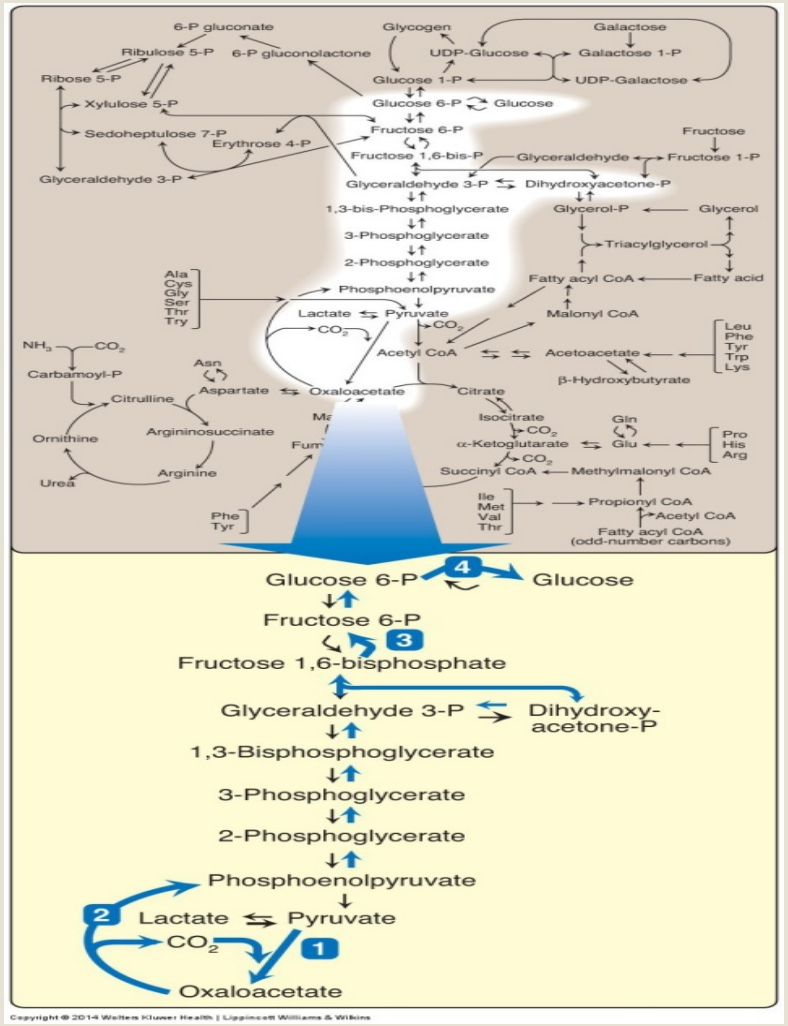
Glucose Metabolism (Gluconeogenesis)

Objectives

- The importance of gluconeogenesis as an important pathway for glucose production
- The main reactions of gluconeogenesis
- The rate-limiting enzymes of gluconeogenesis
- Gluconeogensis is an energy-consuming, anabolic pathway

Gluconeogenesis in general metabolism

The gluconeogenesis pathway shown as one of the essential pathways of energy metabolism.

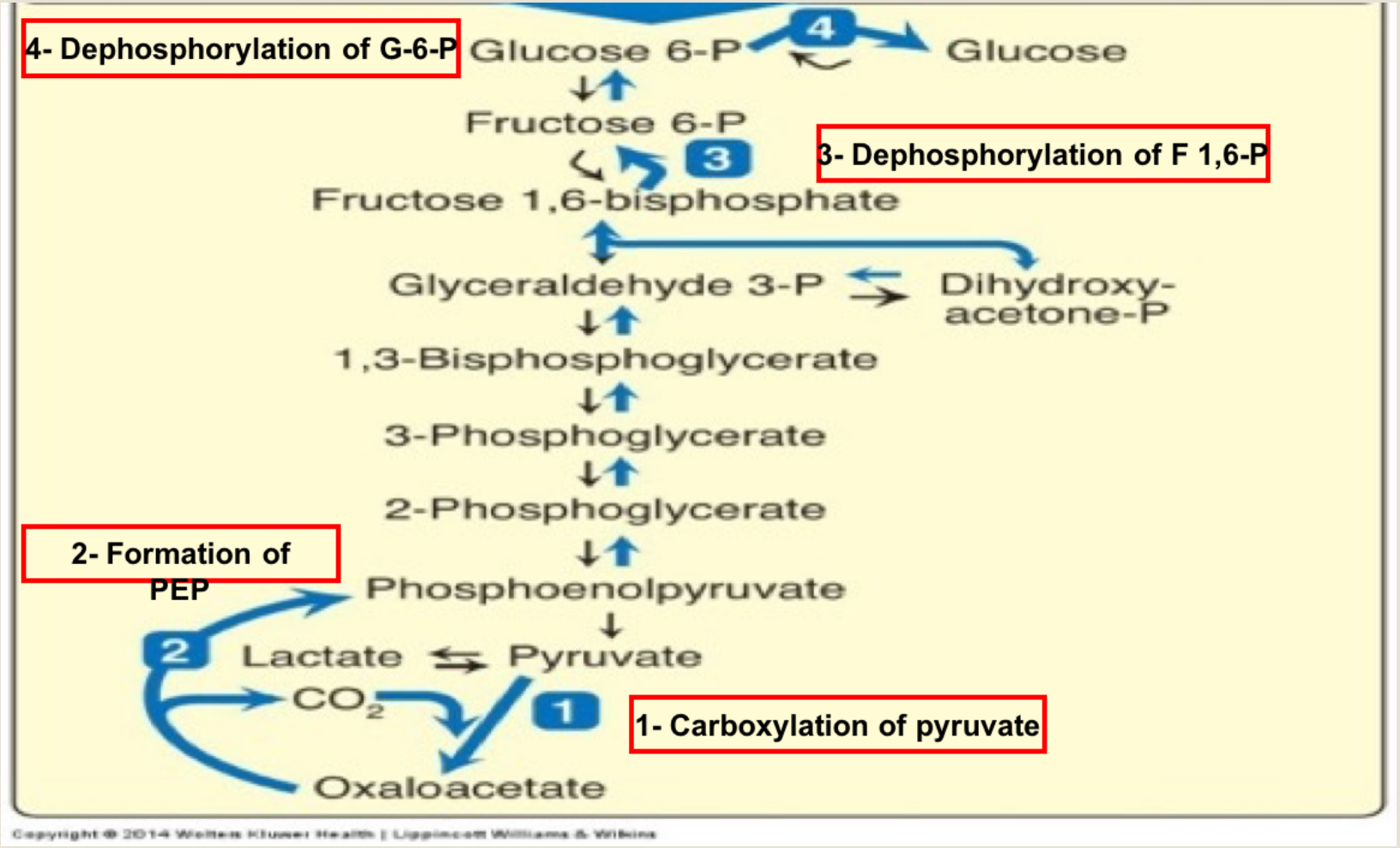


Gluconeogenesis: An Overview

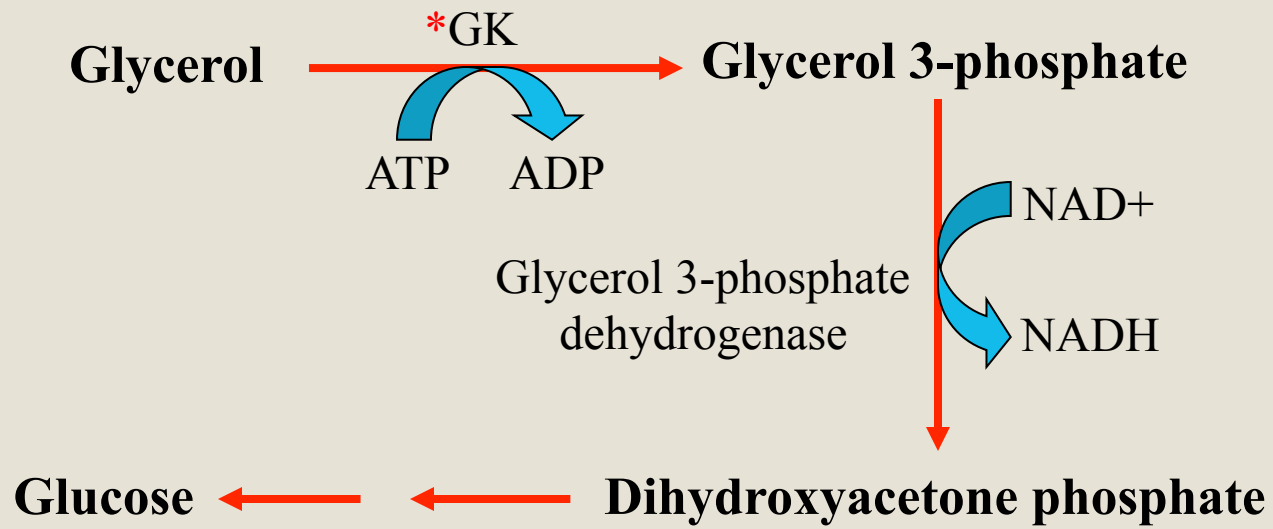
- Site: Liver (mainly) and Kidneys
- Both mitochondria and Cytosol are involved
- Exception: if the substrate is Glycerol: only cytosol
- Gluconeogenic substrates:

Glycerol
Lactate and Pyruvate
Glucogenic amino acids

Gluconeogenesis Pathway

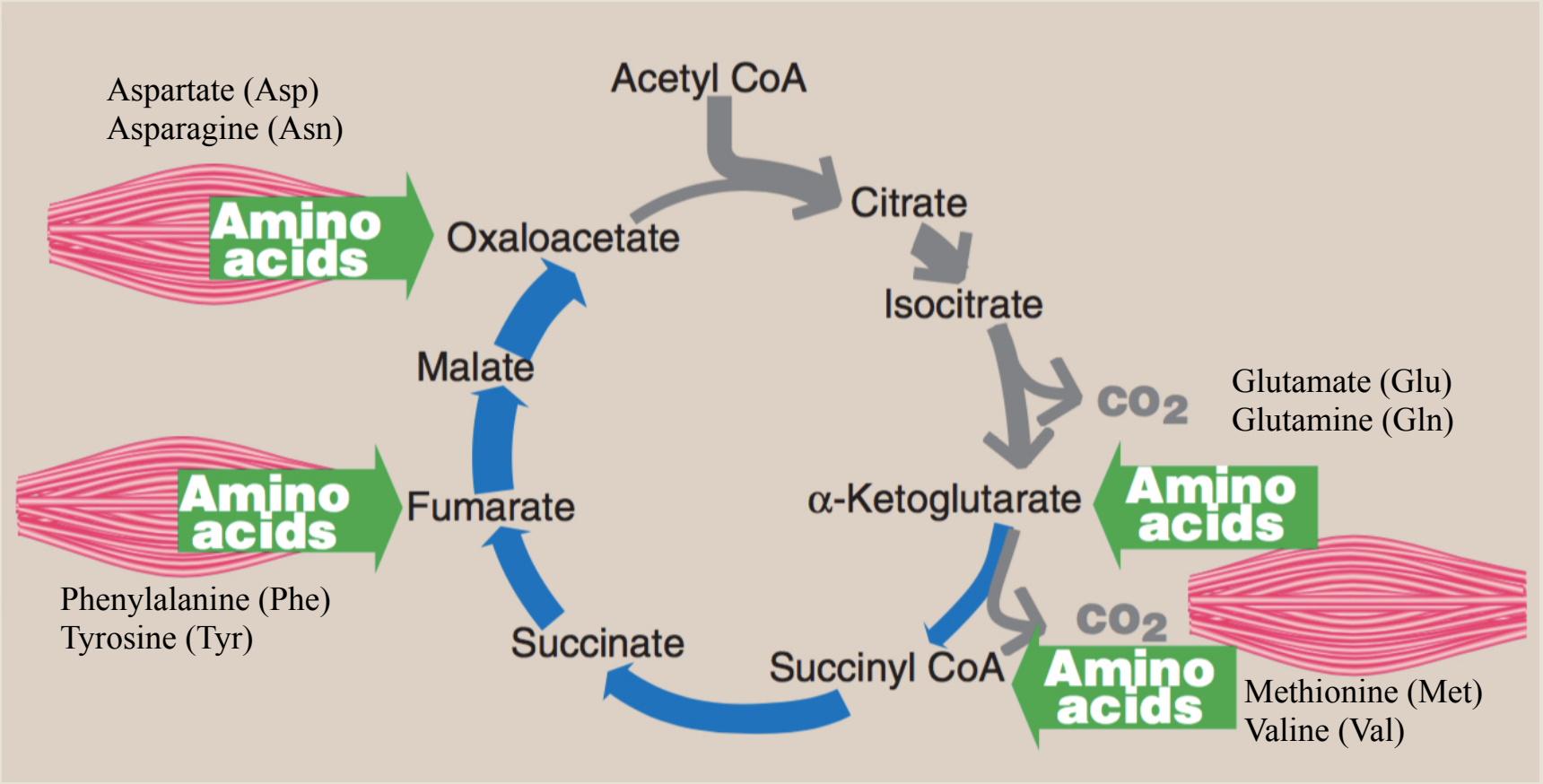


Gluconeogenic Substrates: Glycerol

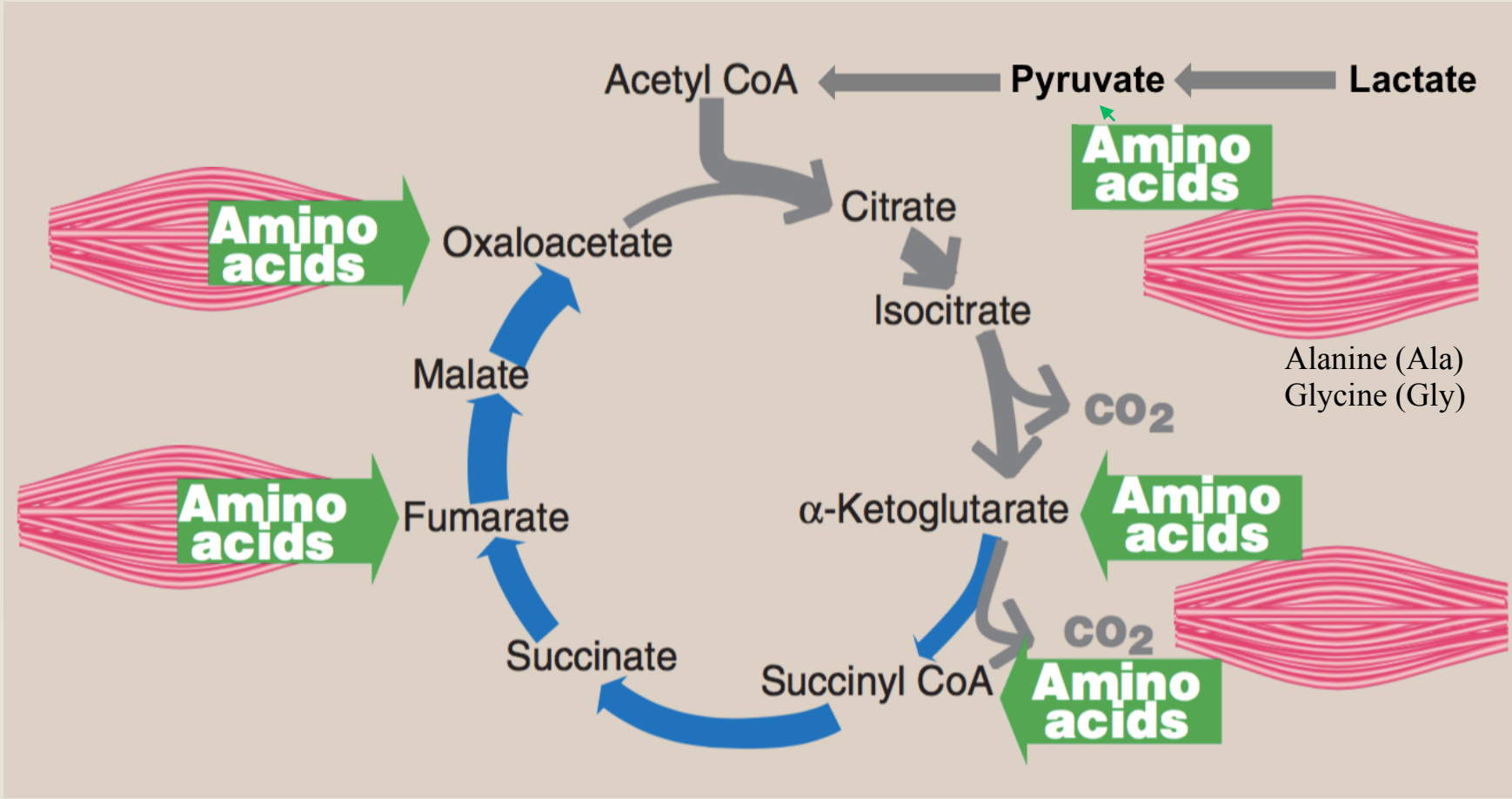


**GK: Glycerol kinase (present only in liver & kidneys)*

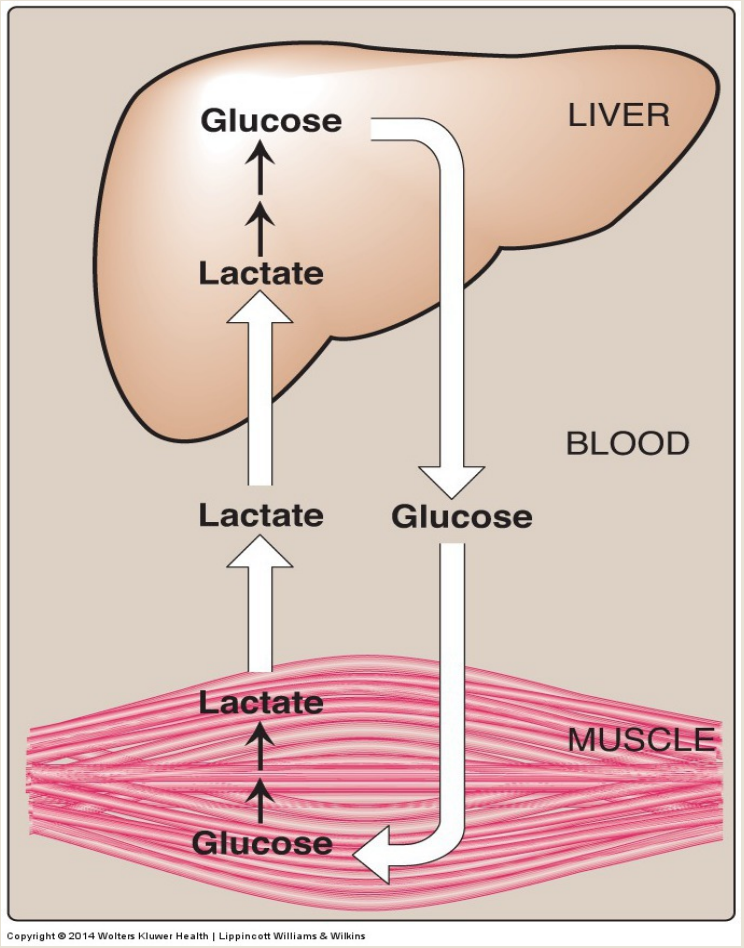
Glucogenic Amino Acids



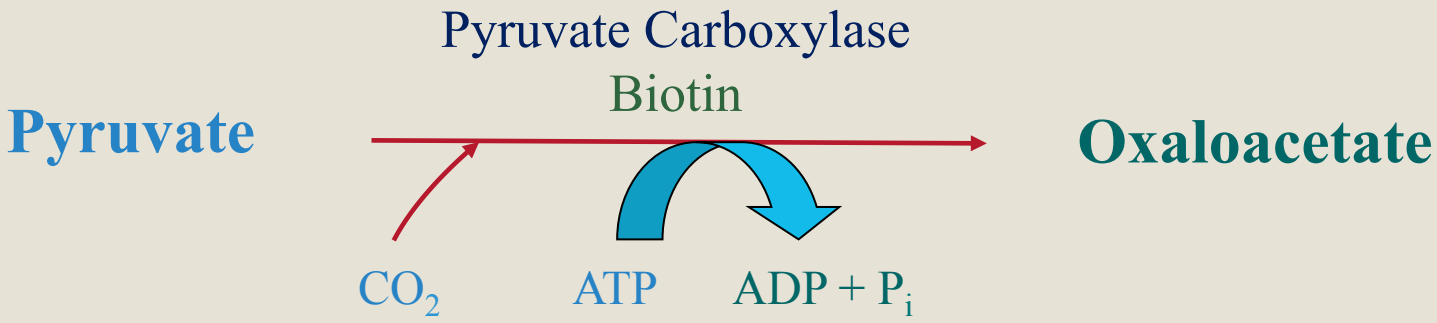
Gluconeogenic Substrates



Gluconeogenic Substrates: Lactate (Cori Cycle)



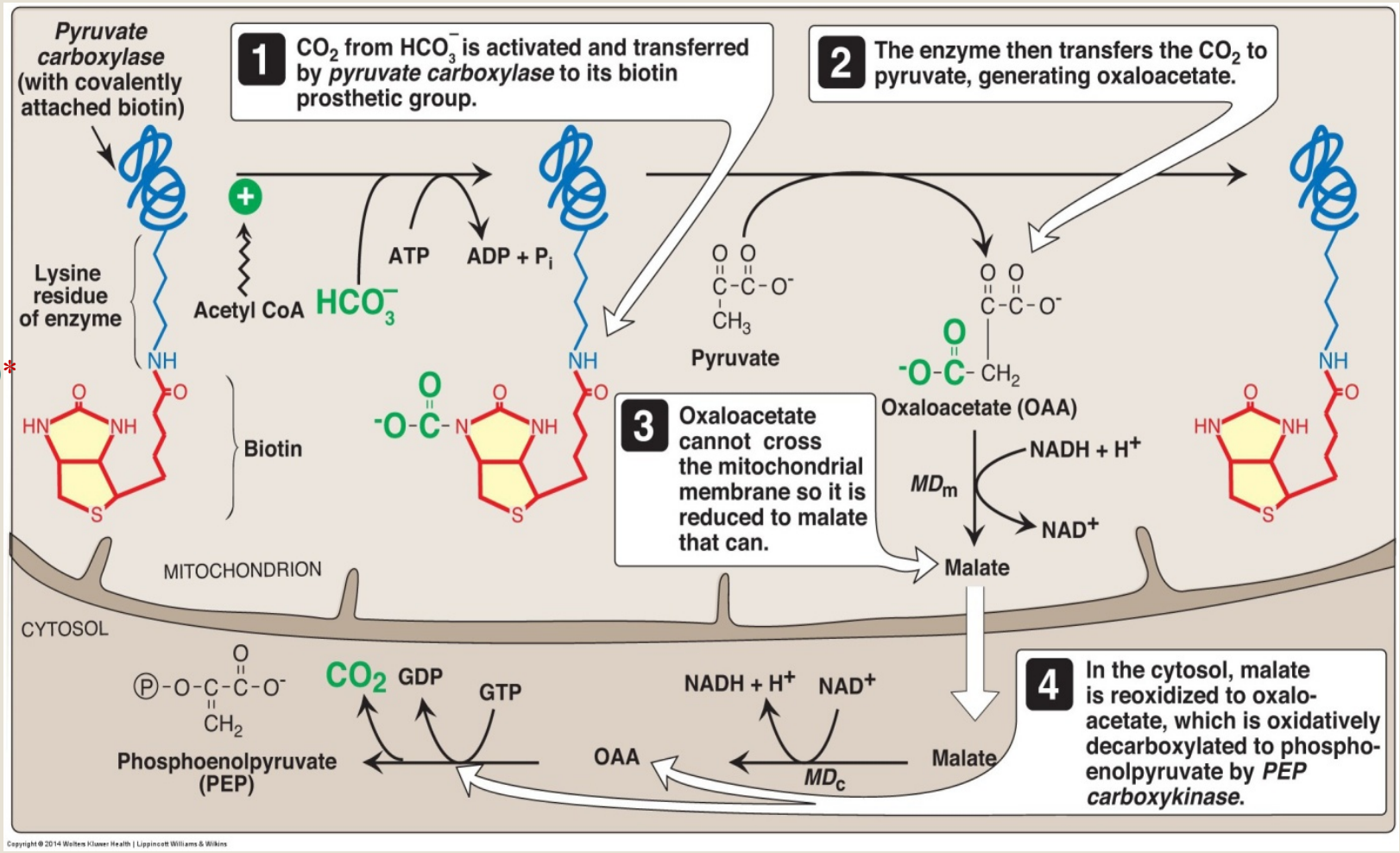
Pyruvate Carboxylation



Pruvate Carboxylase and PEP-CK

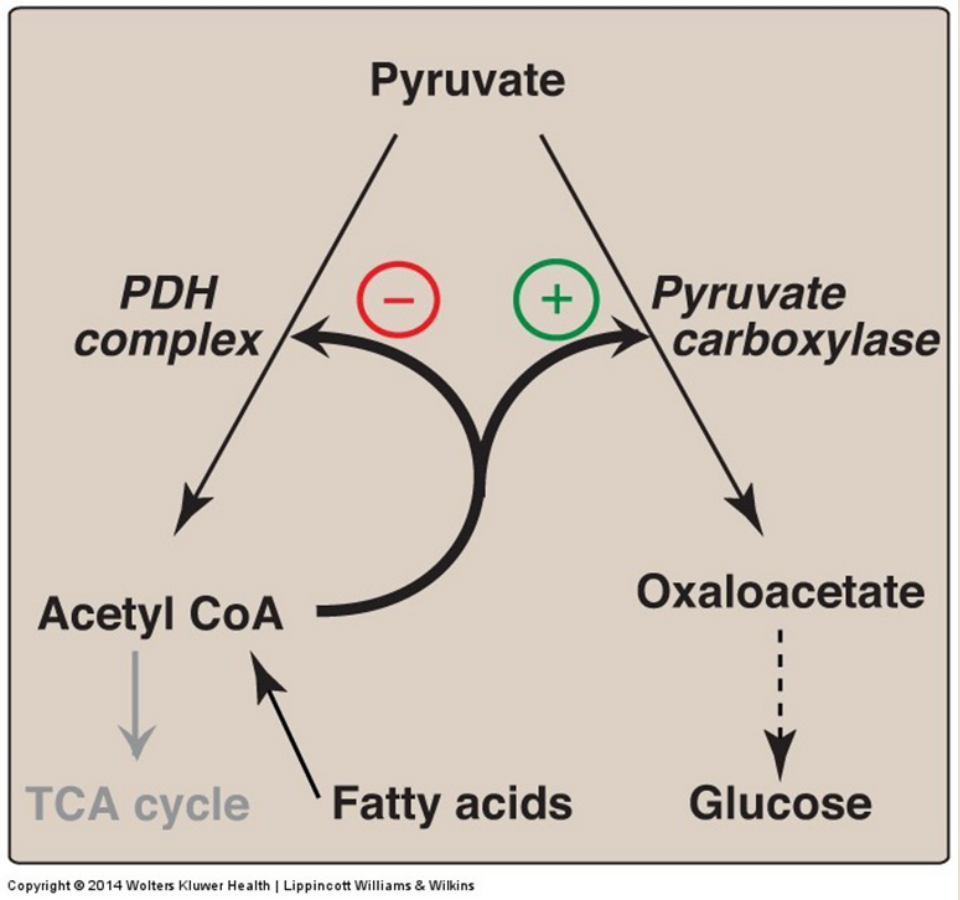
↑ Fasting: Acetyl CoA (From FAO)*

*Fatty Acid Oxidation



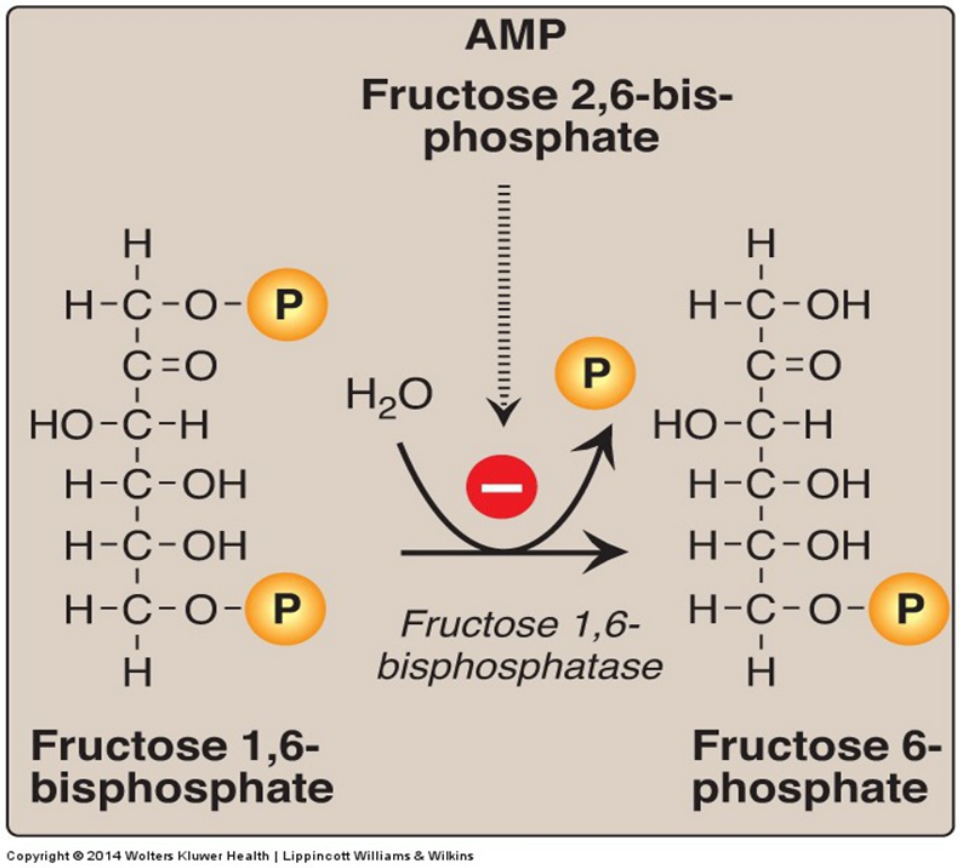
Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Regulation of Pyruvate Carboxylase reaction



Acetyl CoA diverts pyruvate away from oxidation and toward gluconeogenesis

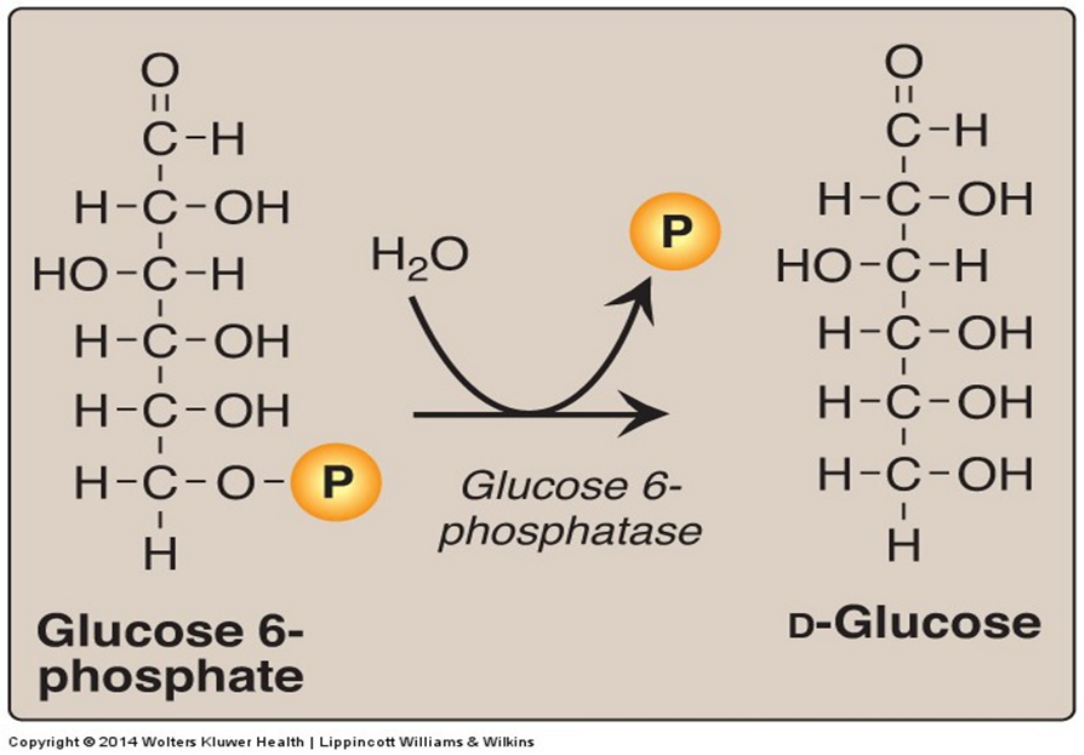
Fructose 1,6-Bisphosphatase



Dephosphorylation of fructose 1,6-bisphosphate

Fructose 1,6-bisphosphatase ≠ PFK-1

Glucose 6-Phosphatase

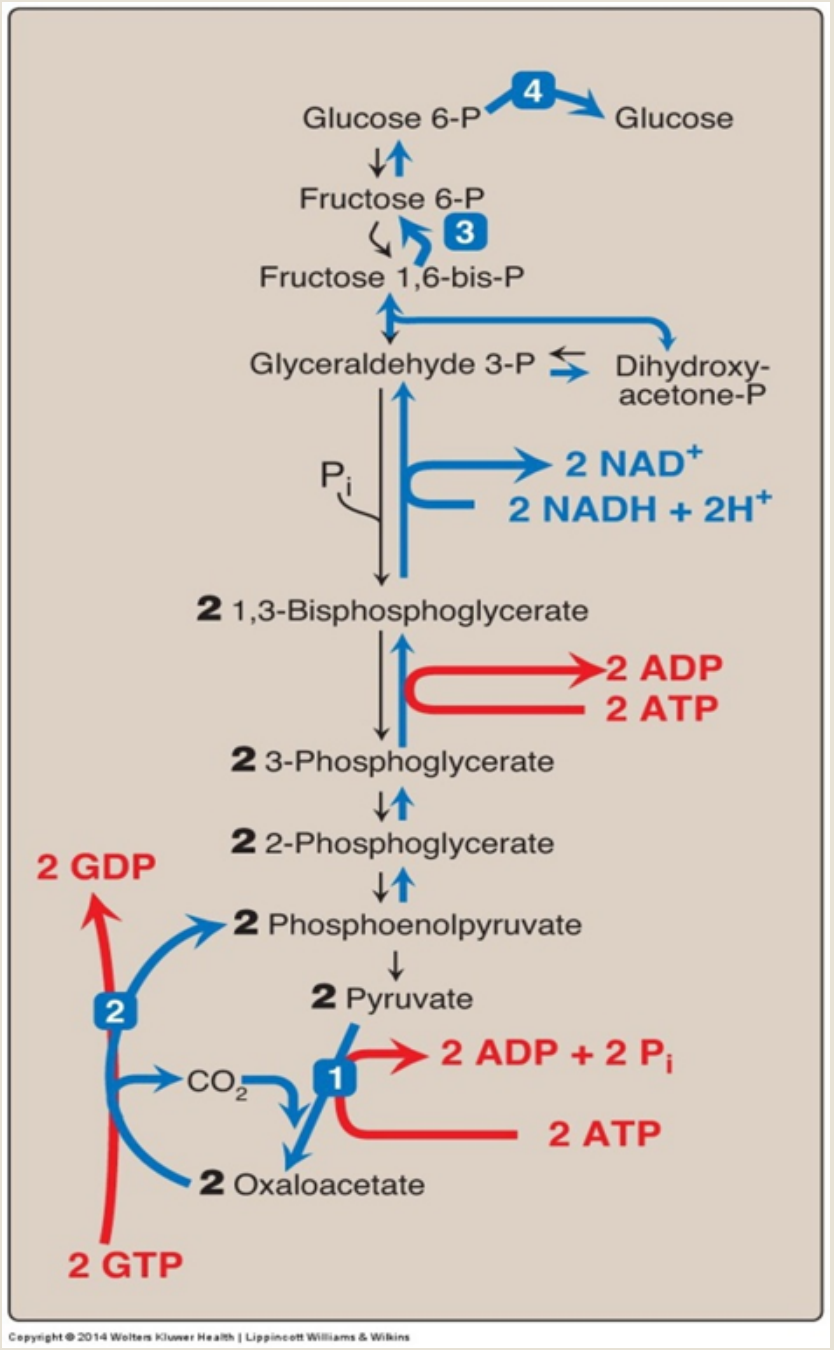


Dephosphorylation of glucose 6-phosphate allows release of free glucose from the liver and kidney into blood

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 1,6-bisphosphatase

  F 2,6-Bisphosphate ⊖ }

- **↑Glucagon (↓I/G ratio) stimulates gluconeogenesis**

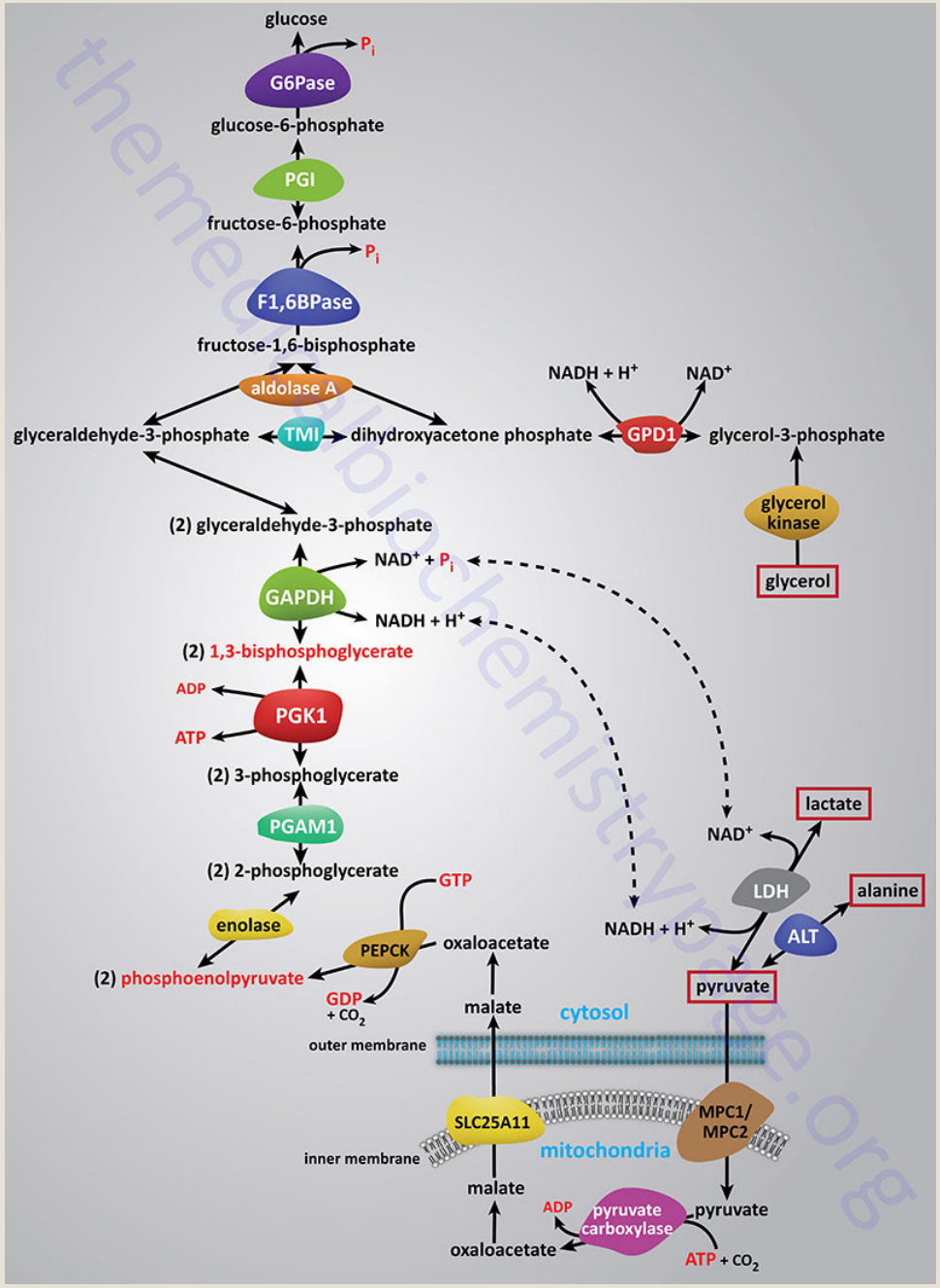
  - Allosteric (↓ F 2,6-Bisphosphate)
  - Induction (PEP-CK)

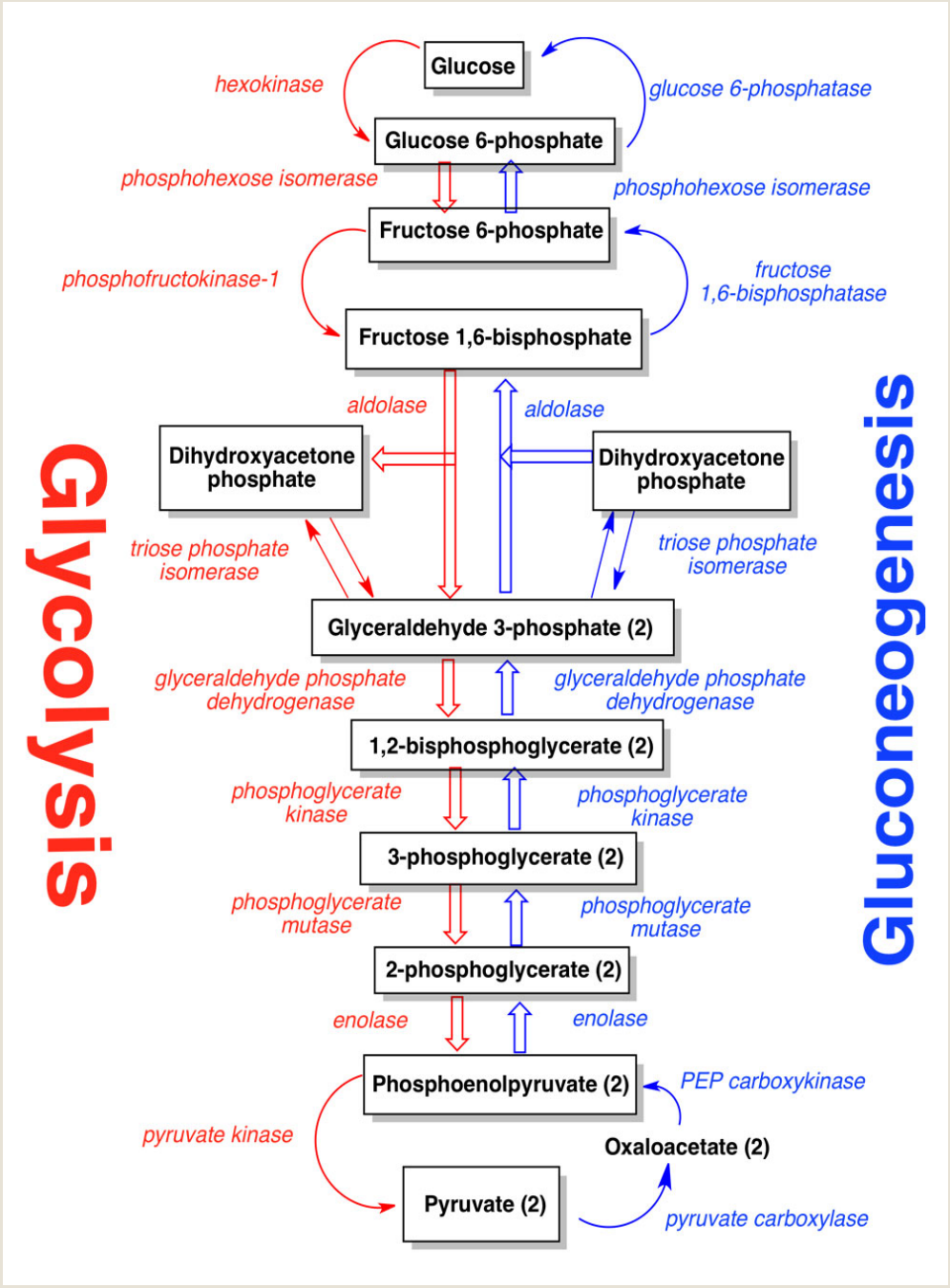
Take Home Messages

- 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.

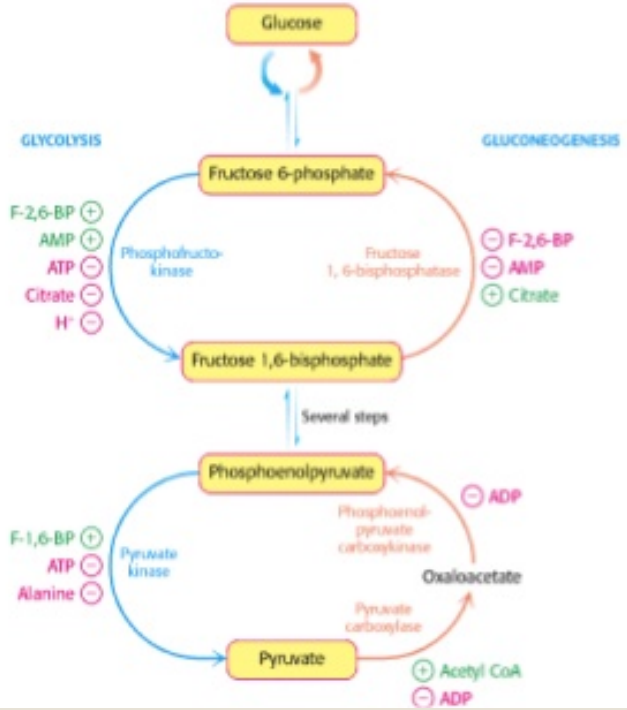
Reference

Lippincott Illustrated Review of Biochemistry, 6th edition, 2014, Unit 2, Chapter 10, Pages 117-124.


glucose
P_i
G6Pase
glucose-6-phosphate
PGI
fructose-6-phosphate
P_i
F1,6BPase
fructose-1,6-bisphosphate
aldolase A
glyceraldehyde-3-phosphate
TMI
dihydroxyacetone phosphate
NADH + H+
NAD+
GPD1
glycerol-3-phosphate
glycerol kinase
glycerol
(2) glyceraldehyde-3-phosphate
NAD+ + P_i
GAPDH
NADH + H+
(2) 1,3-bisphosphoglycerate
ADP
ATP
PGK1
(2) 3-phosphoglycerate
PGAM1
(2) 2-phosphoglycerate
enolase
(2) phosphoenolpyruvate
GTP
PEPCK
GDP + CO_2
oxaloacetate
malate
cytosol
outer membrane
inner membrane
SLC25A11
MPC1/ MPC2
mitochondria
malate
oxaloacetate
ADP
pyruvate carboxylase
ATP + CO_2
pyruvate
NAD+
lactate
LDH
alanine
ALT
NADH + H+
pyruvate


Glycolysis
Gluconeogenesis
Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
triose phosphate isomerase
triose phosphate isomerase
Glyceraldehyde 3-phosphate (2)
glyceraldehyde phosphate dehydrogenase
glyceraldehyde phosphate dehydrogenase
1,2-bisphosphoglycerate (2)
phosphoglycerate kinase
phosphoglycerate kinase
3-phosphoglycerate (2)
phosphoglycerate mutase
phosphoglycerate mutase
2-phosphoglycerate (2)
enolase
enolase
Phosphoenolpyruvate (2)
PEP carboxykinase
pyruvate kinase
Oxaloacetate (2)
Pyruvate (2)
pyruvate carboxylase

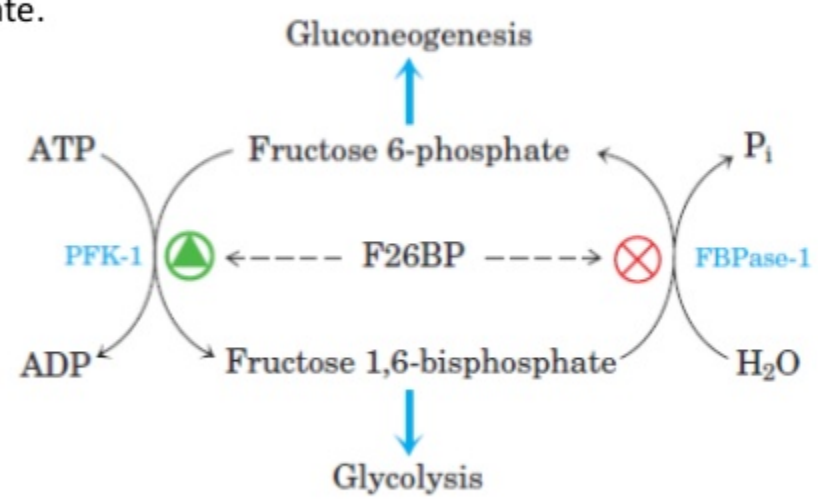
Reciprocal Regulation of Gluconeogenesis and Glycolysis in the Liver



- Glycolysis and Gluconeogenesis are reciprocally regulated .
- When glycolysis is on Gluconeogenesis is turned off especially in the fed state, whereas under conditions of starvation, gluconeogenesis is fully on and glycolysis is turned off.
- Both the cycles are never active at the same pace at the same time.

Hormonal Regulation

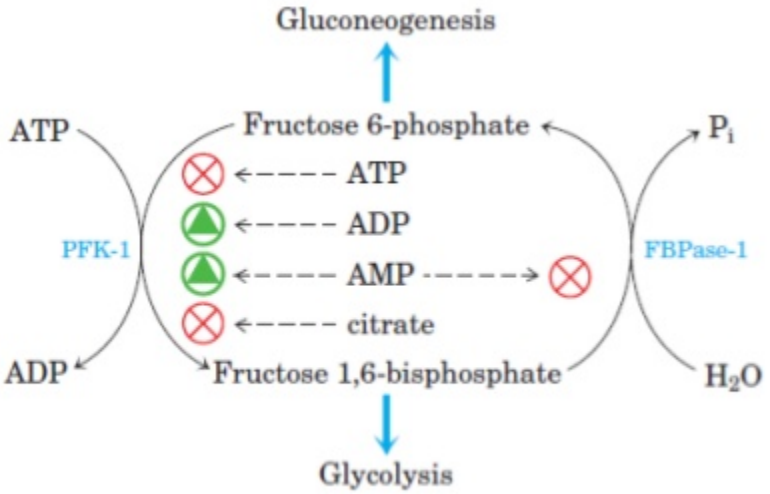
- hormonal regulation of glycolysis and gluconeogenesis is mediated by **fructose 2,6-bisphosphate.**
- F2,6-BP binds to allosteric site on PFK-1 increases that its affinity for substrate F 6-P, & reduces its affinity for the allosteric inhibitors ATP and citrate.



- PFK-1 is virtually inactive in the absence of F2,6-BP
- F2,6-BP *activates PFK-1 and stimulates* glycolysis in liver
- F2,6-BP *inhibits* FBPase-1 slowing gluconeogenesis.

Allosteric regulation

- **Fructose 1,6- bisphosphatase-1 (FBPase1)**
  - Inhibited by AMP, when energy currency ATP is less
  - Thus there gluconeogenesis is down regulated because it is a energy consuming process.
  - The opposing effect of PFK-1 and FBPase-1 helps to regulate glycolysis and gluconeogenesis according to current need of cell



Summary Chart- Regulation of Gluconeogenesis

Enzyme	Effect of substrate concentration	Allosteric modification/ Feed back Inhibition	Induction/ Repression	Clinical Significance
Pyruvate carboxylase	Inhibited by high carbohydrate diet Stimulated during fasting	**Activator-**Acetyl CoA **Inhibitor** ADP	**Induced by** Glucocorticoids, glucagon, epinephrine **Repressed by** Insulin	Activity increases in Diabetes Mellitus
Fructose 1,6 bisphosphatase	Inhibited by high carbohydrate diet Stimulated during fasting	**Activator-**Citrate **Inhibitor** AMP, Fr 2,6 bisphosphate	**Induced by** Glucocorticoids, glucagon, epinephrine **Repressed by** Insulin	Activity increases in Diabetes Mellitus