Gluconeogenesis

Biochemistry II

BY

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Gluconeogenesis

- Liver glycogen, an essential postprandial source of glucose, can meet these needs for only 10–18 hrs in the absence of dietary intake of carbohydrate
- During a prolonged fast, however, hepatic glycogen stores are depleted, and glucose is formed from noncarbohydrate precursors such as lactate, pyruvate, glycerol (derived from the backbone of triacylglycerols and

α-keto acids (derived from the catabolism of glucogenic amino acids)

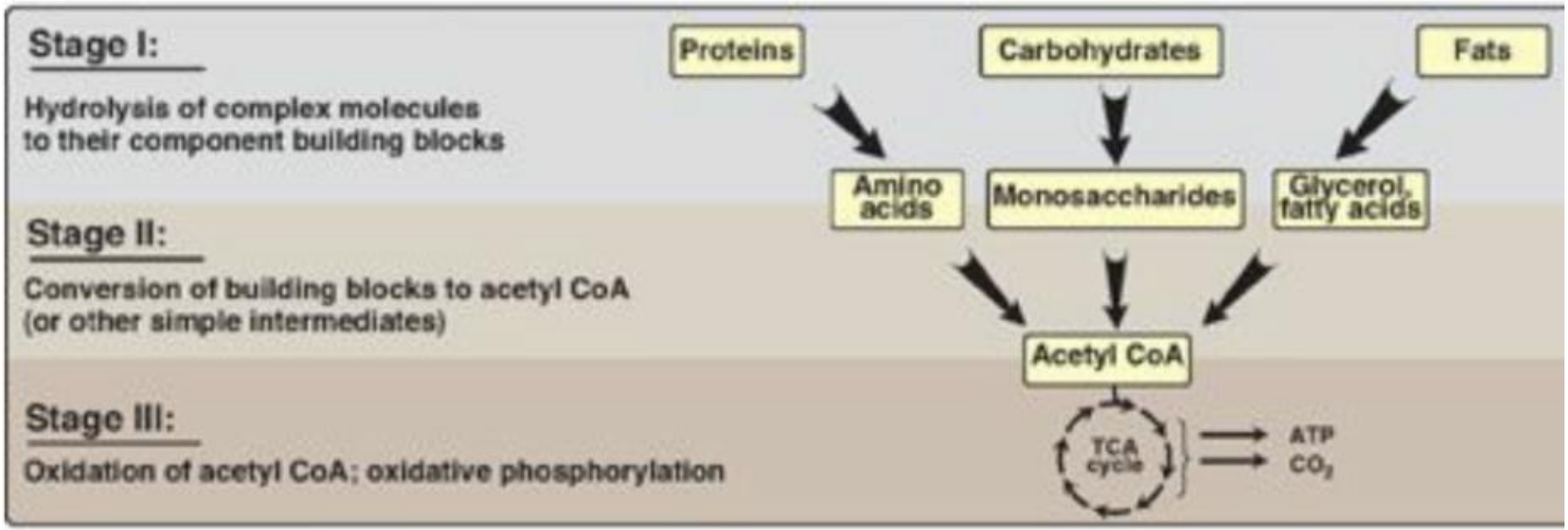
- During an overnight fast, approximately 90% of gluconeogenesis occurs in the liver

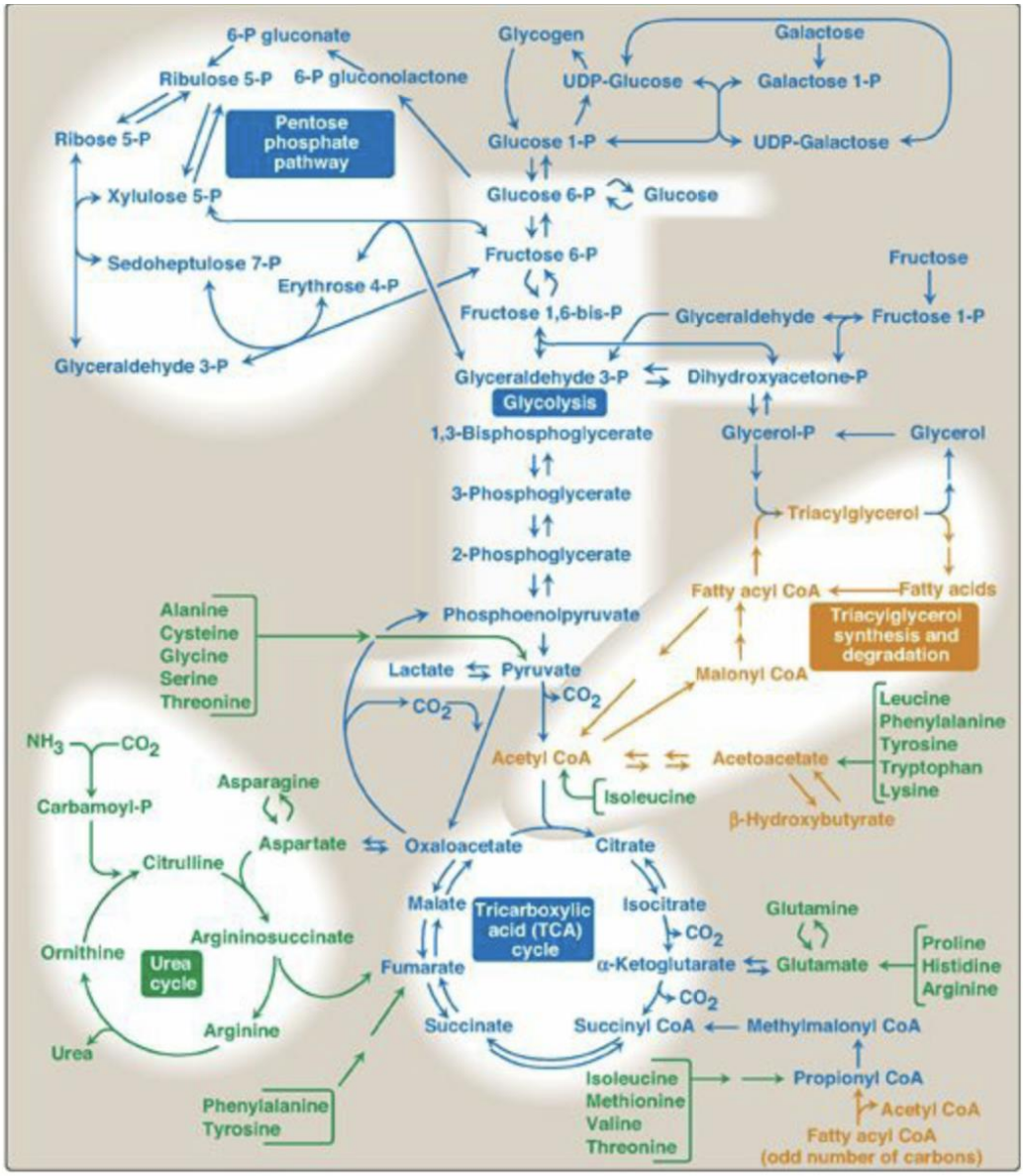
- the remaining 10% occurring in the kidneys. However, during prolonged fasting, the

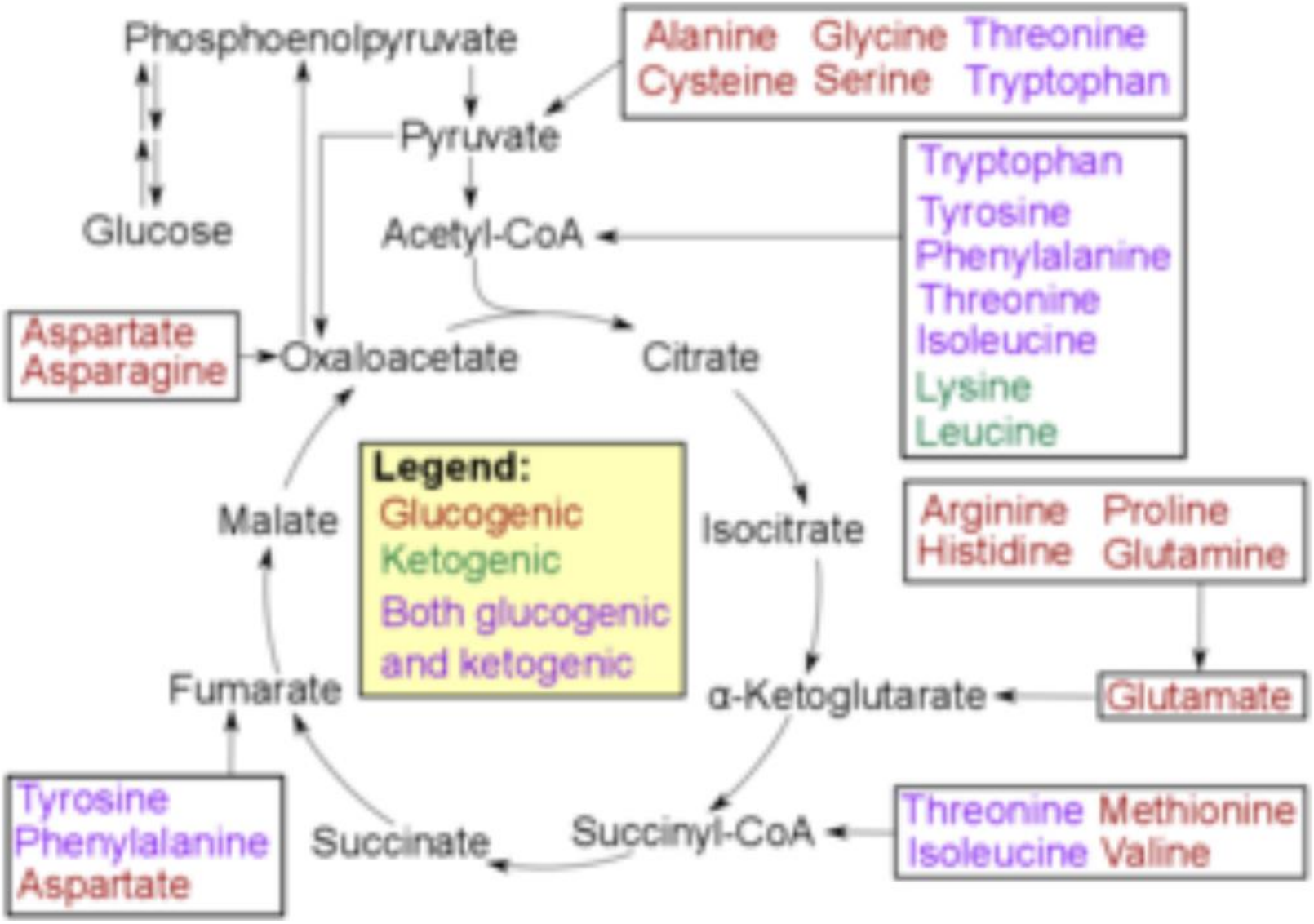
- kidneys become major glucose-producing organs, contributing an estimated 40% of the

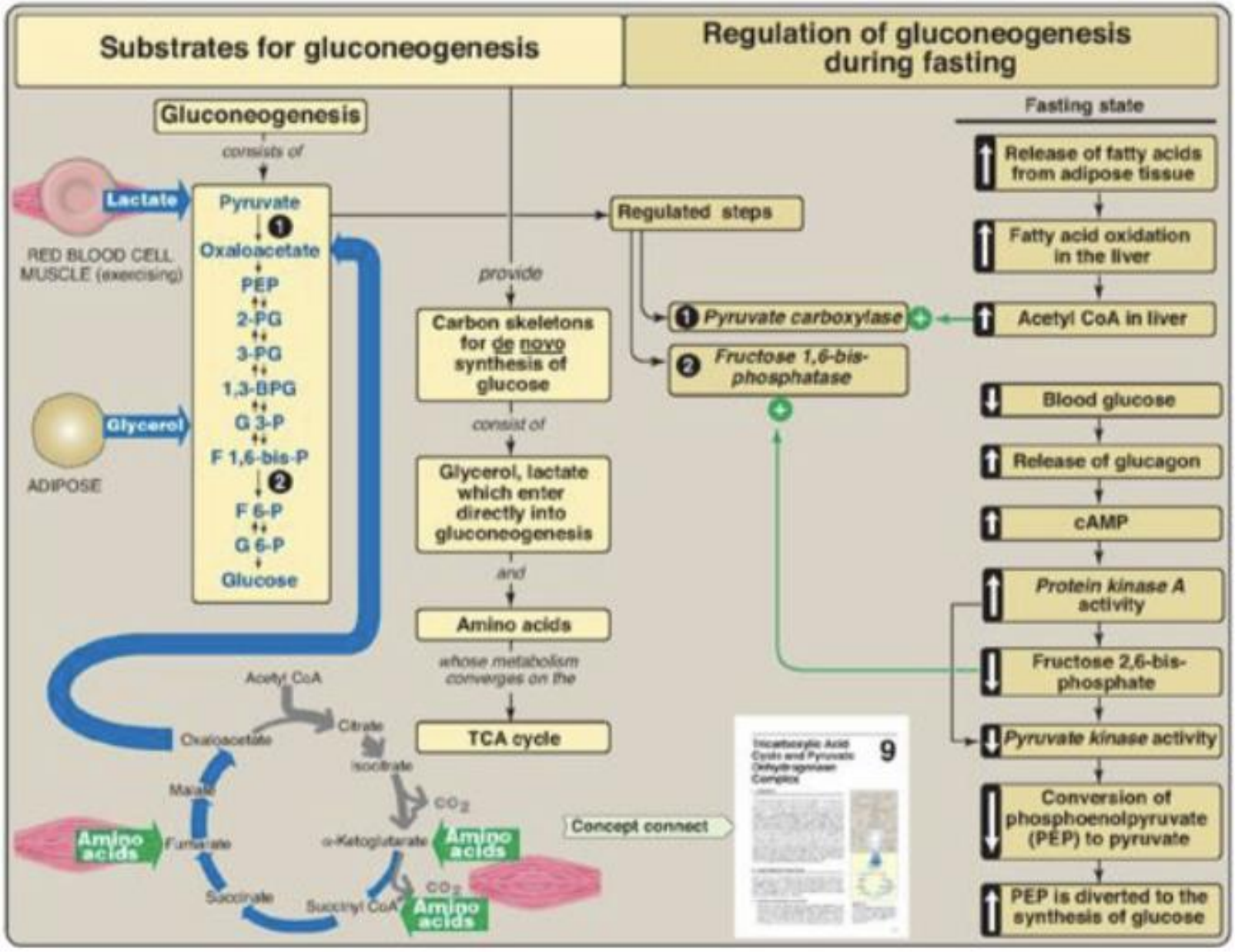
total glucose production.

Gluconeogenesis which requires both mitochondrial and cytosolic enzymes.


Stage I:
Hydrolysis of complex molecules to their component building blocks
Stage II:
Conversion of building blocks to acetyl CoA (or other simple intermediates)
Stage III:
Oxidation of acetyl CoA; oxidative phosphorylation
Proteins
Carbohydrates
Fats
Amino acids
Monosaccharides
Glycerol, fatty acids
Acetyl CoA
TCA cycle
ATP
CO_2


6-P gluconate
Ribulose 5-P
6-P gluconolactone
Ribose 5-P
Pentose phosphate pathway
Xylulose 5-P
Sedoheptulose 7-P
Erythrose 4-P
Glyceraldehyde 3-P
Glycogen
Galactose
UDP-Glucose
Galactose 1-P
Glucose 1-P
UDP-Galactose
Glucose 6-P
Glucose
Fructose 6-P
Fructose
Fructose 1,6-bis-P
Glyceraldehyde
Fructose 1-P
Glyceraldehyde 3-P
Dihydroxyacetone-P
Glycolysis
1,3-Bisphosphoglycerate
Glycerol-P
Glycerol
3-Phosphoglycerate
Triacylglycerol
2-Phosphoglycerate
Fatty acyl CoA
Fatty acids
Triacylglycerol synthesis and degradation
Alanine
Cysteine
Glycine
Serine
Threonine
Phosphoenolpyruvate
Lactate
Pyruvate
Malonyl CoA
CO2
Leucine
Phenylalanine
Tyrosine
Tryptophan
Lysine
NH3
CO2
Acetyl CoA
Acetoacetate
Isoleucine
β-Hydroxybutyrate
Asparagine
Carbamoyl-P
Aspartate
Oxaloacetate
Citrate
Citrulline
Malate
Tricarboxylic acid (TCA) cycle
Isocitrate
Glutamine
Argininosuccinate
Ornithine
Urea cycle
Fumarate
α-Ketoglutarate
Glutamate
Proline
Histidine
Arginine
Arginine
Urea
Succinate
Succinyl CoA
Methylmalonyl CoA
Isoleucine
Methionine
Valine
Threonine
Propionyl CoA
Acetyl CoA
Fatty acyl CoA
(odd number of carbons)
Phenylalanine
Tyrosine


Phosphoenolpyruvate
Alanine Glycine Threonine
Cysteine Serine Tryptophan
Pyruvate
Tryptophan
Tyrosine
Phenylalanine
Threonine
Isoleucine
Lysine
Leucine
Glucose
Acetyl-CoA
Aspartate
Asparagine
Oxaloacetate
Citrate
Legend:
Glucogenic
Ketogenic
Both glucogenic and ketogenic
Malate
Isocitrate
Arginine Proline
Histidine Glutamine
Fumarate
α-Ketoglutarate
Glutamate
Tyrosine
Phenylalanine
Aspartate
Succinate
Succinyl-CoA
Threonine Methionine
Isoleucine Valine


Substrates for gluconeogenesis
Regulation of gluconeogenesis during fasting
Gluconeogenesis
consists of
Lactate
RED BLOOD CELL
MUSCLE (exercising)
Glycerol
ADIPOSE
Pyruvate
1
Oxaloacetate
PEP
2-PG
3-PG
1,3-BPG
G 3-P
F 1,6-bis-P
2
F 6-P
G 6-P
Glucose
provide
Carbon skeletons for de novo synthesis of glucose
consist of
Glycerol, lactate which enter directly into gluconeogenesis
and
Amino acids
whose metabolism converges on the
TCA cycle
Regulated steps
1 Pyruvate carboxylase
2 Fructose 1,6-bis-phosphatase
Fasting state
Release of fatty acids from adipose tissue
Fatty acid oxidation in the liver
Acetyl CoA in liver
Blood glucose
Release of glucagon
cAMP
Protein kinase A activity
Fructose 2,6-bis-phosphate
Pyruvate kinase activity
Conversion of phosphoenolpyruvate (PEP) to pyruvate
PEP is diverted to the synthesis of glucose
Acetyl CoA
Citrate
Oxaloacetate
Isocitrate
Malate
Fumarate
Succinate
Succinyl CoA
α-Ketoglutarate
CO2
Amino acids
Concept connect
9

- Seven of the reactions of glycolysis are

reversible and are used for gluconeogenesis in the liver and kidneys.

- Three reactions are **physiologically irreversible** and must be circumvented. These reactions are catalyzed by the glycolytic enzymes **pyruvate kinase**, **phosphofructokinase**, and **hexokinase**.

- **Pyruvate** is converted to oxaloacetate and then to
- **phosphoenolpyruvate** (**PEP**) by **pyruvate carboxylase** and **PEPcarboxykinase**.
- The carboxylase requires **biotin** and **ATP** and is allosterically
- activated by **acetyl coenzyme A**. PEP-carboxykinase requires **GTP**.
- The transcription of its gene is increased by glucagon and the glucocorticoids and decreased by insulin.

- **Fructose 1,6-bisphosphate** is converted to **fructose 6-phosphate** by **fructose 1,6-bisphosphatase**. This enzyme is **inhibited** by

elevated levels of **AMP** and **activated** when **ATP** levels are elevated.

The enzyme is also **inhibited** by **fructose 2,6-bisphosphate**, the primary allosteric activator of glycolysis.

- **Glucose 6-phosphate** is converted to **glucose** by **glucose 6-phosphatase**. This enzyme of the endoplasmic reticular membrane is required for
- the final step in gluconeogenesis as well as hepatic and renal glycogen degradation.
- Its deficiency results in severe, fasting hypoglycaemia.

Reference

- Lippincott’s
- Illustrated Reviews:
- Biochemistry
- Sixth Edition