Lecture 29 Gluconeogenesis & Maintenance of Blood Glucose Level I

By

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Objectives

Mention definition, site and biological importance of gluconeogenesis

Discuss the gluconeogenic precursors,

Describe pathways of gluconeogenesis

Discuss regulation of gluconeogenesis

Describe variation, hormonal and tissue regulation of blood glucose level, during fed, fasting, and starvation states

Intended learning outcomes

A-Knowledge and understanding:

A7- Describe the central pathways that provide living organisms with energy.

B- Intellectual skills

B7- Explain regulation and integration of the major metabolic pathways.

B8- Illustrate examples where defects in biochemical processes result in diseases, and predict potential outcomes of biochemical defects.

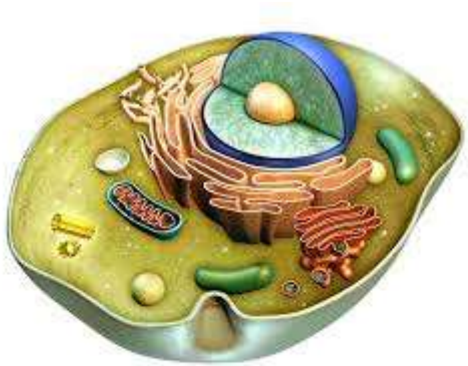
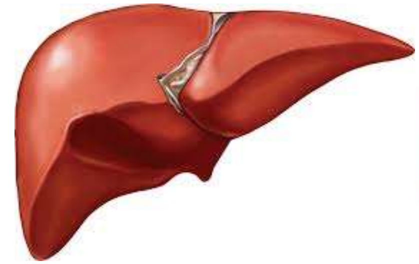
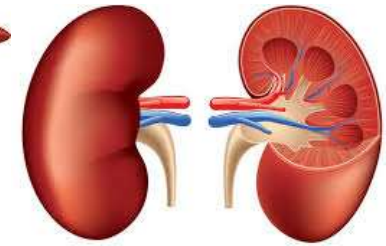
Gluconeogenesis

Definition
Site
Biological importance
Steps
Regulation
Bioenergetics

Gluconeogenesis

Definition:

- It is the **formation of glucose from non-carbohydrate precursors**.
- **These non-carbohydrate precursors** include
  - Lactate
  - Pyruvate
  - Propionate
  - Glycerol
  - Glucogenic amino acids
- **It occurs during:**
  - Fasting,
  - Starvation
  - Intense exercise.

Site:

It occur in mitochondria and cytoplasm of :

- **Major site; Liver**
- **Minor site: kidney**

- Very limited in:

a) Skeletal muscle and adipose tissue due to deficiency of glucose-6-phosphatase.

b) Heart and smooth muscles due to deficiency of fructose-1,6-diphosphatase.

Biological importance of gluconeogenesıs:

1. Gluconeogenesis supplies body cells with glucose after 4 - 6 hours of last meal.
2. It is used to meet the needs of the body for glucose especially **brain** and nervous system, **RBCs**, renal medulla, Lens, cornea.
3. Glucose is especially needed for mammary gland as a precursor of lactose.
4. Gluconeogenesis produces oxaloacetate (from pyruvate) and other intermediates of citric acid cycle in many tissues.
5. Gluconeogenesis is the way by which **lactate** produced during muscular contraction and in RBCs is **converted into glucose**.

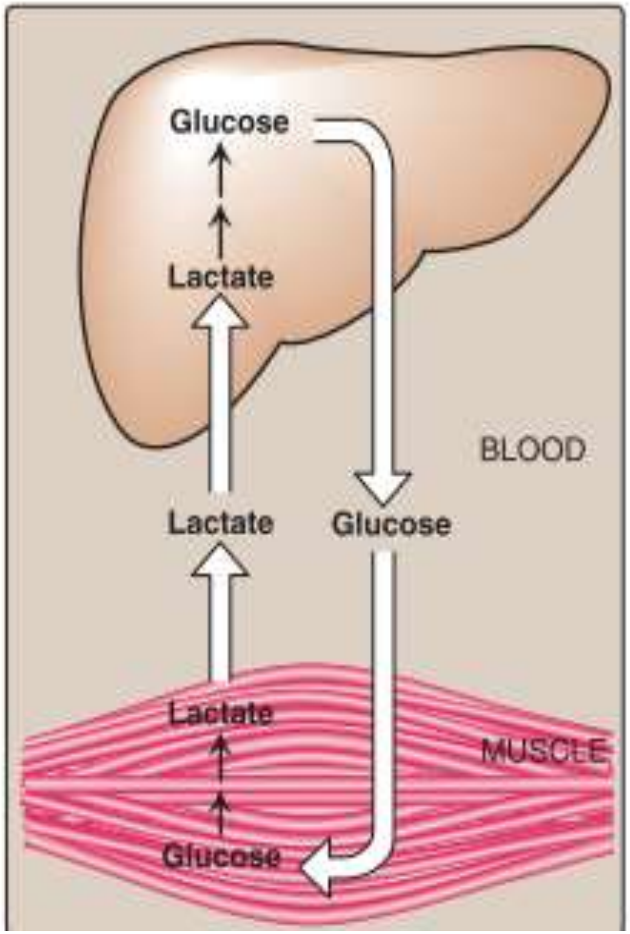
Steps:

- It is essentially **the reverse of glycolysis**, except at the three irreversible reactions that require different enzyme(s) to be reversed.

Gluconeogenesis from Lactate and Pyruvate

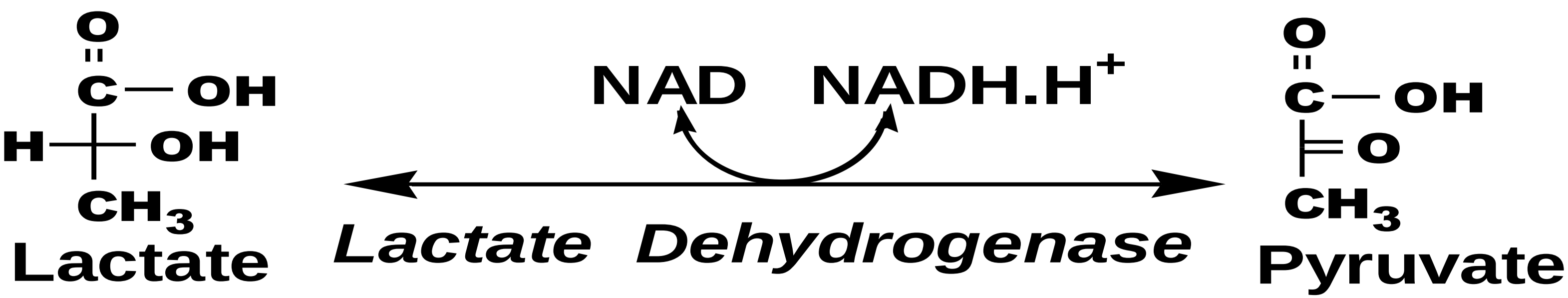
(Cori's Cycle)

- Lactate formed by the anaerobic oxidation of glucose from skeletal **muscle** glycogen or glycolysis in **RBCs**, diffuse to blood stream and is transported to the **liver** where it is transformed into glucose by gluconeogenesis.



Steps:

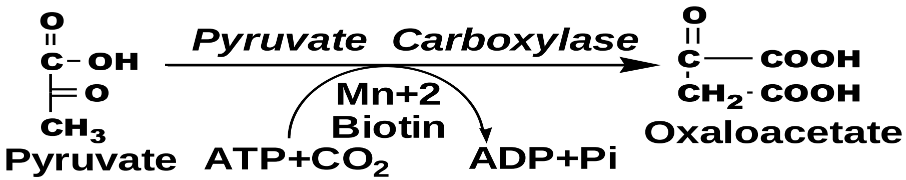
Conversion of **lactate into pyruvate** is reversibly activated by lactate dehydrogenase.



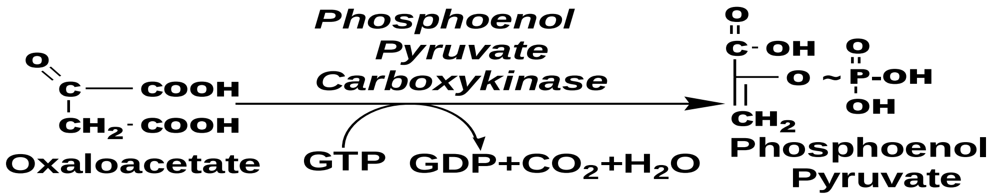
- **The three irreversible steps of glycolysis are:**

1. **Conversion of phosphoenol pyruvate to Pyruvate activated by pyruvate kinase is reversed by** the combined action of two enzymes:

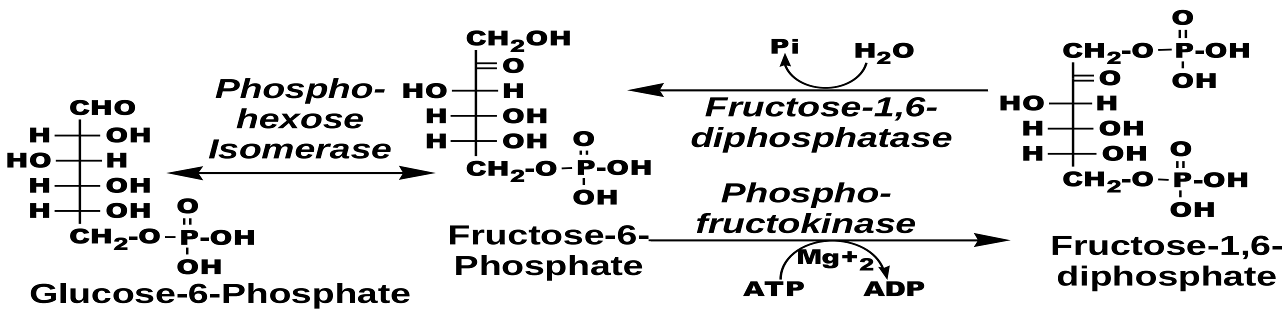
A. Pyruvate carboxylase in **mitochondria** requires CO_2, ATP, biotin as a coenzyme and Mn^{2+} as a cofactor. The reaction is activated by accumulation of acetyl-CoA (and ATP).



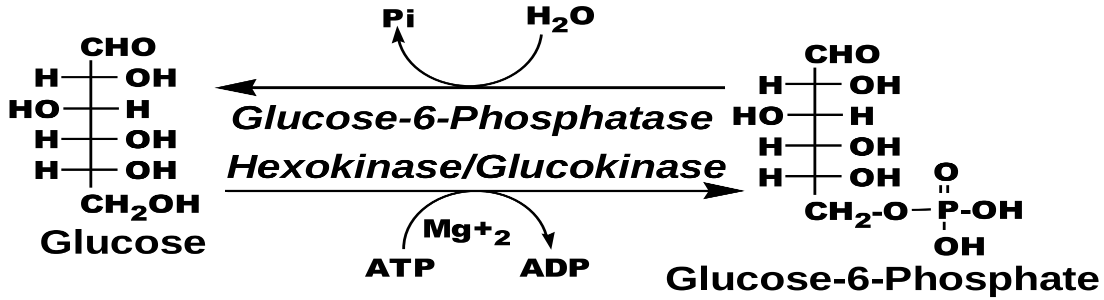
B. Phosphoenol pyruvate carboxykinase in the **cytoplasm**. Cytoplasmic oxaloacetate is converted into phosphoenol pyruvate by phosphoenol pyruvate carboxykinase utilizing GTP as phosphate donor and releasing H_2O and CO_2.

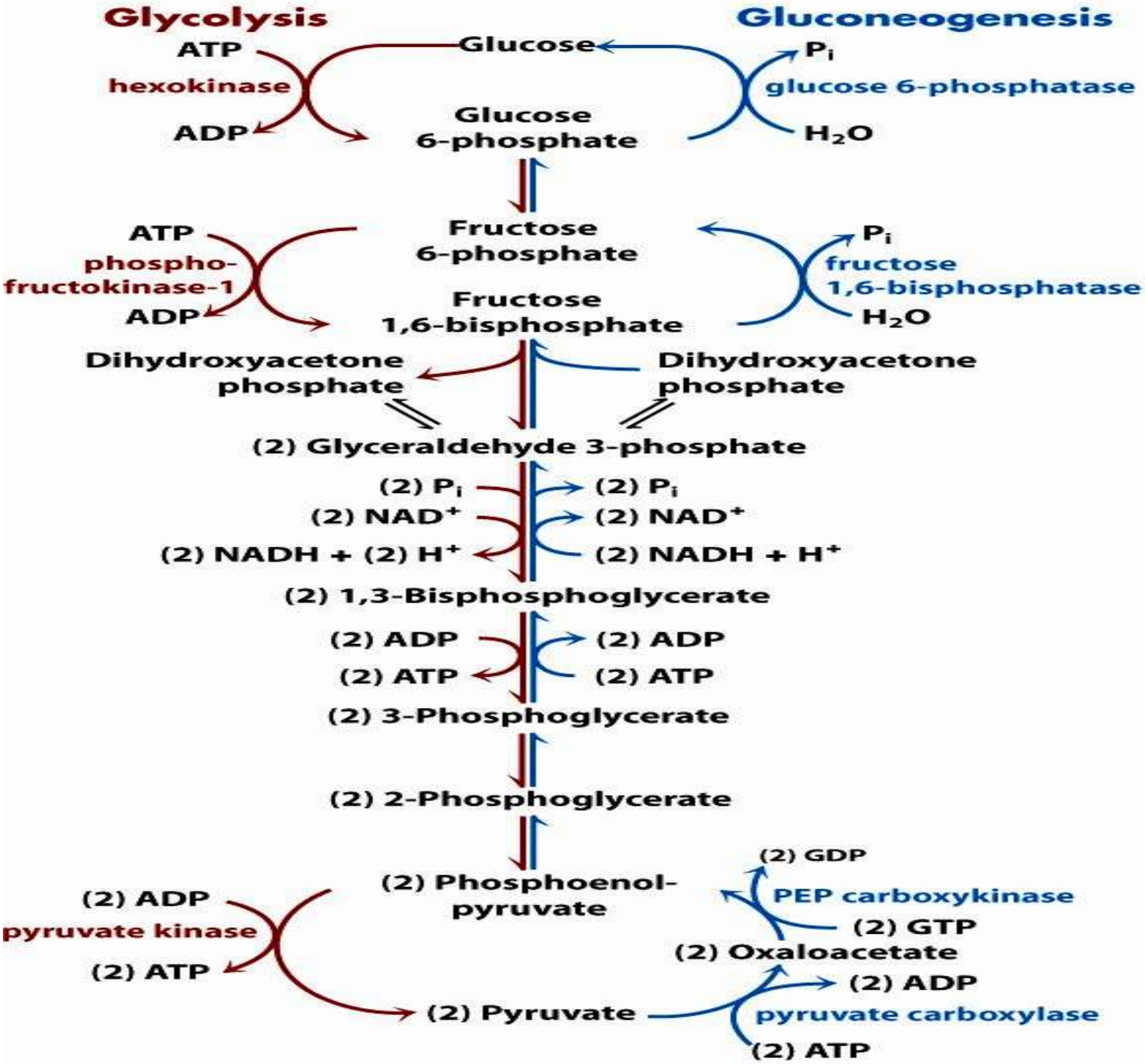


2. **Conversion of fructose-6-phosphate into Fructose-1,6-diphosphate activated by phosphofructokinase-1 is reversed by fructose-1,6-diphosphatase.** Then Fructose-6-phosphate is isomerized to glucose-6-phosphate by the reversible action of phosphohexose isomerase.



3. **Conversion of glucose into Glucose-6-phosphate activated by glucokinase is reversed by glucose-6-phosphatase.** Glucose is transported from liver into blood.




Glycolysis
Gluconeogenesis
ATP
hexokinase
ADP
Glucose
P_i
glucose 6-phosphatase
H_2O
Glucose 6-phosphate
ATP
phospho-fructokinase-1
ADP
Fructose 6-phosphate
P_i
fructose 1,6-bisphosphatase
H_2O
Fructose 1,6-bisphosphate
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) NAD^+
(2) NADH + (2) H^+
(2) P_i
(2) NAD^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenol-pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) ADP
pyruvate kinase
(2) ATP
(2) Oxaloacetate
(2) ADP
pyruvate carboxylase
(2) Pyruvate
(2) ATP

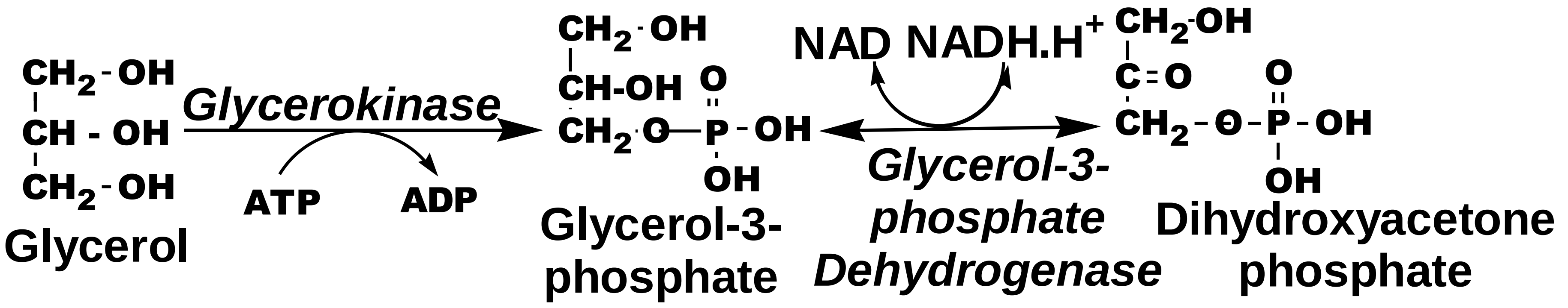
Irreversible glycolytic steps bypassed

Glycolysis	Gluconeogenesis
1. Glucokinase	by Glucose-6-phosphatase
2. Phosphofructokinase-1	by Fructose 1,6-bisphosphatase
3. Pyruvate kinase (PyrK)	by Pyruvate Carboxylase and Phosphoenolpyruvate carboxykinase

Gluconeogenesis from Glycerol

- Glycerol derived from lipolysis of fat is activated by **glycerol kinase** in **liver, kidney**, lactating mammary gland, heart and intestine into glyerol-3-phosphate.

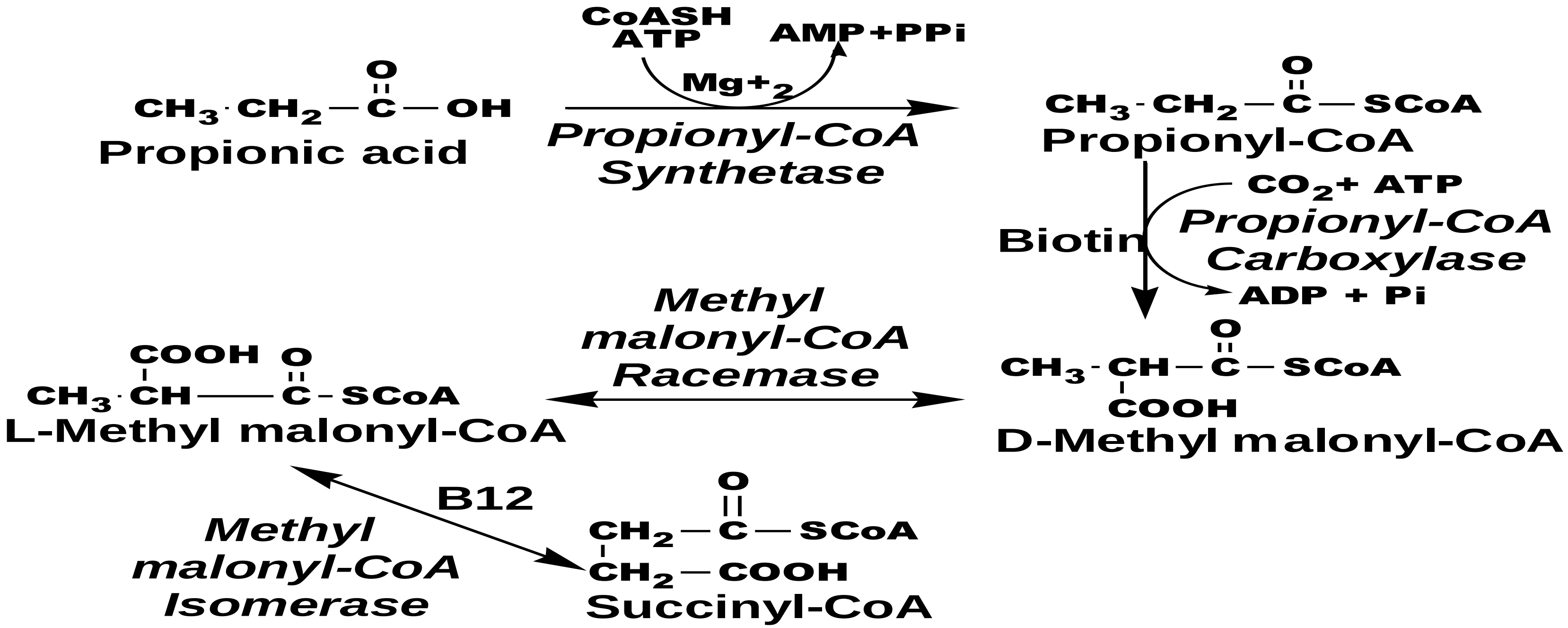
- **Glyerol-3-phosphate dehydrogenase** oxidizes glyerol-3-phosphate into dihydroxyacetone-phosphate to cross glycolysis into glucose.



Gluconeogenesis from Propionic Acid

- Propionic acid is derived from**,**

- methionine,
- isoleucine,
- β-oxidation of odd number fatty acid,
- large intestinal and ruminal fermentation of fibers.

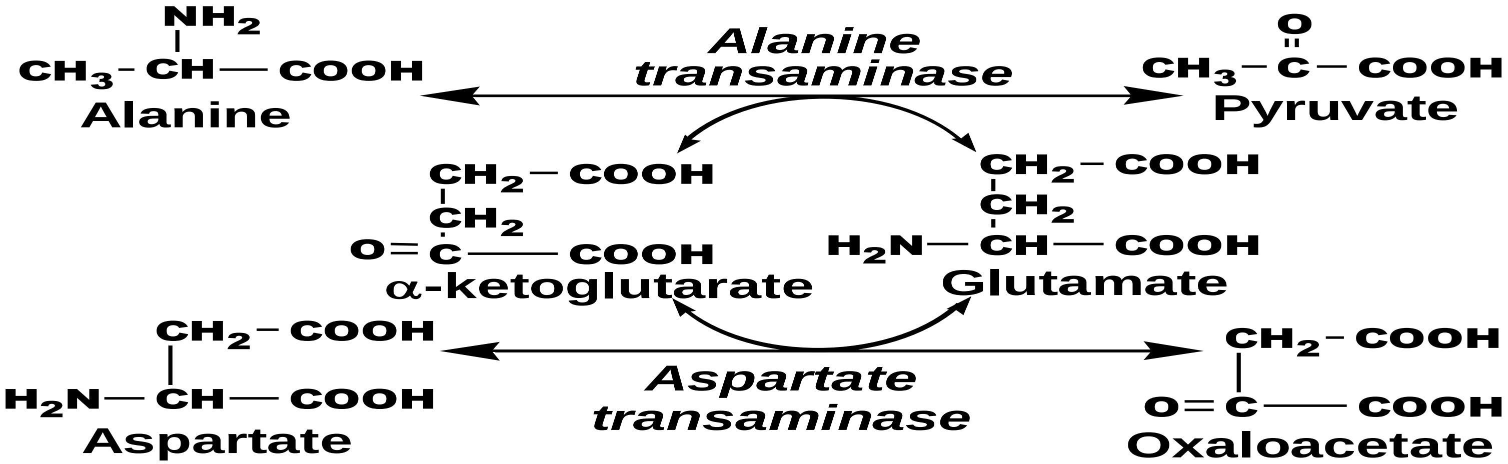


Gluconeogenesis from Glucogenic Amino Acids

- Glucogenic amino acids from **tissue proteins** during starvation are transformed to **glycolytic or Krebs' intermediates** either by transamination or deamination.

- **Glutamate** gives **α-ketoglutarate**, **aspartate** gives **oxaloacetate** and **alanine** gives **pyruvate** by transamination.

- **Serine, threonine, and cysteine** give **pyruvate** and **proline, arginine, histidine, lysine and glutamate** give **α-ketoglutarate** by deamination



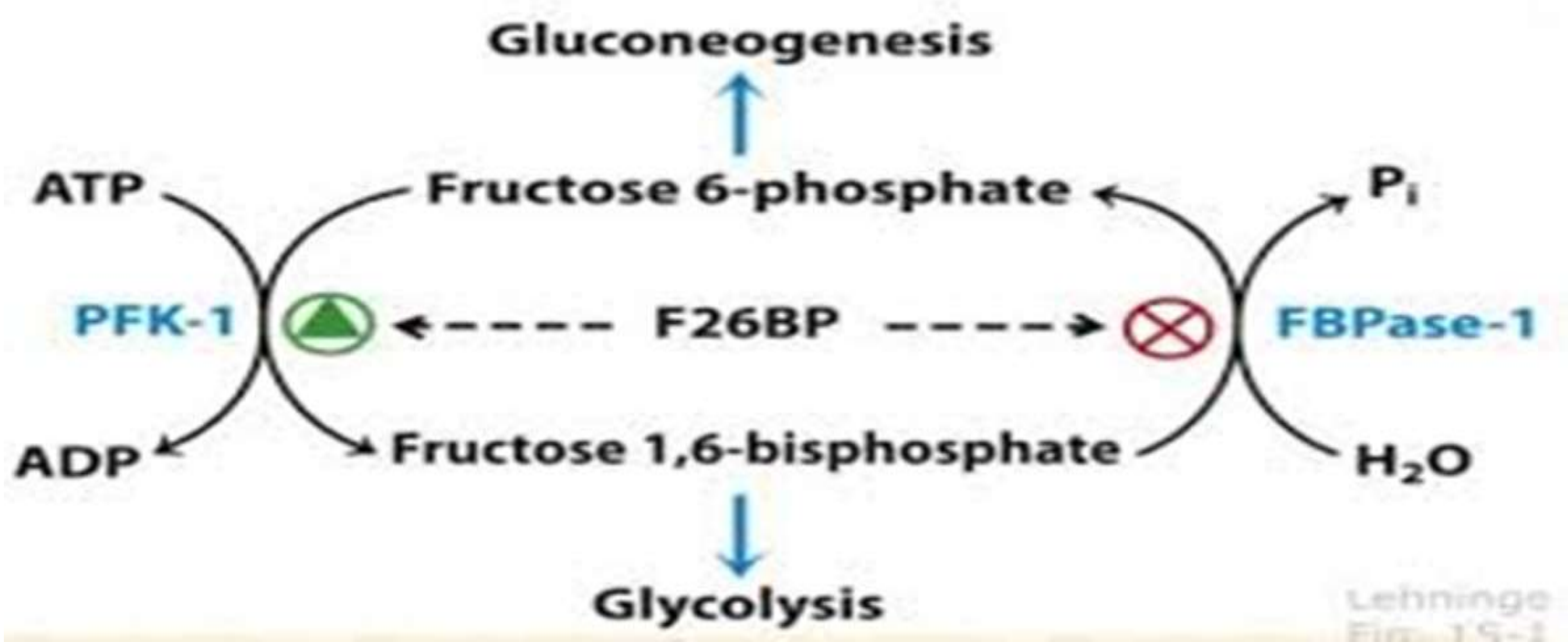
Regulation of gluconeogenesis:

1. **The key regulatory enzymes**. Glucose-6-phosphatase, fructose-1,6-diphosphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxylase
2. **Hormones:** glucocorticoids, adrenaline and glucagon are released in prolonged fasting and starvation. They induce synthesis of the key regulatory enzymes. Insulin inhibit gluconeogenesis. It inhibit synthesis of the key regulatory enzymes.
3. **Allosteric effectors:** excess ATP, citrate, acetyl-CoA and $NADH.H^+$ stimulate, whereas, ADP and AMP inhibit the key regulatory enzymes.
4. **Conditions characterized by active gluconeogenesis:** Severe muscular exercises (more lactate), Cushing's syndrome and high doses of cortisone or ACTH (more cortisol), diabetes mellitus (no insulin).

5. **To prevent the waste of a futile cycle, Glycolysis & Gluconeogenesis are reciprocally regulated.** **<u>by fructose-2,6-bisphosphate:</u>**

- **It is formed by phosphofructokinase-2 (PFK-2)**
- It **stimulates Glycolysis** by activating Phosphofructokinase-1.
- It **inhibits gluconeogenesis** by inhibiting Fructose-1,6-bisphosphatase.

Fructose1,6-Bisphosphatase is the most important control site in Gluconeogenesis.



Energy cost of gluconeogenesis:

Gluconeogenesis is endergonic process. For conversion of two molecules of pyruvate to one molecule of glucose, **4** molecules of **ATP**, **2** molecules of **GTP** and **2** molecules of **NADH.H$^+$** are utilized as follow:

A.ATP and GTP

Two pyruvate → 2 oxaloacetate (-2ATP)

Two Oxaloacetate → 2 phosphoenolpyruvate (-2GTP)

Two 3-phosphoglycerate → two 1,3 biphosphoglycerate (-2ATP)

B. NADH.H$^+$

two 1,3 biphosphoglycerate → two glyceraldehyde 3- phosphate (-2 NADH.H$^+$)

1. Gluconeogenesis is decreased by

(A) Glucagon (B) Epinephrine

(C) Glucocorticoids <u>(D) Insulin</u>

2. Lactate formed in muscles can be utilized through

(A) Rapoport-Luebeling cycle (B) Urea cycle

<u>(C) Cori's cycle</u> (D) Citric acid cycle

3. Glucose-6-phosphatase is not present in

(A) Liver and kidneys (B) Kidneys and muscles

(C) Kidneys and adipose tissue <u>(D) Muscles and adipose tissue</u>

4. Fructose-2, 6-biphosphate is formed by the action of

(A) Phosphofructokinase-1 <u>(B) Phosphofructokinase-2</u>

(C) Fructose biphosphate isomerase (D) Fructose-1, 6-biphosphatase

5. Cori's cycle transfers

(A) Glucose from muscles to liver (B) Lactate from muscles to liver

(C) Lactate from liver to muscles (D) Pyruvate from liver to muscles

6. Fatty acids cannot be converted into carbohydrates in the body as the following reaction is not possible.

(A) Conversion of glucose-6-phosphate into glucose

(B) Fructose 1, 6-bisphosphate to fructose-6- phosphate

(C) Transformation of acetyl CoA to pyruvate

(D) Formation of acetyl CoA from fatty acids

7. The 4 rate limiting enzymes of gluconeogenesis are

(A) Glucokinase, Pyruvate carboxylae, phosphoenol pyruvate carboxykinase and glucose-6-phosphatase

(B) Pyruvate carboxylase, phosphoenol pyruvate carboxykinase, fructose1,6 diphosphatase and glucose-6-phosphatase

(C) Pyruvate kinase, pyruvate carboxylase, phosphoenol pyruvate carboxykinase and glucose-6-phosphatase

(D) Phospho fructokinase, pyruvate carboxylase, phosphoenol pyruvate carboxykinase and fructose 1, 6 diphosphatase

8. Formation of one molecule of glucose from pyruvate requires

(A) 4 ATP, 2 GTP and 2 NADH

(B) 3 ATP, 2 GTP and 2 NADH

(C) 4 ATP, 1 GTP and 2 NADH

(D) 2 ATP, 2 GTP and 2 NADH

9- Gluconeogenesis is useful for

(A) maintaining blood glucose level

(B) avoiding low blood glucose level

(C) both A and B

(D) Maintain respiration rate

10-The enzyme which catalyzes the conversion of pyruvate to oxaloacetate

(A) Pyruvate carboxylase

(B) Pyruvate dehydrogenase

(C) Pyruvate kinase

(D) Phosphofructokinase-1


Thank You