Gluconeogenesis

- Suggested Reading:
- Lippincot's Illustrated reviews: Biochemistry

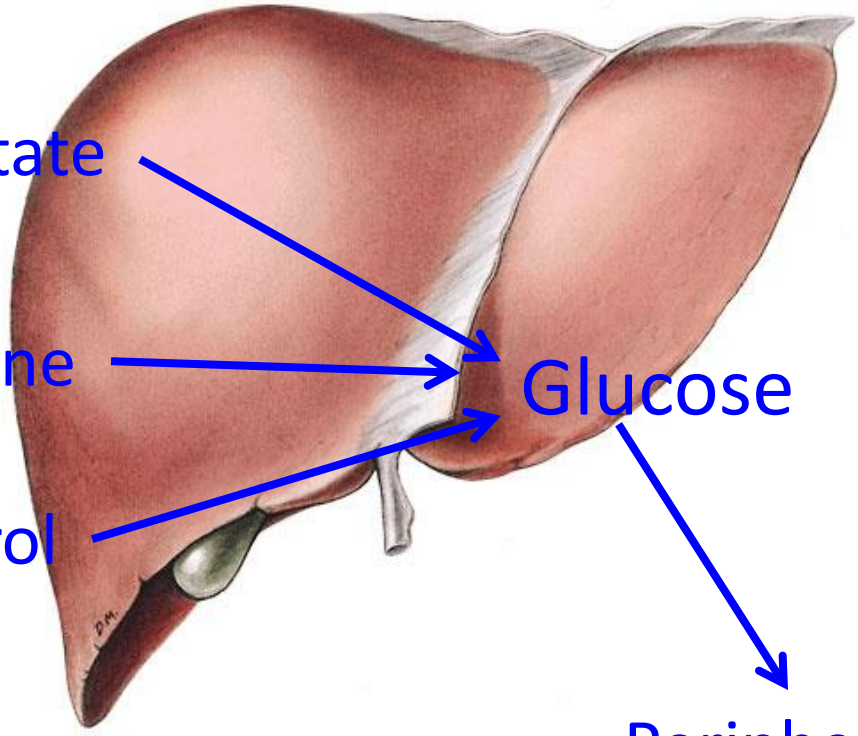
Glucose Synthesis is Required for Survival

- Brain is dependent on glucose 120g/day
- Body glucose reserve is limited
  - ≈ 20 g (extra cellular fluid)
  - ≈ 75 g (liver glycogen); enough for 16 hours
  - ≈ 400 g (muscle glycogen); for muscle use only
  - Main source of energy for resting muscle in postabsobtive state is fatty acids. 80% of glucose is used by brain & rbc
- 70 Kg man has ≈ 15 Kg fat
  - Fatty acids can not be converted to glucose
  - Utilization of FA is increased 4-5 X in prolonged fasting
  - In prolonged fasting; FA ➔ ketone bodies at high rate

Gluconeogenesis occurs mainly in the liver

Tissues that do not oxidize glc. completely
e.g RBC
Excercising muscle

Lactate



alanine

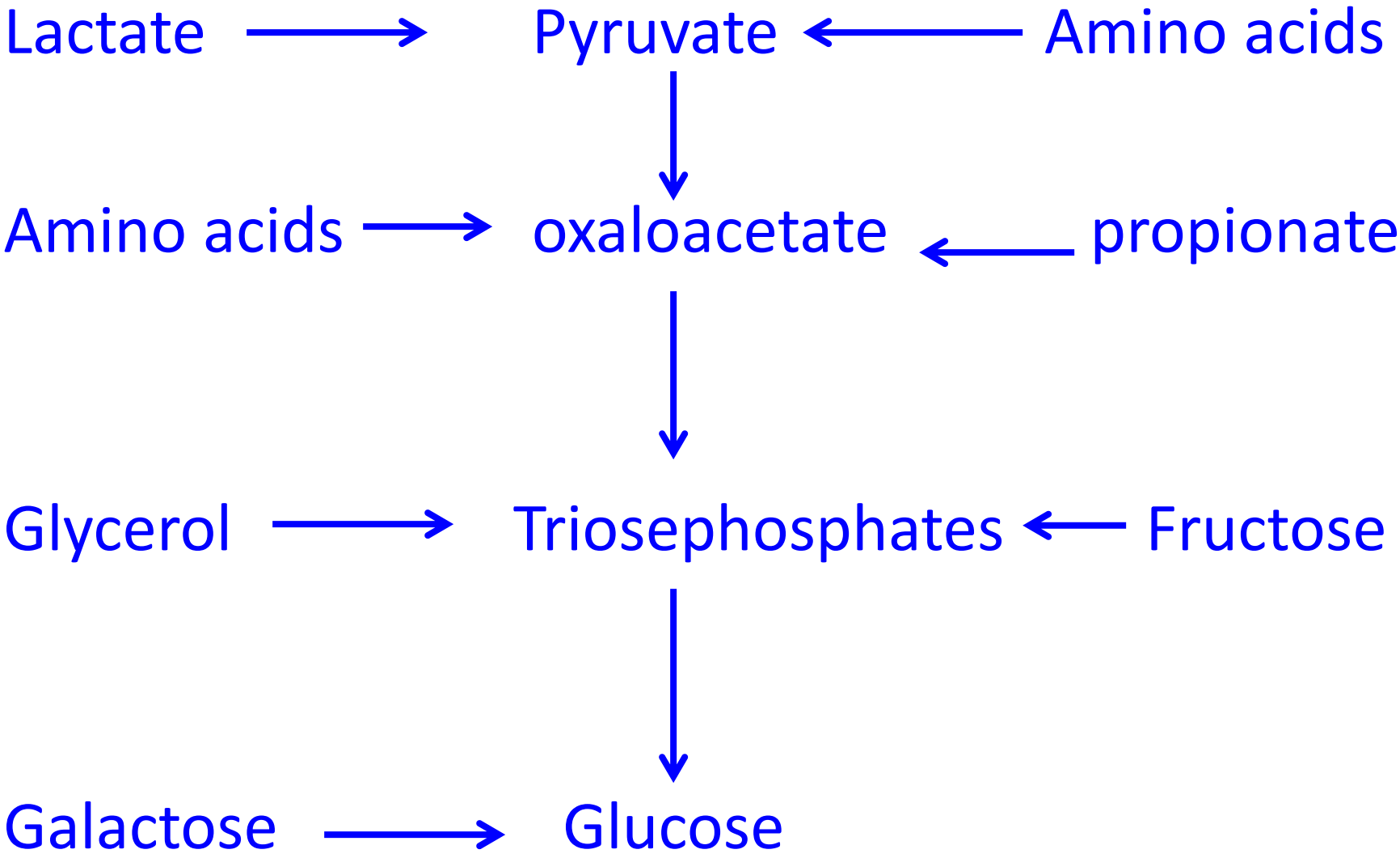
Glucose

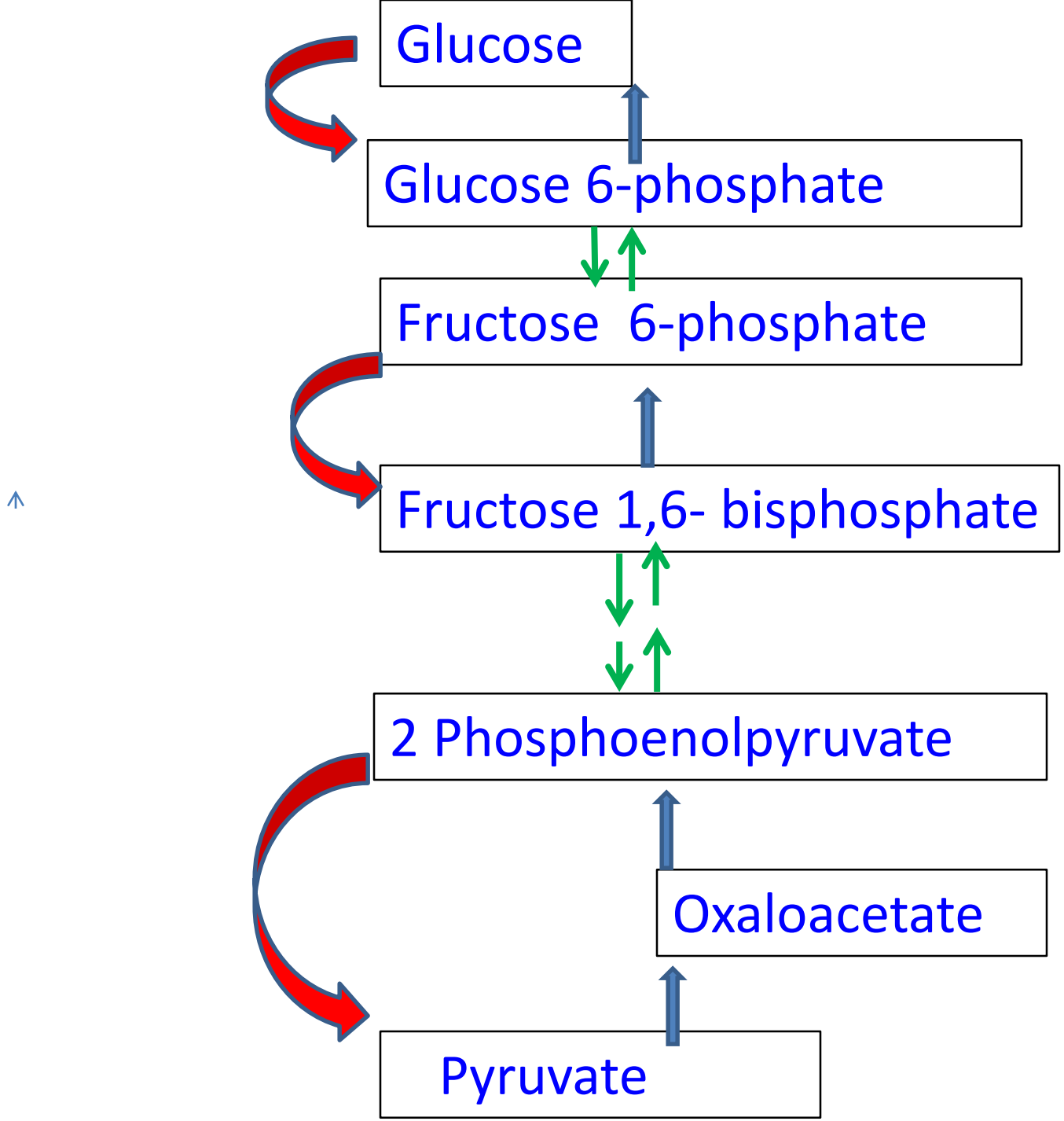
Muscle
A.Acids

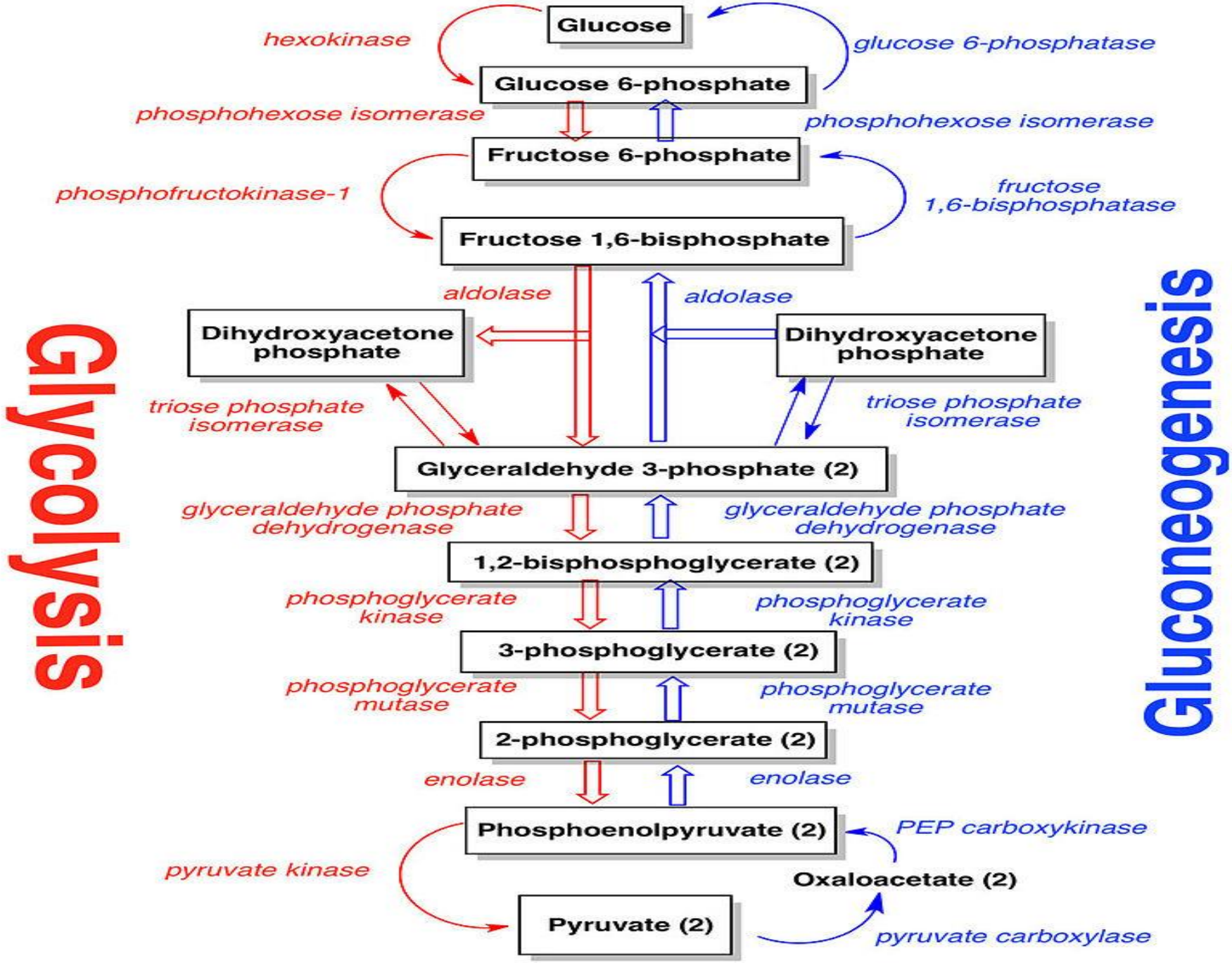
glycerol

Adipose tissue

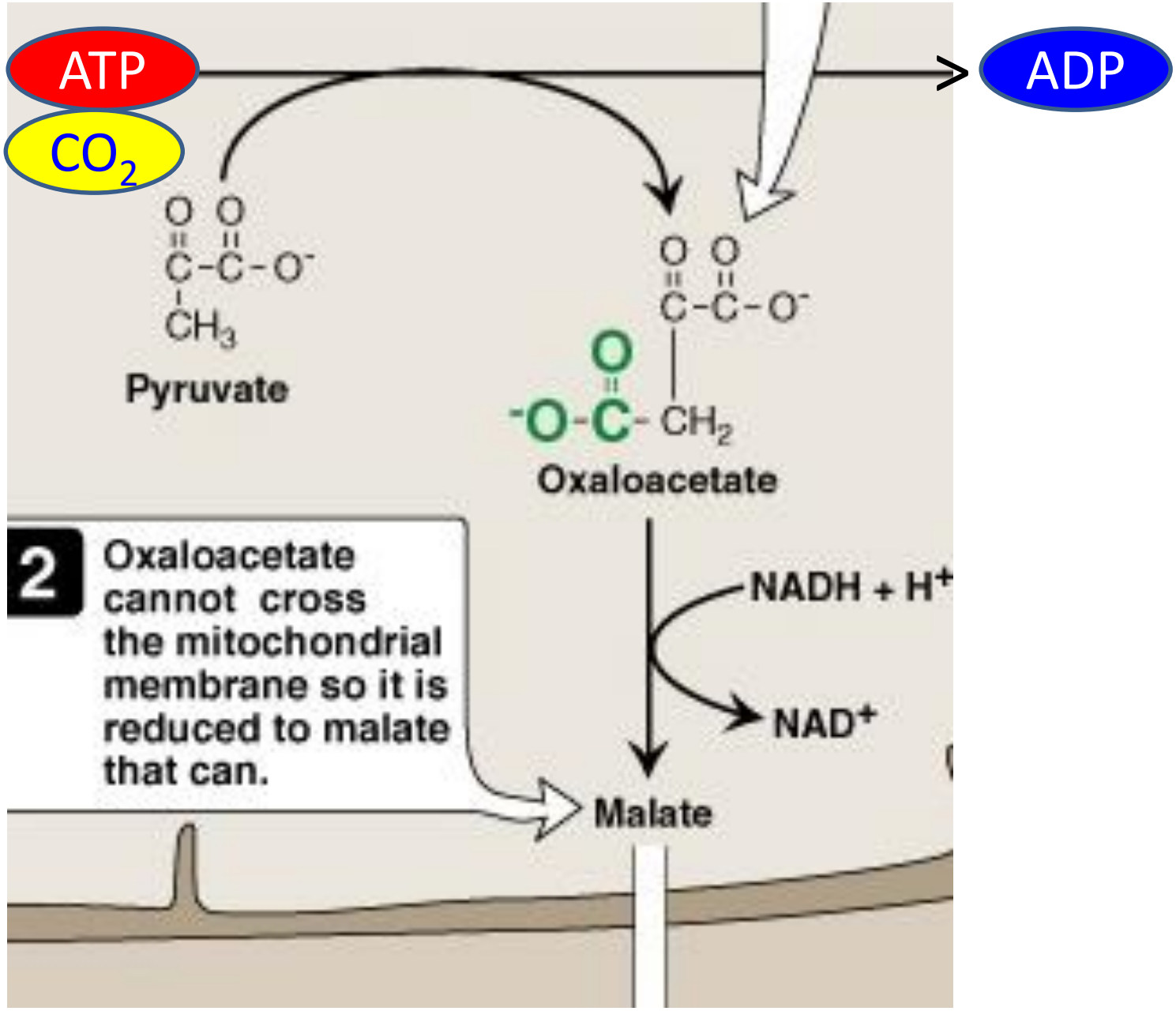
Peripheral tissues

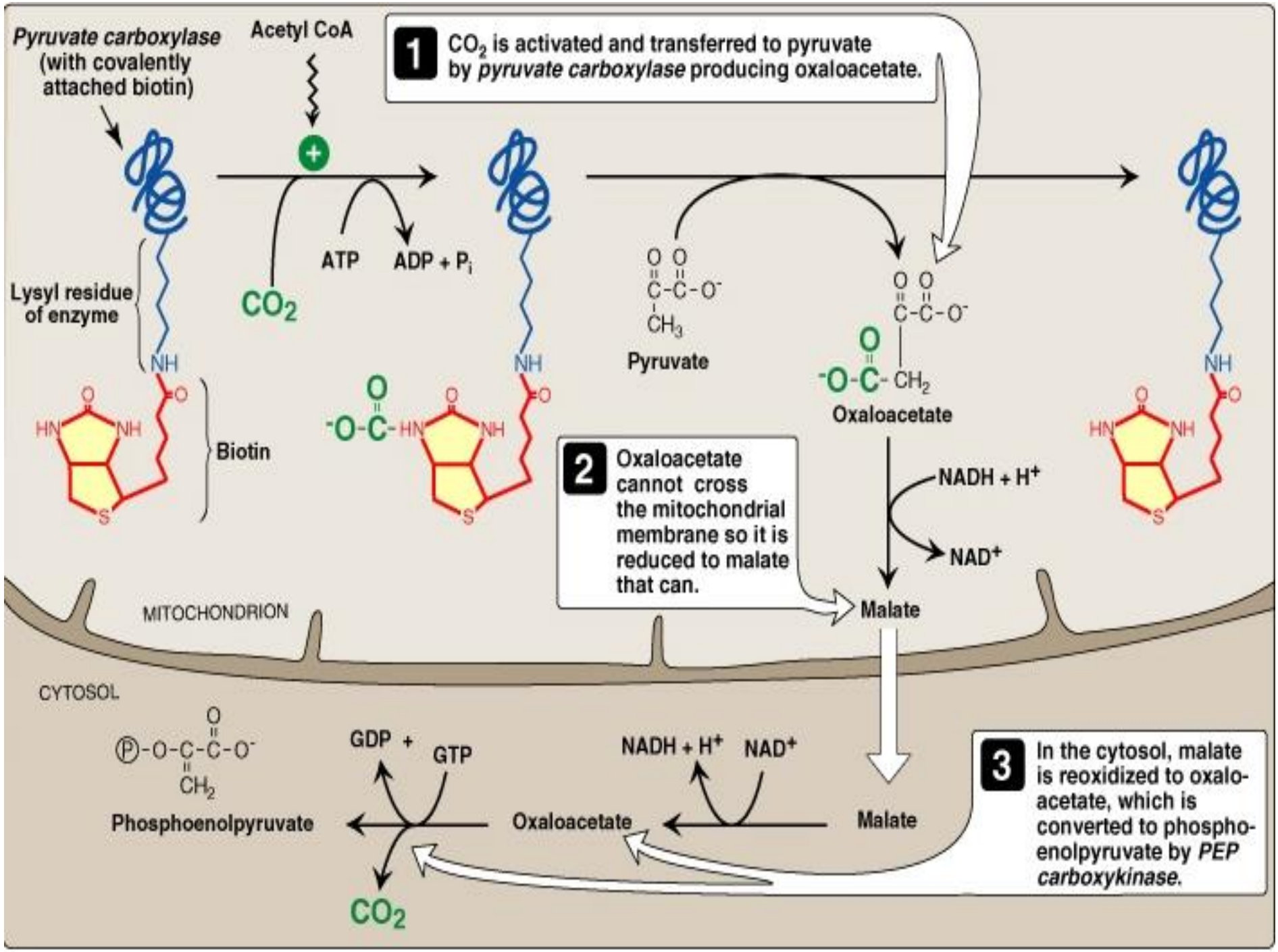

Lactate
Pyruvate
Amino acids
Amino acids
oxaloacetate
propionate
Glycerol
Triosephosphates
Fructose
Galactose
Glucose

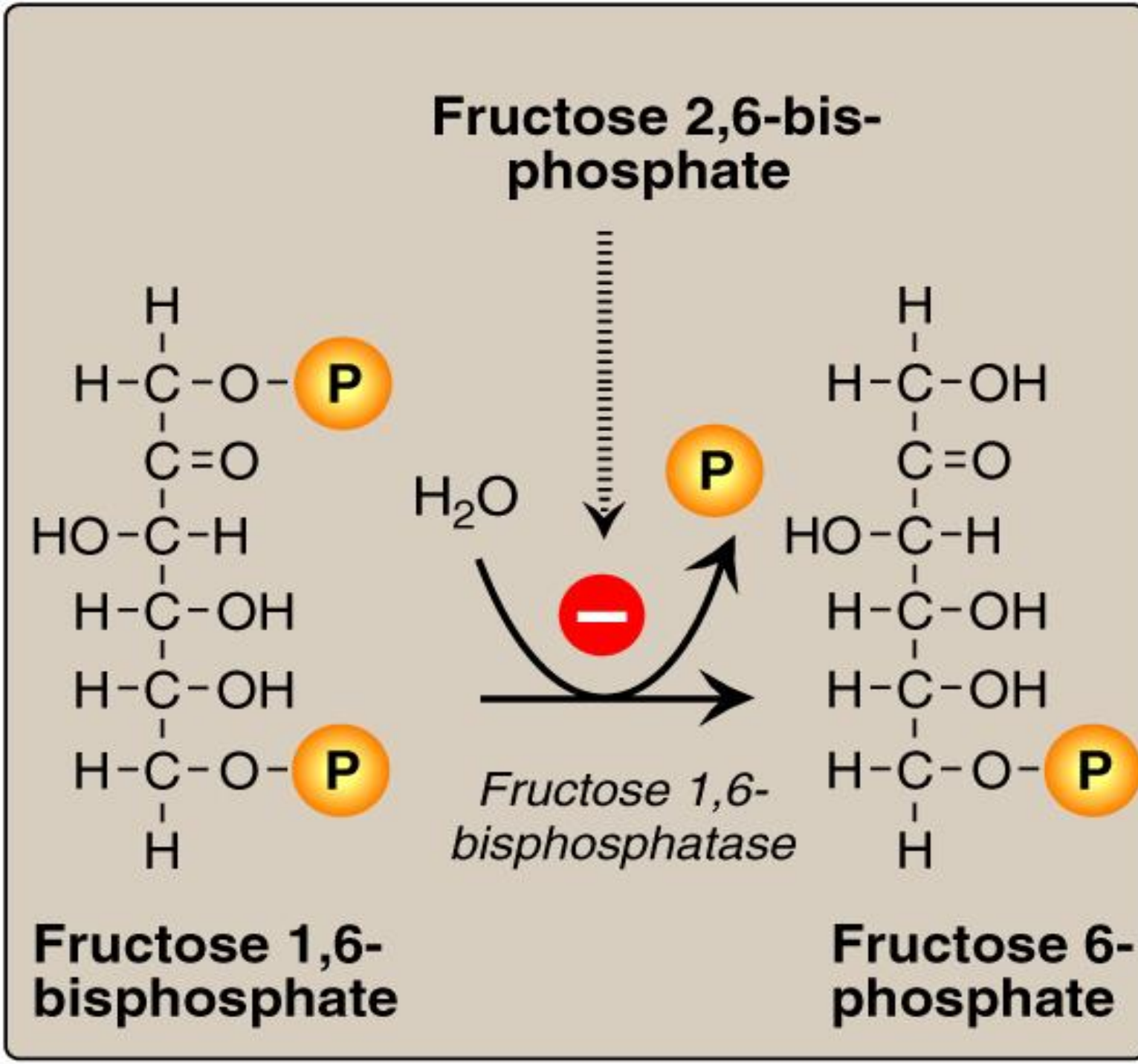

Glucose
Glucose 6-phosphate
Fructose 6-phosphate
Fructose 1,6- bisphosphate
2 Phosphoenolpyruvate
Oxaloacetate
Pyruvate

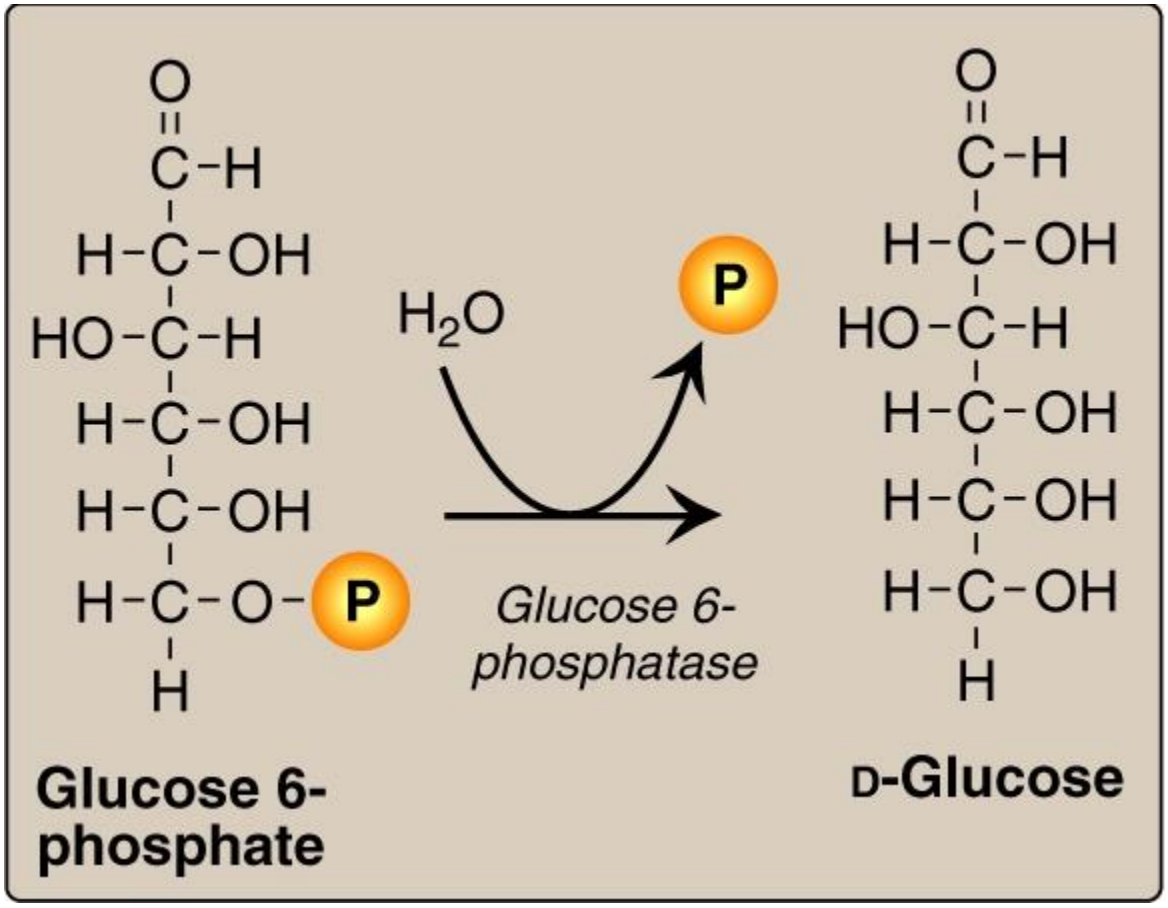

Glycolysis
Gluconeogenesis
Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
phosphohexose isomerase
phosphohexose isomerase
Fructose 6-phosphate
phosphofructokinase-1
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
aldolase
aldolase
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
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

Carboxylation of Pyruvate Produces Oxaloacetate




Pyruvate carboxylase (with covalently attached biotin)
Acetyl CoA
1 CO_2 is activated and transferred to pyruvate by *pyruvate carboxylase* producing oxaloacetate.
ATP
ADP + P_i
CO_2
Lysyl residue of enzyme
Biotin
Pyruvate
Oxaloacetate
2 Oxaloacetate cannot cross the mitochondrial membrane so it is reduced to malate that can.
NADH + H^+
NAD^+
Malate
MITOCHONDRION
CYTOSOL
Phosphoenolpyruvate
GDP + GTP
CO_2
Oxaloacetate
NADH + H^+
NAD^+
Malate
3 In the cytosol, malate is reoxidized to oxaloacetate, which is converted to phosphoenolpyruvate by *PEP carboxykinase*.


Fructose 2,6-bis-phosphate
H
H–C–O–P
C=O
HO–C–H
H–C–OH
H–C–OH
H–C–O–P
H
H2O
P
Fructose 1,6-bisphosphatase
H
H–C–OH
C=O
HO–C–H
H–C–OH
H–C–OH
H–C–O–P
H
Fructose 1,6-bisphosphate
Fructose 6-phosphate


O
C–H
H–C–OH
HO–C–H
H–C–OH
H–C–OH
H–C–O–P
H
H_2O
P
Glucose 6-phosphatase
O
C–H
H–C–OH
HO–C–H
H–C–OH
H–C–OH
H–C–OH
H
Glucose 6-phosphate
D-Glucose

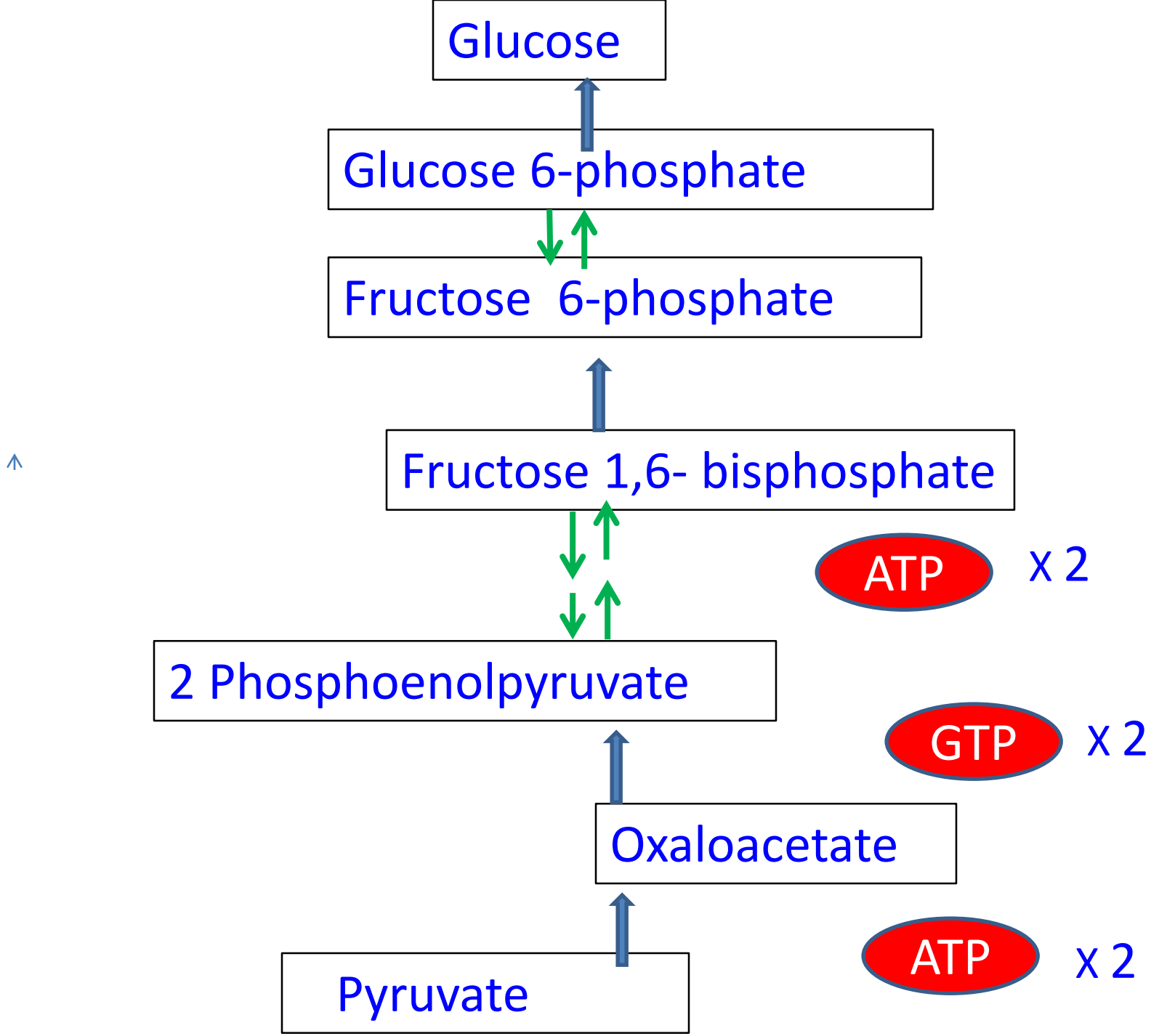
Formation and Hydrolysis of Glucose 6-phosphate

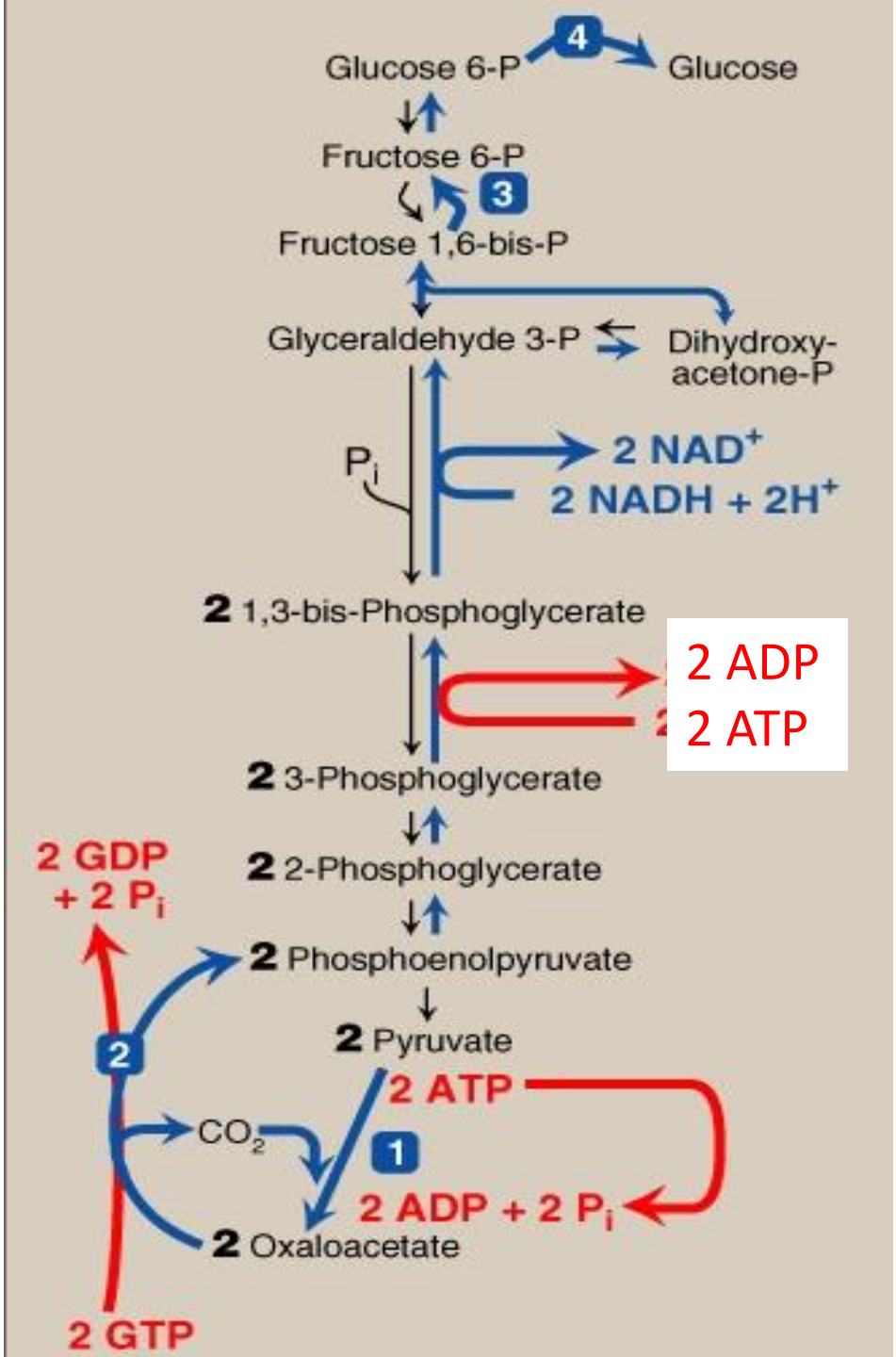
Glc. + Pi ⟶ Glc. 6-phosphate + H_2O ΔG = +ve

ATP + H_2O ⟶ ADP + P_i ΔG = -ve

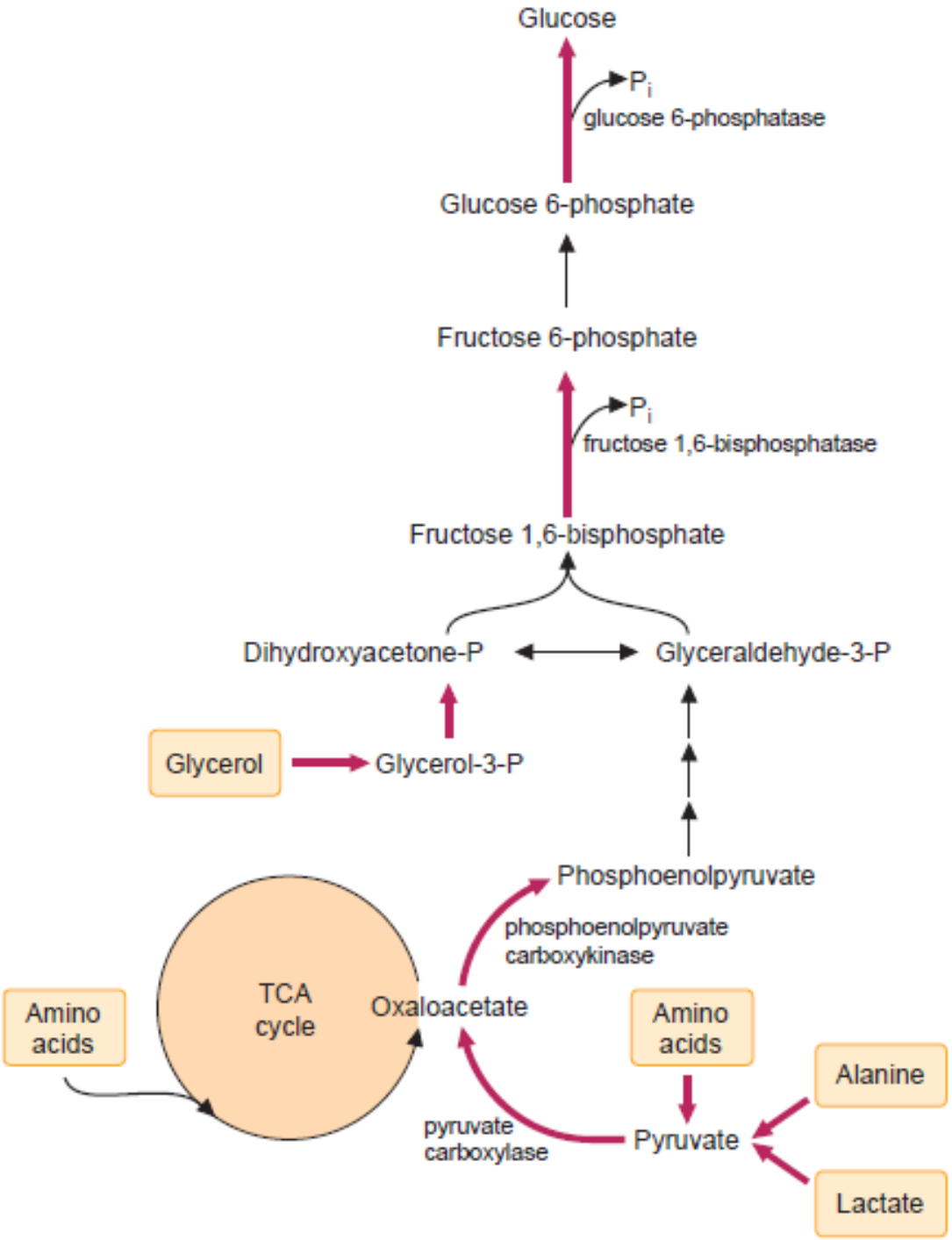
Glc. + ATP —(HK)→ Glc. 6-phosphate + ADP ΔG = -ve

Glc. 6-phosphate + H_2O —(Phosphatase)→ Glc. + P_i ΔG = -ve

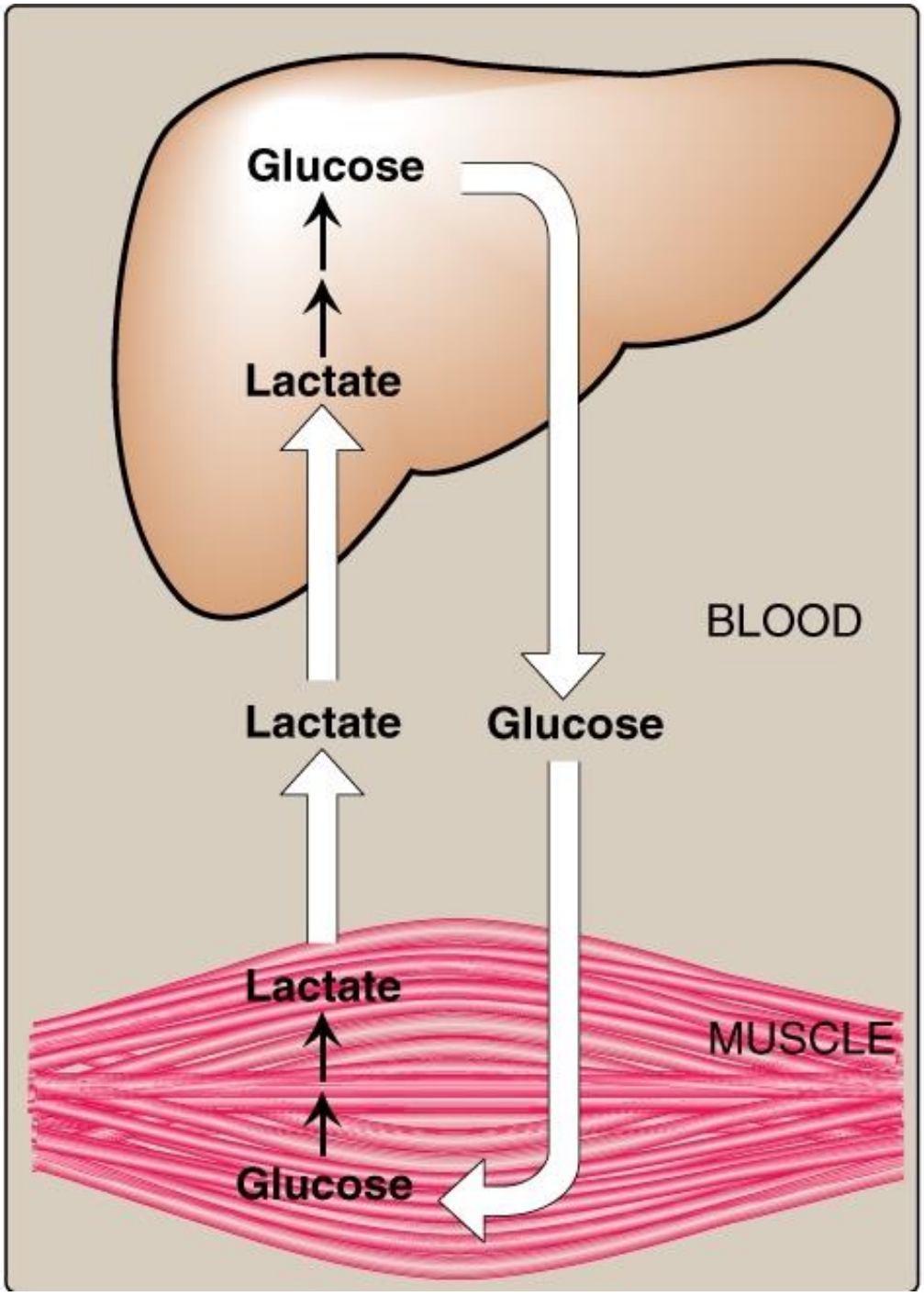

Glucose
Glucose 6-phosphate
Fructose 6-phosphate
Fructose 1,6- bisphosphate
ATP
X 2
2 Phosphoenolpyruvate
GTP
X 2
Oxaloacetate
ATP
X 2
Pyruvate

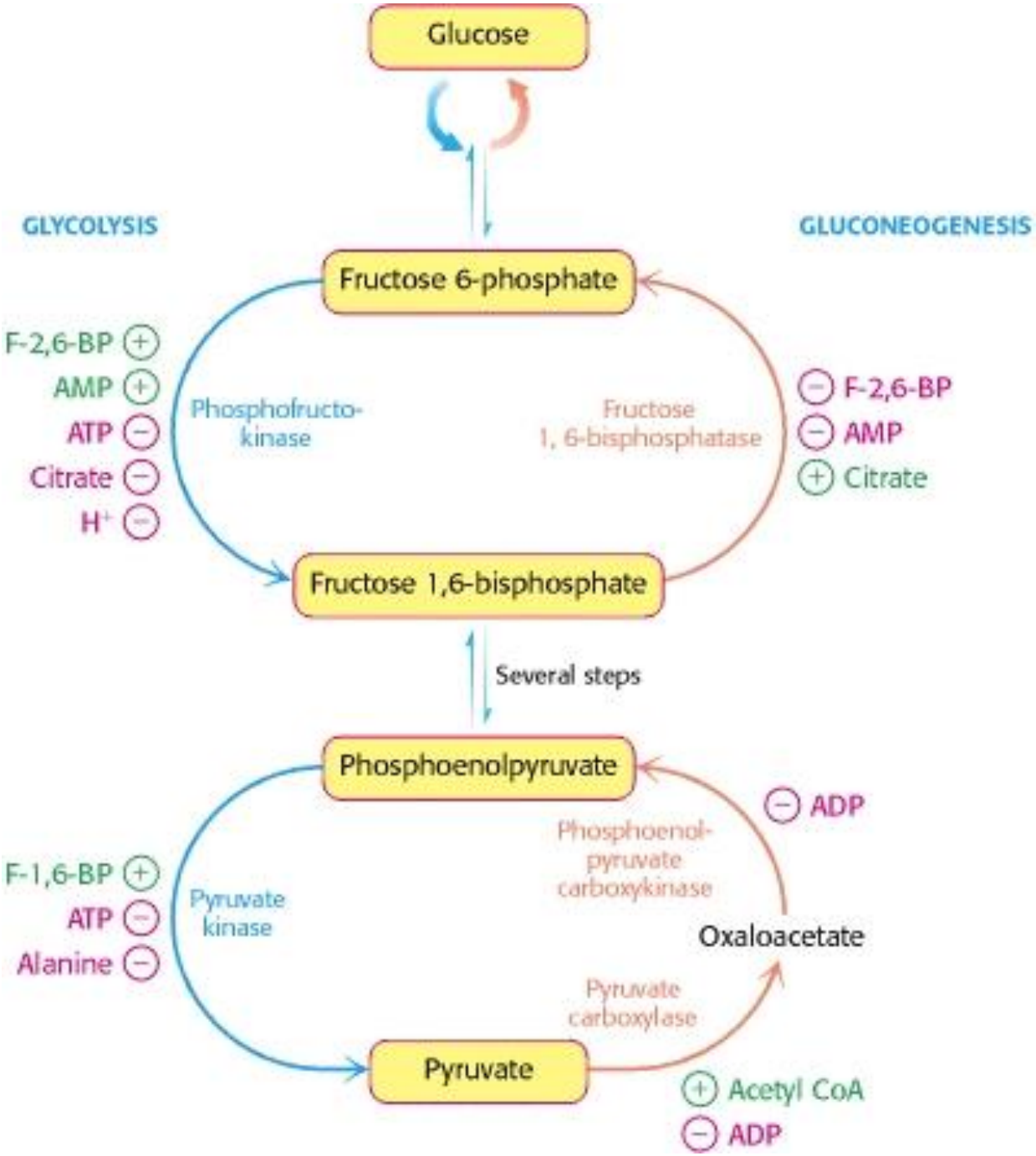

Glucose 6-P
4
Glucose
Fructose 6-P
3
Fructose 1,6-bis-P
Glyceraldehyde 3-P
Dihydroxy-acetone-P
P_i
2 NAD^+
2 NADH + $2H^+$
2 1,3-bis-Phosphoglycerate
2 ADP
2 ATP
2 3-Phosphoglycerate
2 2-Phosphoglycerate
2 GDP + 2 P_i
2 Phosphoenolpyruvate
2 Pyruvate
2
2 ATP
CO_2
1
2 ADP + 2 P_i
2 Oxaloacetate
2 GTP

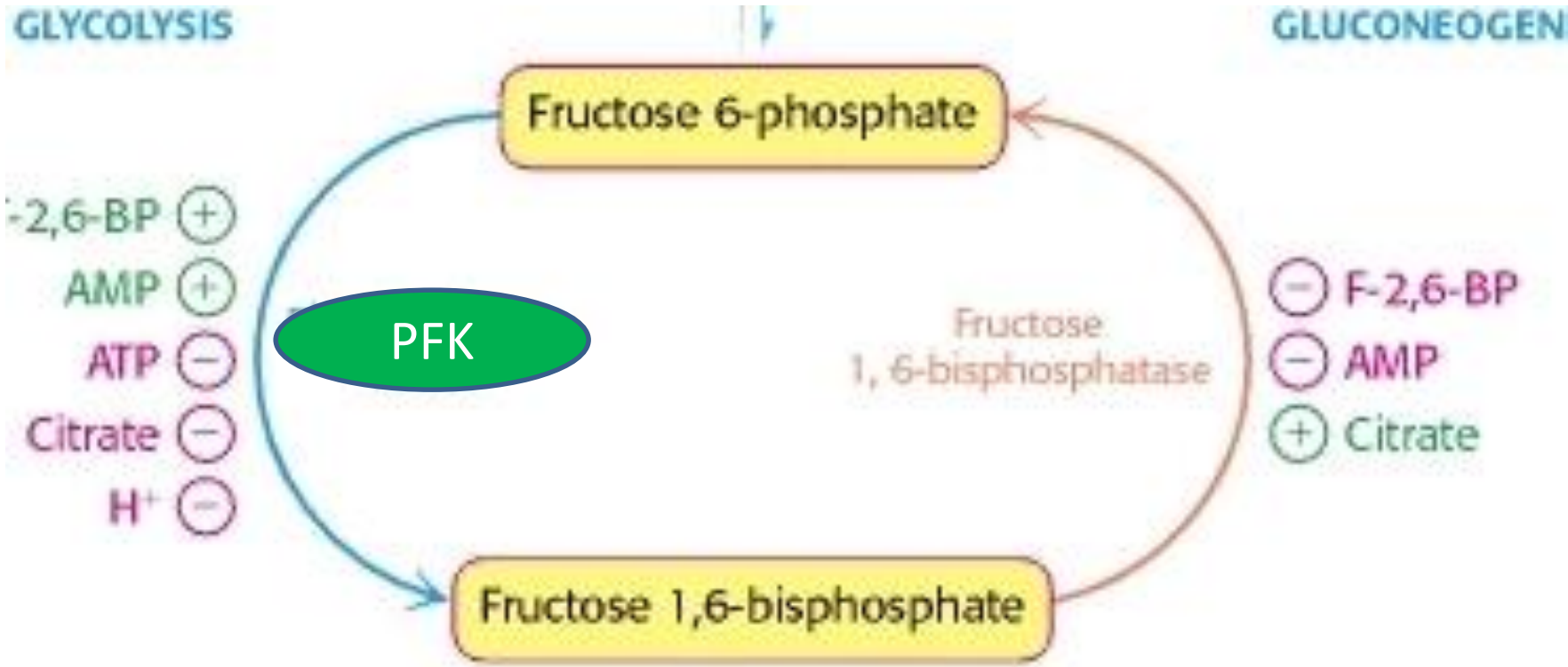
T

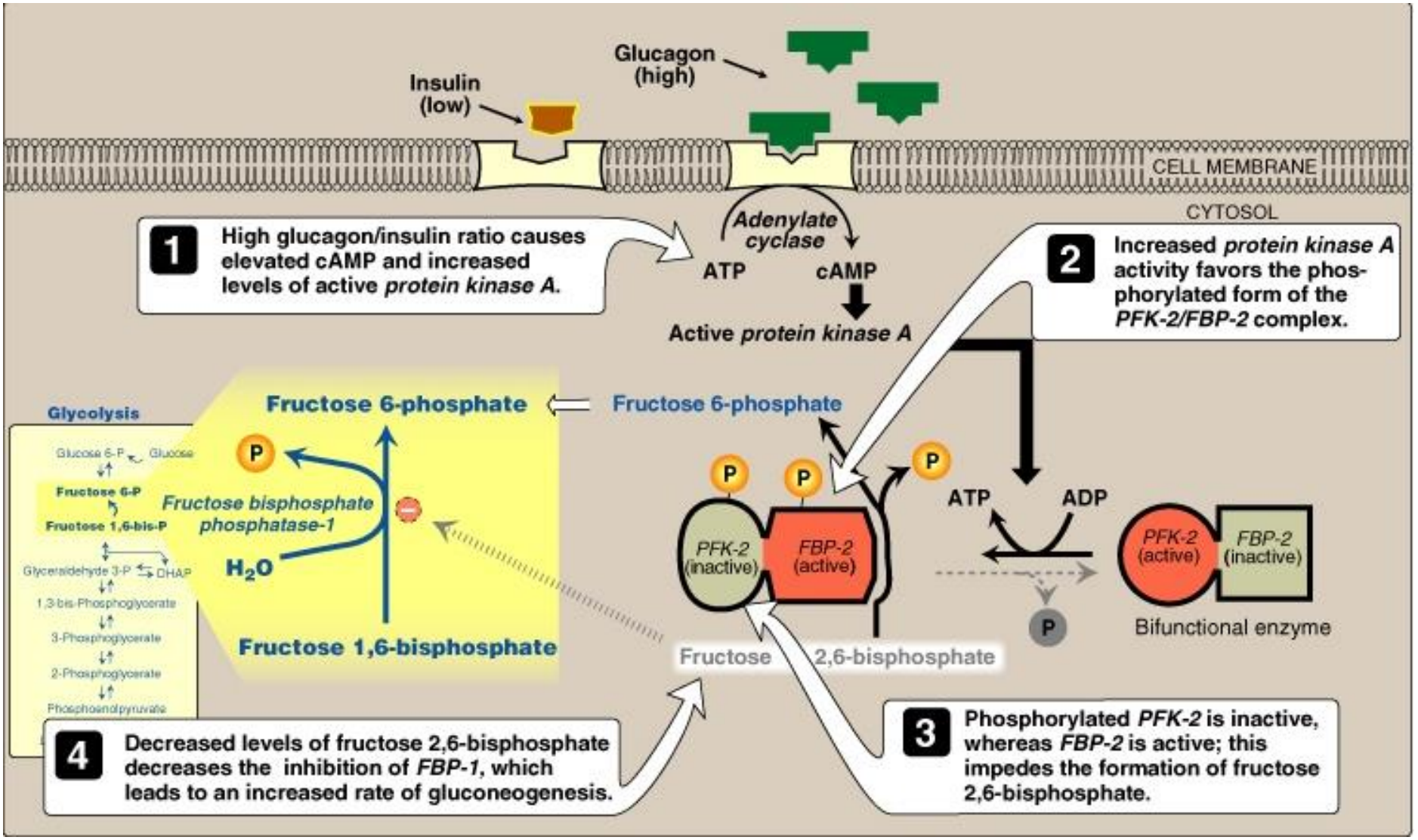

Glucose
P_i
glucose 6-phosphatase
Glucose 6-phosphate
Fructose 6-phosphate
P_i
fructose 1,6-bisphosphatase
Fructose 1,6-bisphosphate
Dihydroxyacetone-P
Glyceraldehyde-3-P
Glycerol
Glycerol-3-P
Phosphoenolpyruvate
phosphoenolpyruvate carboxykinase
Amino acids
TCA cycle
Oxaloacetate
Amino acids
Alanine
pyruvate carboxylase
Pyruvate
Lactate

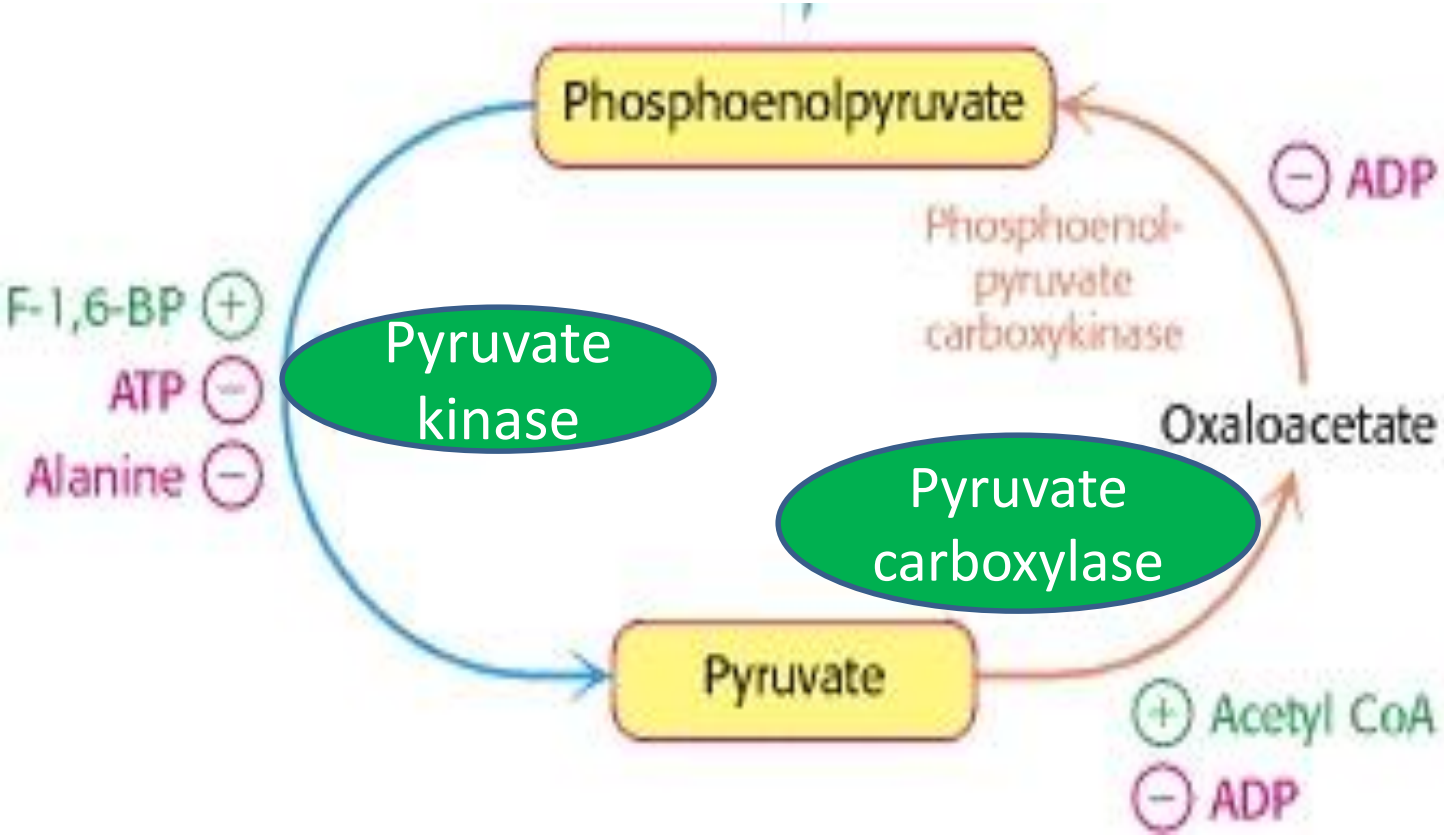
The Cori Cycle

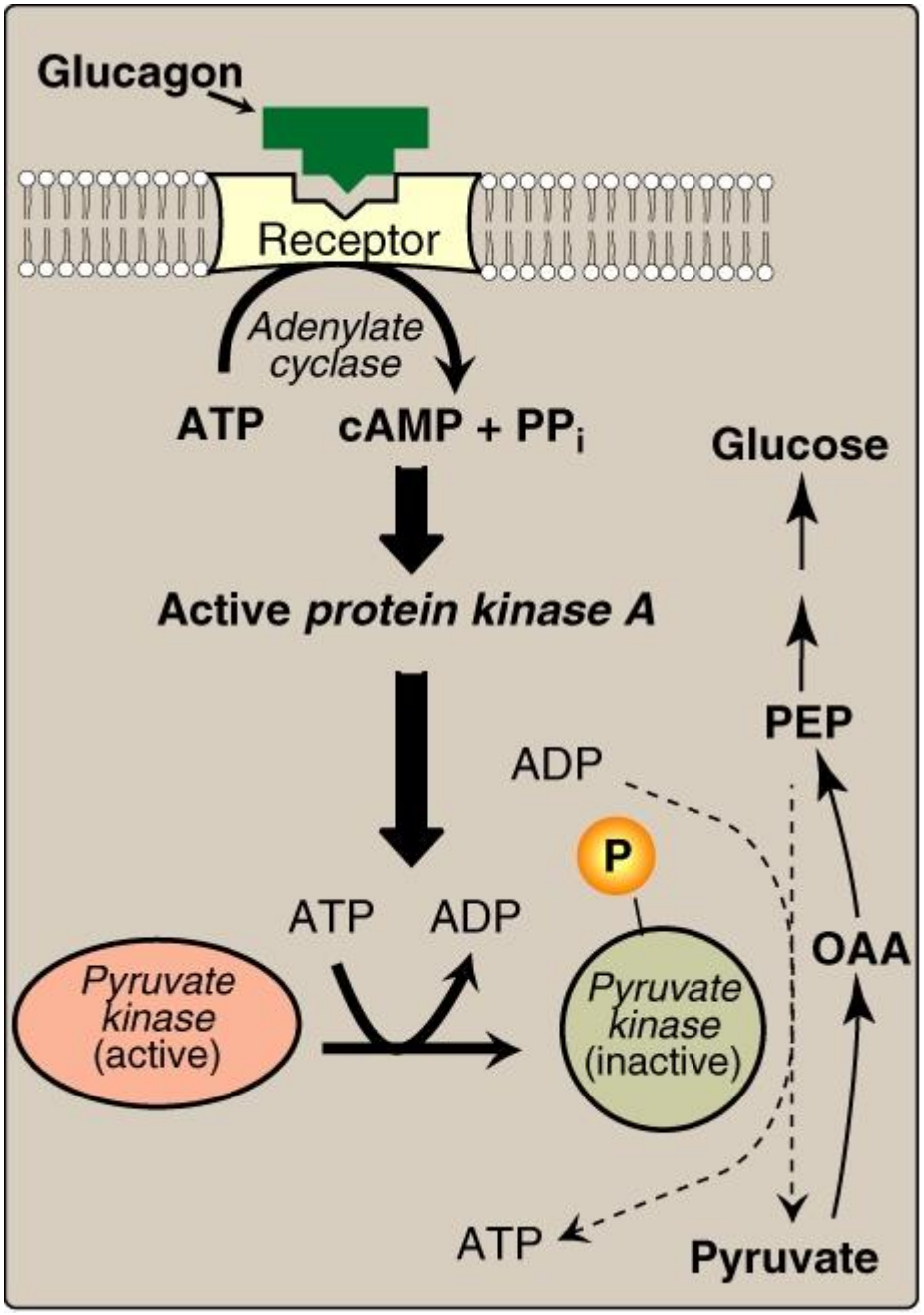


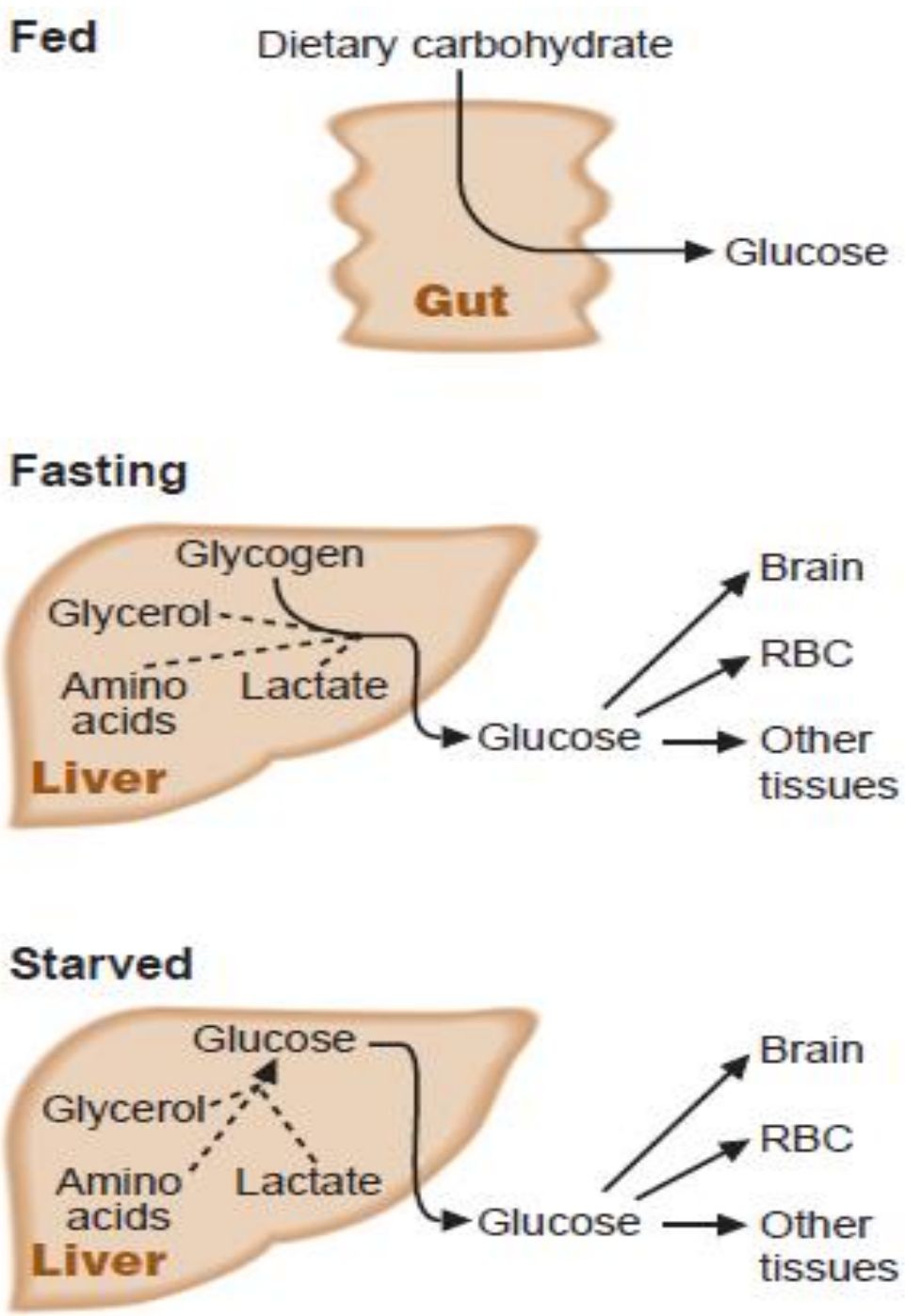

Glucose
GLYCOLYSIS
GLUCONEOGENESIS
Fructose 6-phosphate
F-2,6-BP
AMP
ATP
Citrate
H+
Phosphofructo-kinase
Fructose 1, 6-bisphosphatase
F-2,6-BP
AMP
Citrate
Fructose 1,6-bisphosphate
Several steps
Phosphoenolpyruvate
ADP
Phosphoenol-pyruvate carboxykinase
F-1,6-BP
ATP
Alanine
Pyruvate kinase
Oxaloacetate
Pyruvate carboxylase
Pyruvate
Acetyl CoA
ADP

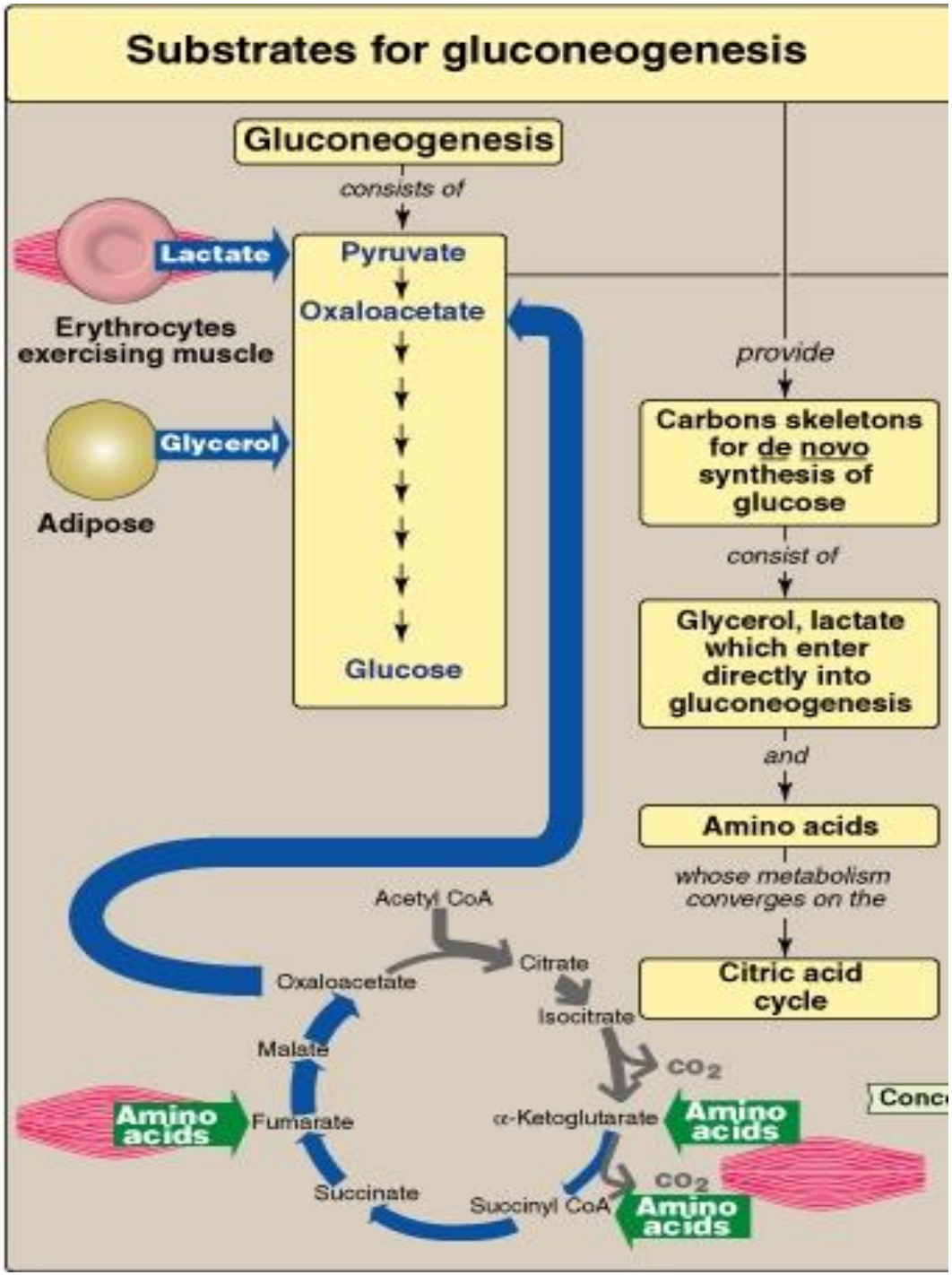

GLYCOLYSIS
GLUCONEOGENESIS
Fructose 6-phosphate
-2,6-BP
AMP
ATP
Citrate
H+
PFK
Fructose
1, 6-bisphosphatase
F-2,6-BP
AMP
Citrate
Fructose 1,6-bisphosphate


Insulin (low)
Glucagon (high)
CELL MEMBRANE
CYTOSOL
Adenylate cyclase
ATP
cAMP
Active protein kinase A
1 High glucagon/insulin ratio causes elevated cAMP and increased levels of active protein kinase A.
2 Increased protein kinase A activity favors the phosphorylated form of the PFK-2/FBP-2 complex.
Glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
DHAP
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Fructose 6-phosphate
Fructose bisphosphate phosphatase-1
H2O
Fructose 1,6-bisphosphate
Fructose 6-phosphate
P
PFK-2 (inactive)
FBP-2 (active)
ATP
ADP
PFK-2 (active)
FBP-2 (inactive)
Bifunctional enzyme
Fructose
2,6-bisphosphate
3 Phosphorylated PFK-2 is inactive, whereas FBP-2 is active; this impedes the formation of fructose 2,6-bisphosphate.
4 Decreased levels of fructose 2,6-bisphosphate decreases the inhibition of FBP-1, which leads to an increased rate of gluconeogenesis.

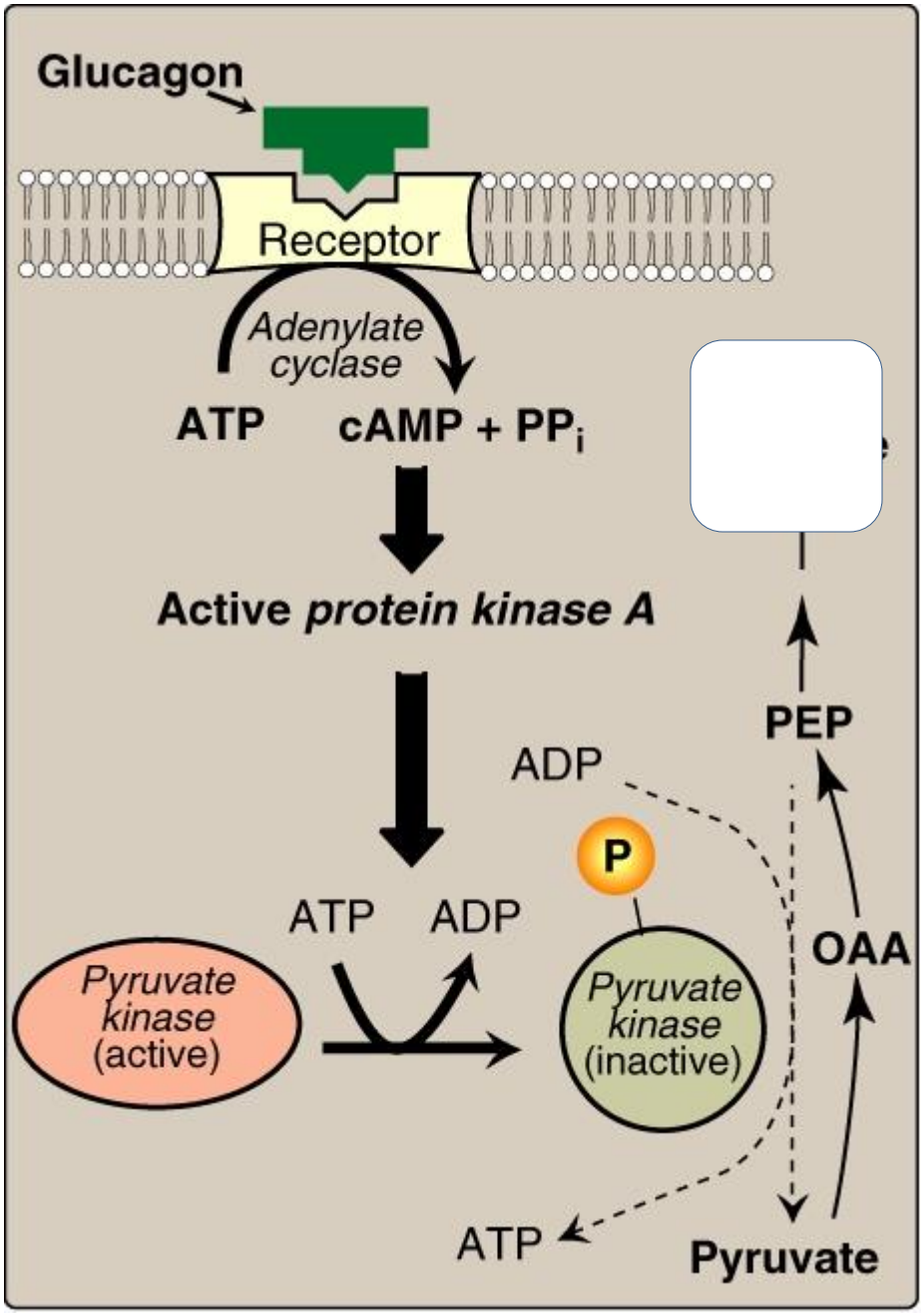

Phosphoenolpyruvate
ADP
Phosphoenol-
pyruvate
carboxykinase
F-1,6-BP
ATP
Alanine
Pyruvate
kinase
Oxaloacetate
Pyruvate
carboxylase
Pyruvate
Acetyl CoA
ADP


Glucagon
Receptor
Adenylate cyclase
ATP
cAMP + PPi
Active protein kinase A
Glucose
PEP
ADP
P
ATP
ADP
OAA
Pyruvate kinase (active)
Pyruvate kinase (inactive)
ATP
Pyruvate


Fed
Dietary carbohydrate
Glucose
Gut
Fasting
Glycogen
Glycerol
Amino acids
Lactate
Liver
Glucose
Brain
RBC
Other tissues
Starved
Glucose
Glycerol
Amino acids
Lactate
Liver
Glucose
Brain
RBC
Other tissues


Substrates for gluconeogenesis
Gluconeogenesis
consists of
Lactate
Pyruvate
Oxaloacetate
Erythrocytes exercising muscle
Glycerol
Adipose
Glucose
provide
Carbons skeletons for de novo synthesis of glucose
consist of
Glycerol, lactate which enter directly into gluconeogenesis
and
Amino acids
whose metabolism converges on the
Citric acid cycle
Acetyl CoA
Citrate
Oxaloacetate
Isocitrate
Malate
CO2
Amino acids
Fumarate
α-Ketoglutarate
Amino acids
Conc
CO2
Succinate
Succinyl CoA
Amino acids

Next topic: Glycogen Metabolism


Glucagon
Receptor
Adenylate cyclase
ATP
cAMP + PPi
Active protein kinase A
PEP
ADP
P
ATP
ADP
Pyruvate kinase (active)
Pyruvate kinase (inactive)
OAA
ATP
Pyruvate