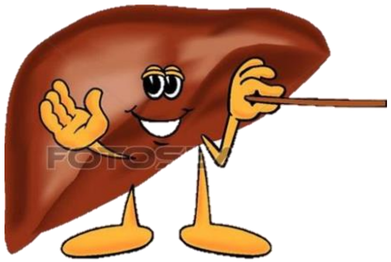
434 Biochemistry Team

Glucose Metabolism: Gluconeogenesis

Foundation block..

Objectives:

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



Gluconeogenesis:

Overview

- Gluconeogenesis is an energy-consuming, anabolic* pathway

Gluconeogenesis is important to provide the body with glucose when there is no external source of glucose (during prolonged fasting or starvation)

- Occurs in **Liver** mainly, and in **Kidney**

  <u>During Overnight fast:</u>
    - 90% of gluconeogenesis occurs in liver
    - 10% of gluconeogenesis occurs in Kidneys

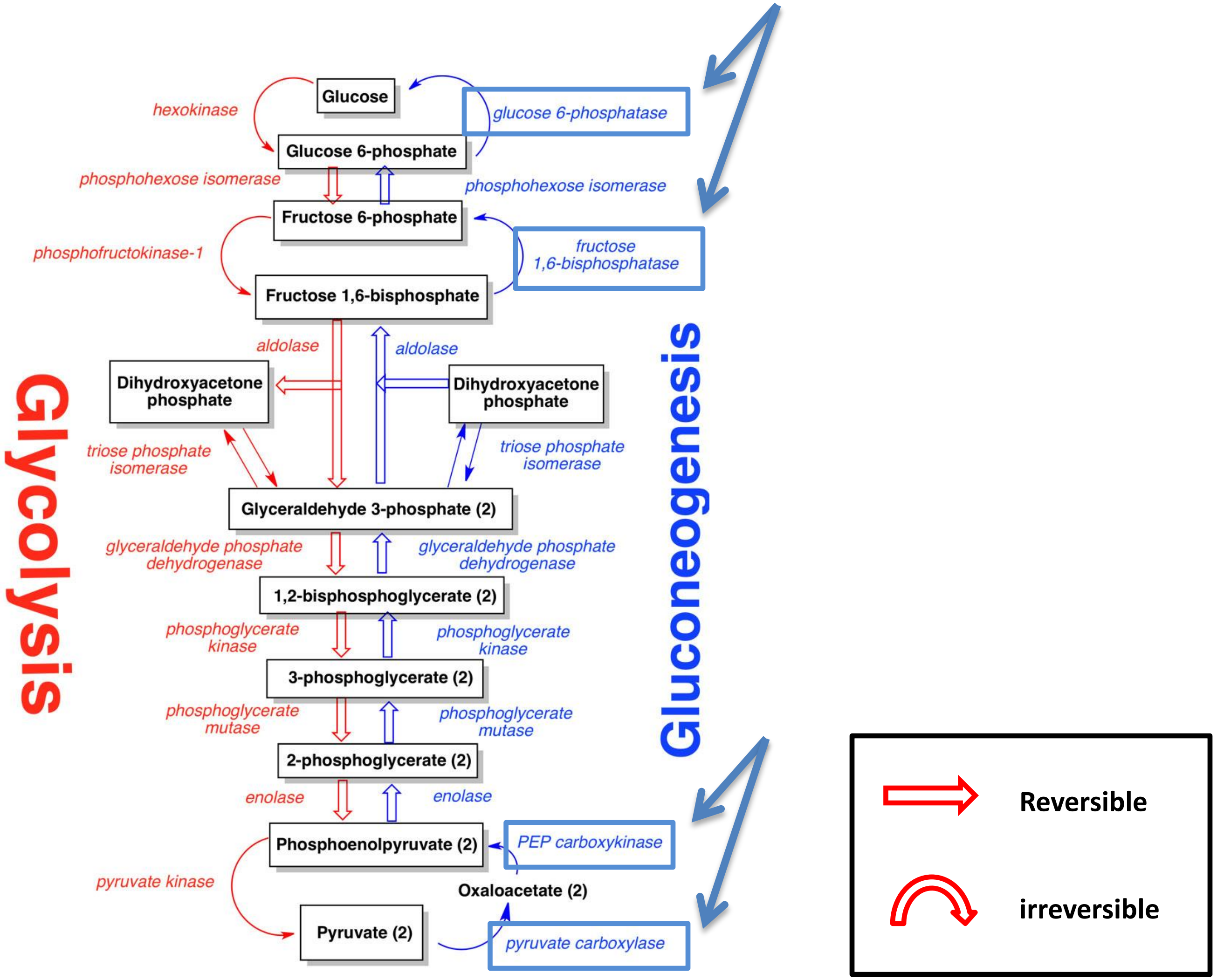
  <u>During Prolonged fast:</u>
    - 60% of gluconeogenesis occurs in liver
    - 40% of gluconeogenesis occurs in Kidneys

- Gluconeogenesis requires both **mitochondrial** & **cytosolic** enzymes. **EXCEPTION!** if gluconeogenesis starts by **Glycerol**, it will need only the **cytosol**

*anabolic: بناء، وهذا يجعله مستهلكاً للطاقة

Gluconeogenic Pathway

- **Seven** glycolytic reactions are reversible & are used in gluconeogenesis from lactate or pyruvate.
- **Three** glycolytic reactions are irreversible & must be reversed (by **4** alternate reactions) in gluconeogenesis.



The 4 alternate reactions in gluconeogenesis to the 3 irreversible glycolytic steps:

Pyruvate Kinase:
(PEP → Pyruvate)

PFK-1:
(Fructose 6-P → Fructose 1,6 Bisphosphate)

Hexokinase:
(Glucose → Glucose 6-P)

1- Pyruvate Carboxylase:
Carboxylation reaction, requires Biotin and ATP, occurs in the mitochondria, allosterically activated by acetyl CoA. OAA has to be transported from mitochondria to cytosol.
(Pyruvate→Oxaloacetate "OAA")

2- 

PEPCK:
Decarboxylation & phosphorylation reaction, requires energy (GTP), occurs in cytosol, the enzyme's gene is induced by glucagon & repressed by insulin
(Oxaloacetate → PEP)

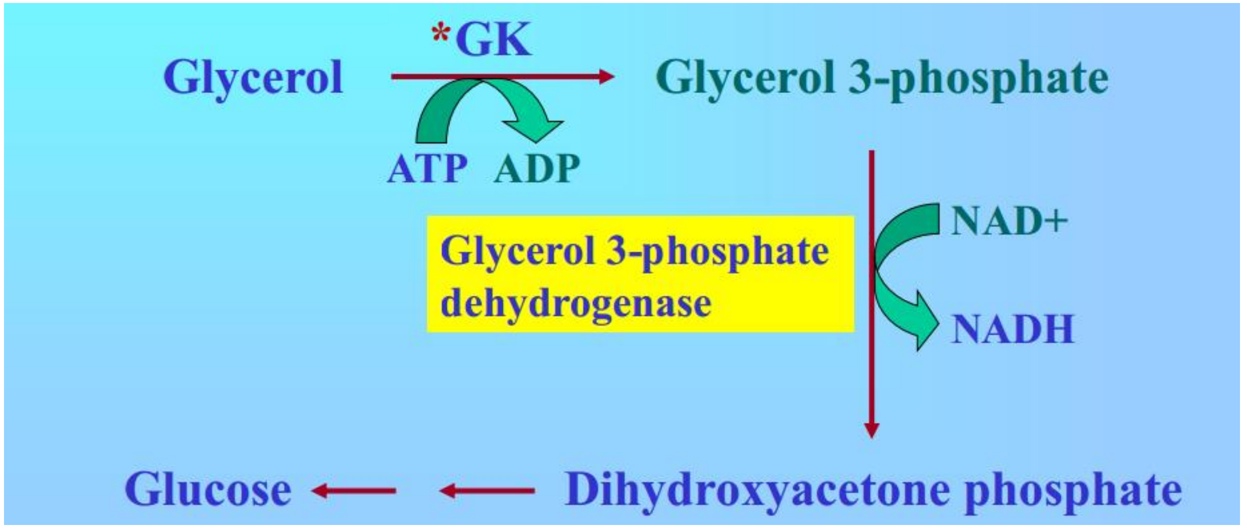
3- Fructose 1,6 Bisphosphatase:
Dephosphorylation reaction. It is inhibited by high levels of AMP, and activated by high levels of ATP & low levels of AMP. It is allosterically inhibited by Fructose 2,6-bisphosphate (reciprocal regulation with glycolysis)
(Fructose 1,6 Bisphosphate→Fructose 6-P)

4- Glucose 6-Phosphatase:
Dephosphorylation reaction, enzyme is found only in liver and kidney
(Glucose 6-P → Glucose)

Gluconeogenic Substrates*

Glycerol

- Glycerol is released during the hydrolysis of Triacylglycerol (TAG) in adipose tissue.
- In liver and kidney, glycerol will be phosphorylated by glycerol kinase (GK)* to glycerol-P.
- Glycerol-P will be oxidized by glycerol-P dehydrogenase to dihydroxyacetone phosphate(DHAP: an intermediate of glycolysis).

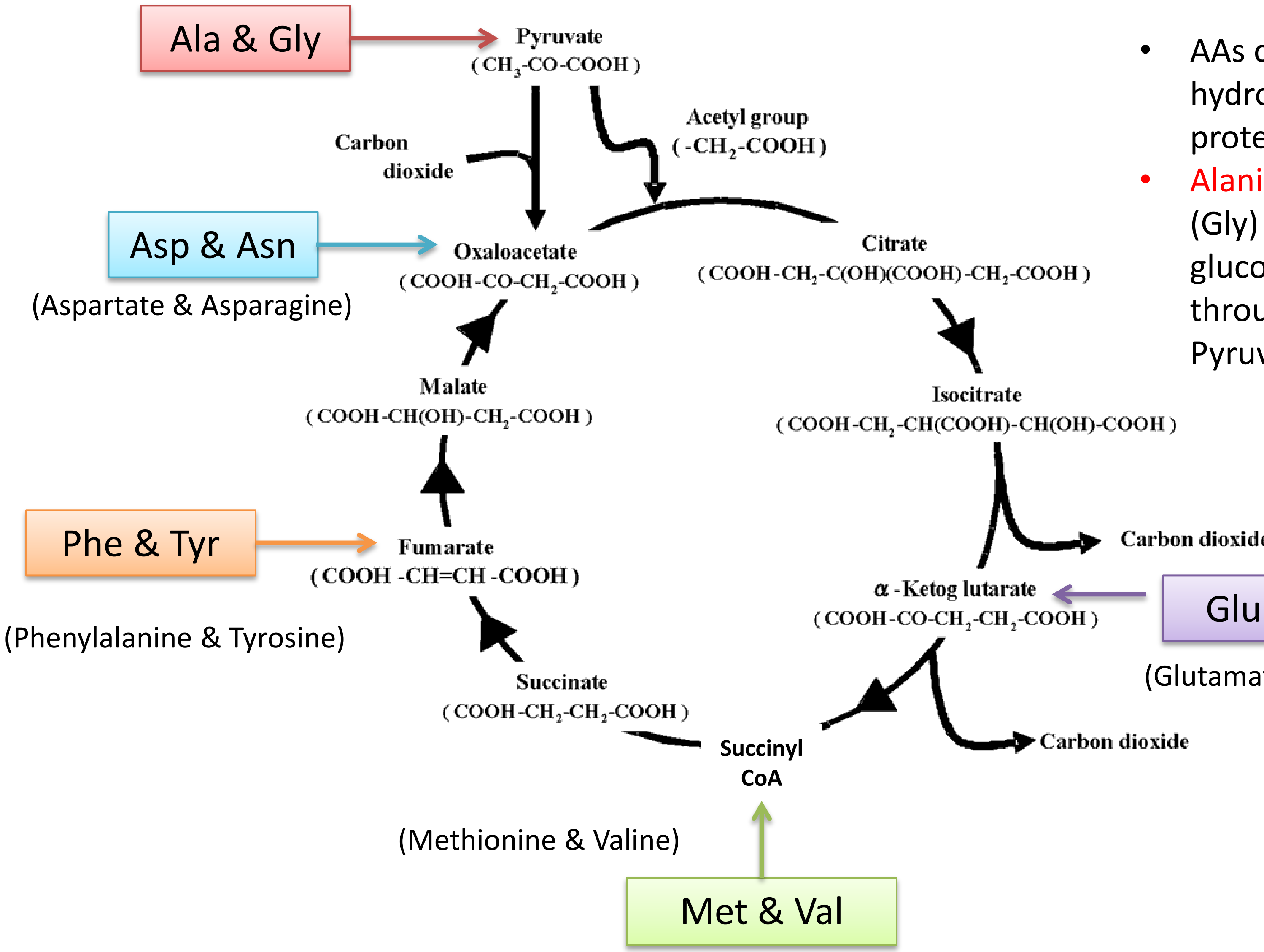


*__Gluconeogenic Substrates__: molecules that can be used to produce glucose through gluconeogenesis pathway

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

Gluconeogenic Substrates

Glucogenic Amino Acids (AAs)

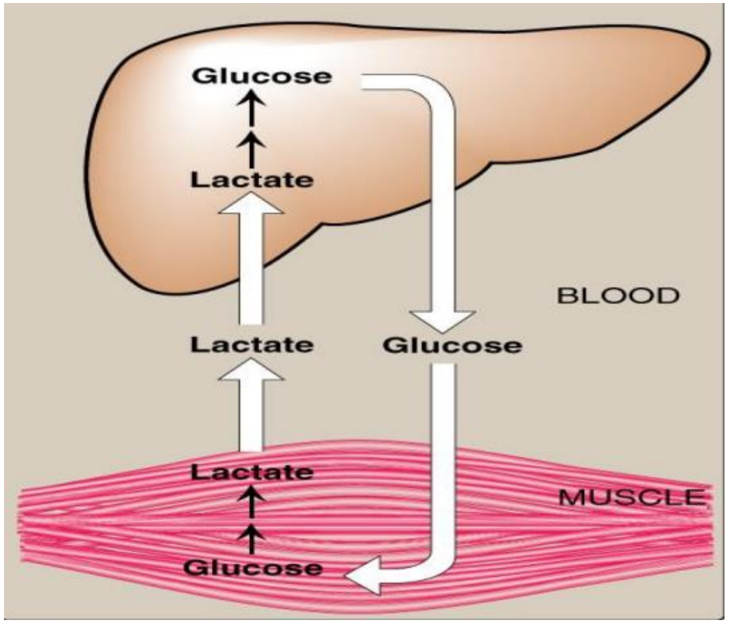


- AAs can be derived from hydrolysis of tissue proteins.
- Alanine (Ala) & Glycine (Gly) amino acids are gluconeogenic substrates through conversion to Pyruvate

Gluconeogenic Substrates

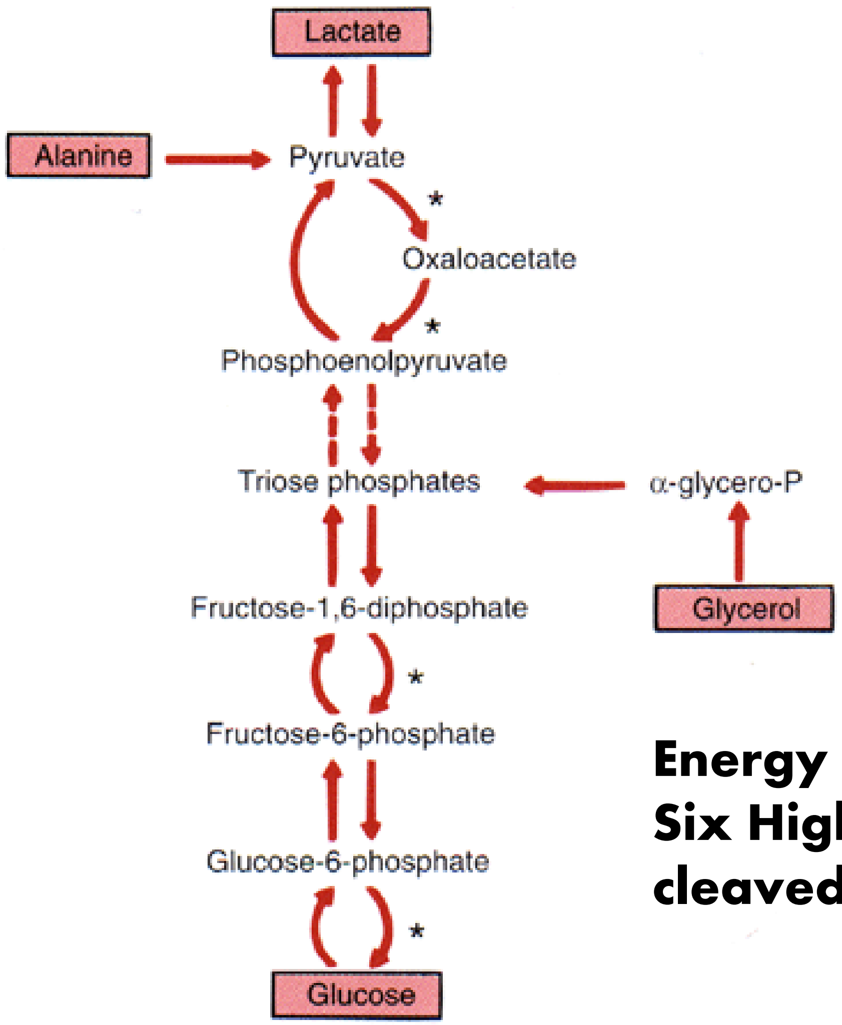
Lactate (Cori Cycle)

- Lactate is released into the blood by exercising skeletal muscle & by cells lacking mitochondria (Anaerobic glycolysis of glucose).
- Lactate is taken up by the liver and reconverted to glucose (gluconeogenesis)
- Glucose will then be released to the circulation to be used by skeletal muscles.



Gluconeogenic pathway

There are 4 unique enzymes required for reversal of the 3 irreversible reactions (rate limiting) of Glycolysis :



1-Pyruvate carboxylase
(reverses the action of Pyruvate kinase)

2-PEP-carboxykinase
(reverses the action of Pyruvate kinase)

3- Fructose 1,6 Bisphosphatase
(reverses the action of PFK-1)

4- Glucose 6-phosphatase
(reverses the action of Glucokinase)

Energy consumed
Six High-Energy phosphate Bonds are cleaved & Two NADH are oxidized

Gluconeogenic pathway

Enzyme	Function
Pyruvate carboxylase (reverses the action of Pyruvate kinase)	Transferring CO2 to Pyruvate (Mitochondria) → Oxaloacetate (has to be transformed to cytosol so it's reduced to malate) Requires Biotin and ATP – Activated by acetyl CoA
PEP-carboxykinase (reverses the action of Pyruvate kinase)	Malate is reoxidized to oxaloacetate in the cytosol. PEP-CK converts oxaloacetate to phosphoenolpyruvate. The enzyme's gene is induced by glucagon & repressed by insulin
Fructose 1,6 Bisphosphatase (reverses the action of PFK-1)	Dephospholyration of F1,6-P → F6-P Inhibited by High AMP and allostrically by F2,6-P , Activated by High ATP and Low AMP
Glucose 6-phosphatase (reverses the action of Glucokinase)	Only In Liver and kidney ! Dephospholyrstion of Glucose 6-P → Glucose .

Gluconeogenic Regulation

AMP

- Elevated AMP Inhibits Gluconeogenesis(F1,6-P) and stimulates glycolysis (PFK-1)

Acetyl CoA

- Accumulation of Acetyl CoA in fasting Allostrically activates (pyruvate carboxylase) to increase the Gluconeogenesis rate

Glucagon

- Stimulates gluconeogenesis by :
- Allosteric (glucagon ↓ F2,6-P) leads to inhibition of PFK-1 and activation of F1,6-bisphosphatase
- Induction (Glucagon ↑ Induction of PEP-CK)

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Quiz