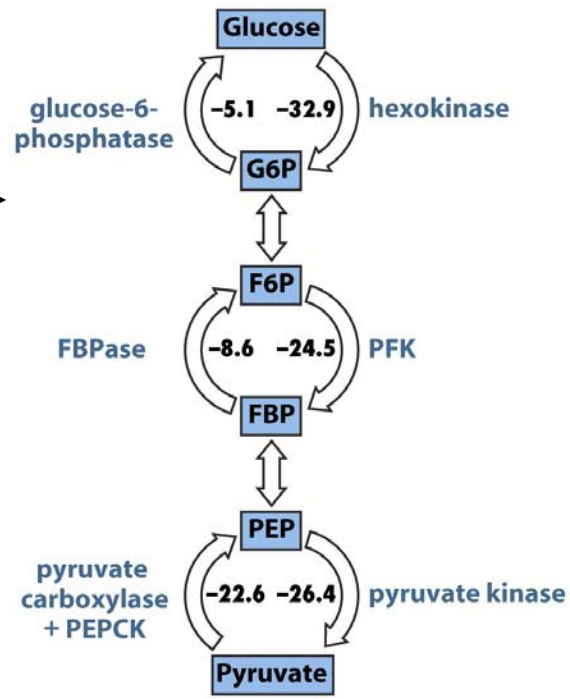
The net energetic cost of gluconeogenesis

6 ATP equivalents: try calculation

Regulation of gluconeogenesis

Reciprocal regulation of glycolysis and gluconeogenesis
3 potential points for regulation

3 substrate cycles



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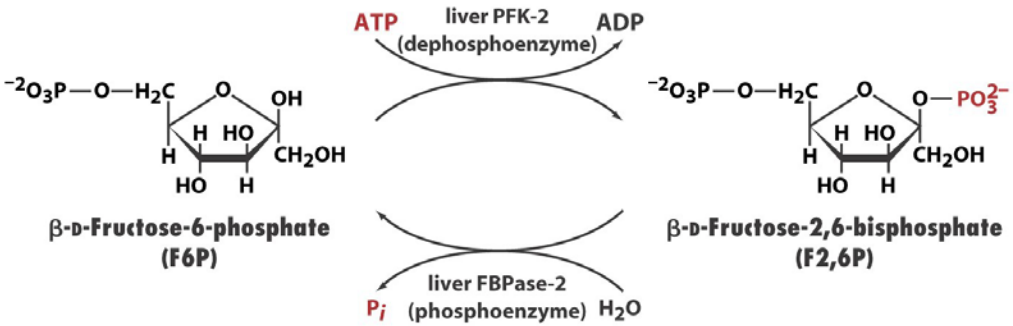
Fructose-2,6-bisphosphate

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



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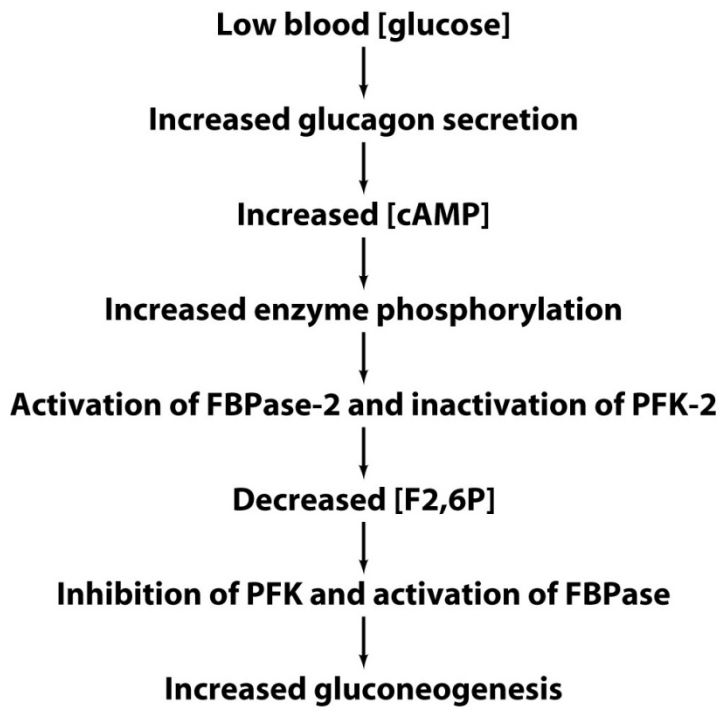
In liver



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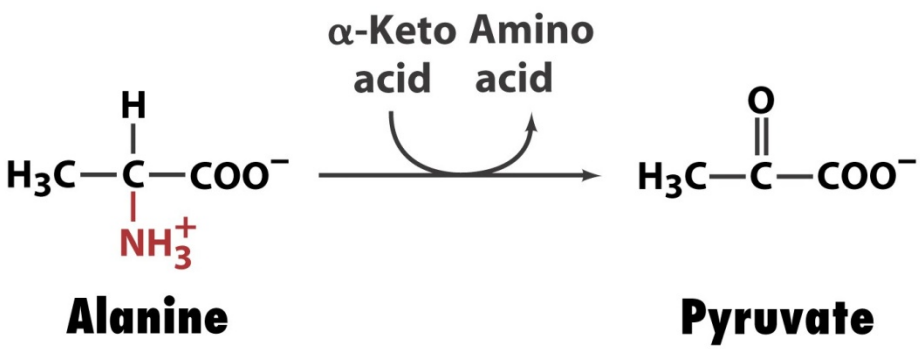
In muscle (not a gluconeogenic tissue)
Different PFK-2/FBPase-2 isozymes
Ex. Heart & skeletal muscle

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)



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