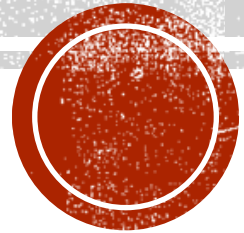
Gluconeogenesis



Students Learning Outcomes

❖ By the end of this lecture, the students should be able to:

1. Recognize the importance of gluconeogenesis
2. Describe the steps of gluconeogenesis
3. Enumerate the substrates of gluconeogenesis
4. Identify the regulating factors of gluconeogenesis
5. Differentiate between glycolysis and gluconeogenesis
6. Illustrate Cori cycle, Glucose alanine cycle

Content

Gluconeogenesis

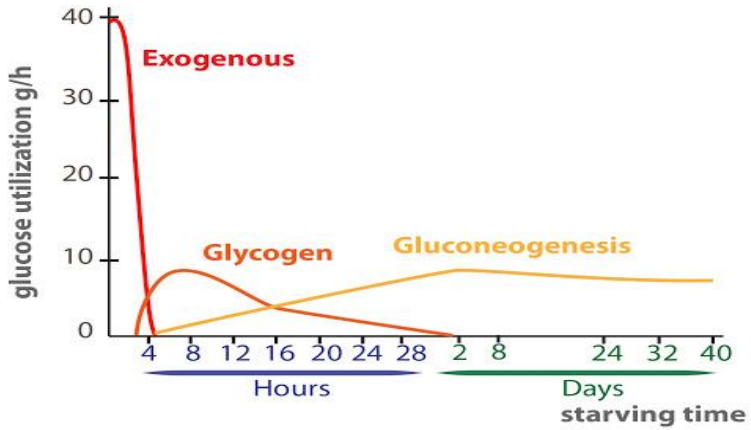
1. Definition
2. Site
3. Phases (Steps)
4. Products
5. Importance
6. Regulation

Gluconeogenesis: Overview

Gluconeogenesis

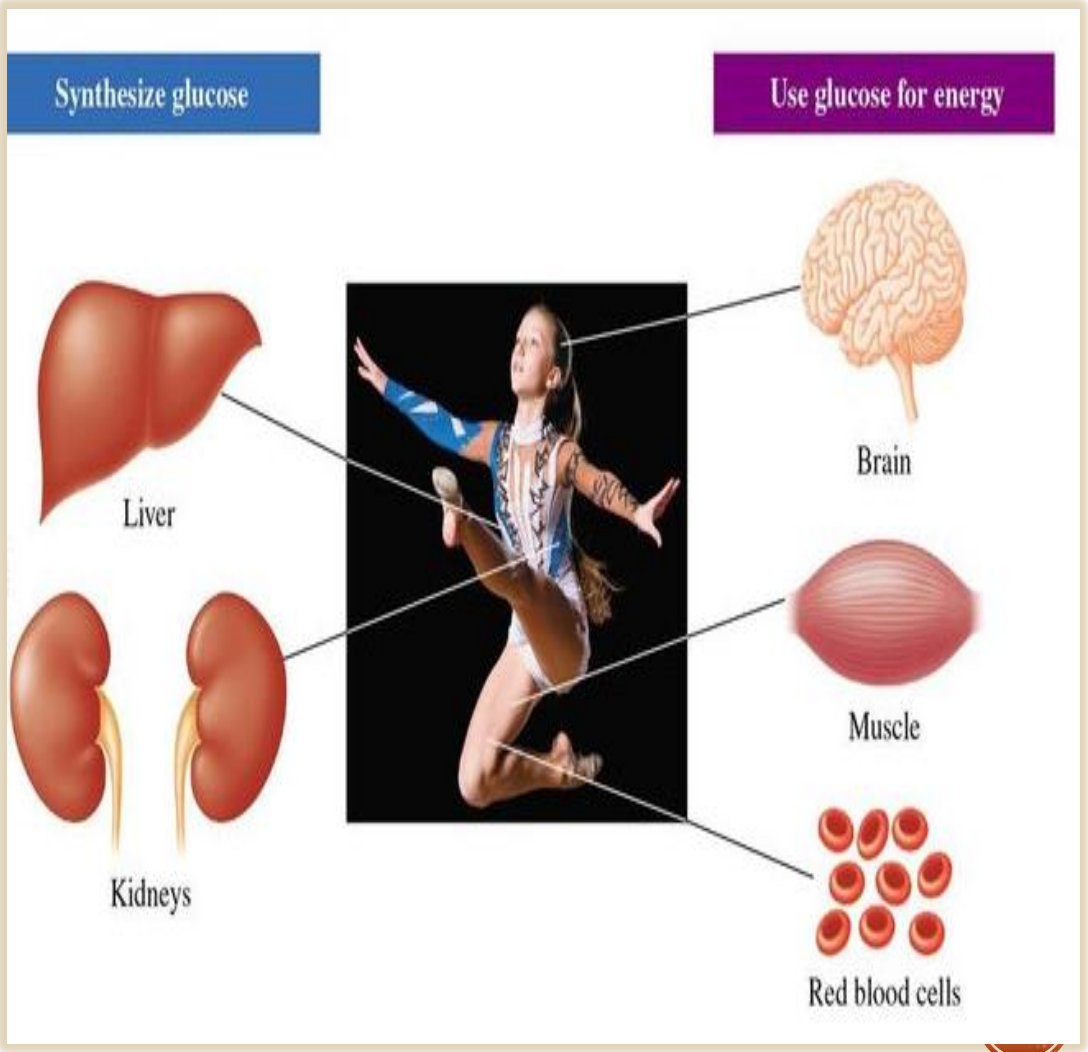
Glucose new synthesis

- **Synthesis of new glucose from (non- carbohydrate sources).**



Gluconeogenesis: Overview

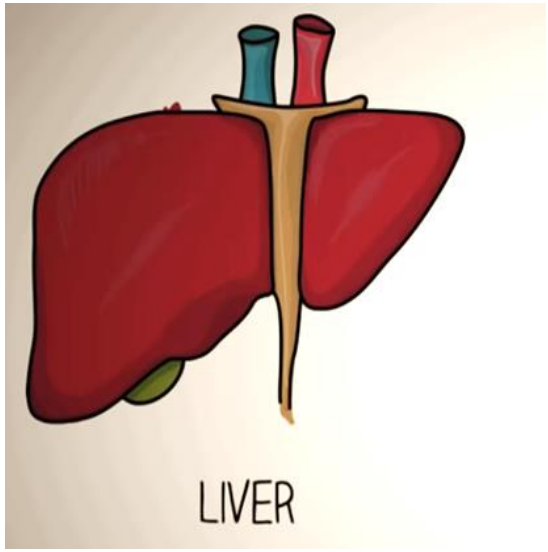
- **Its main function is to** supply blood glucose in case of CHO deficiency (fasting, starvation and low CHO diet).
- **This is especially important for** tissues requiring continuous supply of glucose as a source of energy (eg: Brain, RBCs, skeletal muscle…etc)

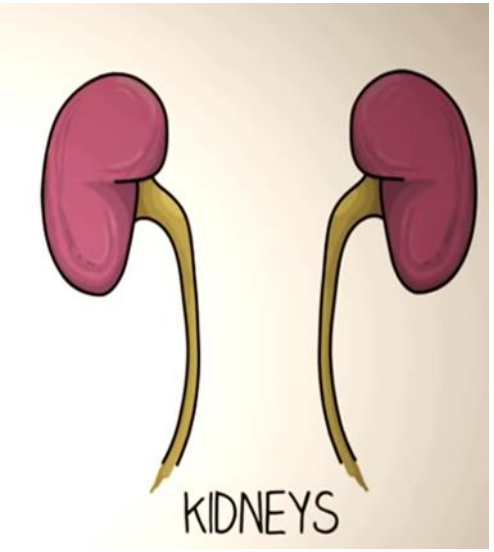


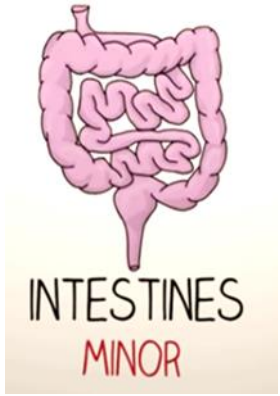
Gluconeogenesis: Overview

❑Sites:

- **Liver and kidney** (main site)
- Intestine (minor site)
- Cytoplasm, Mitochondria

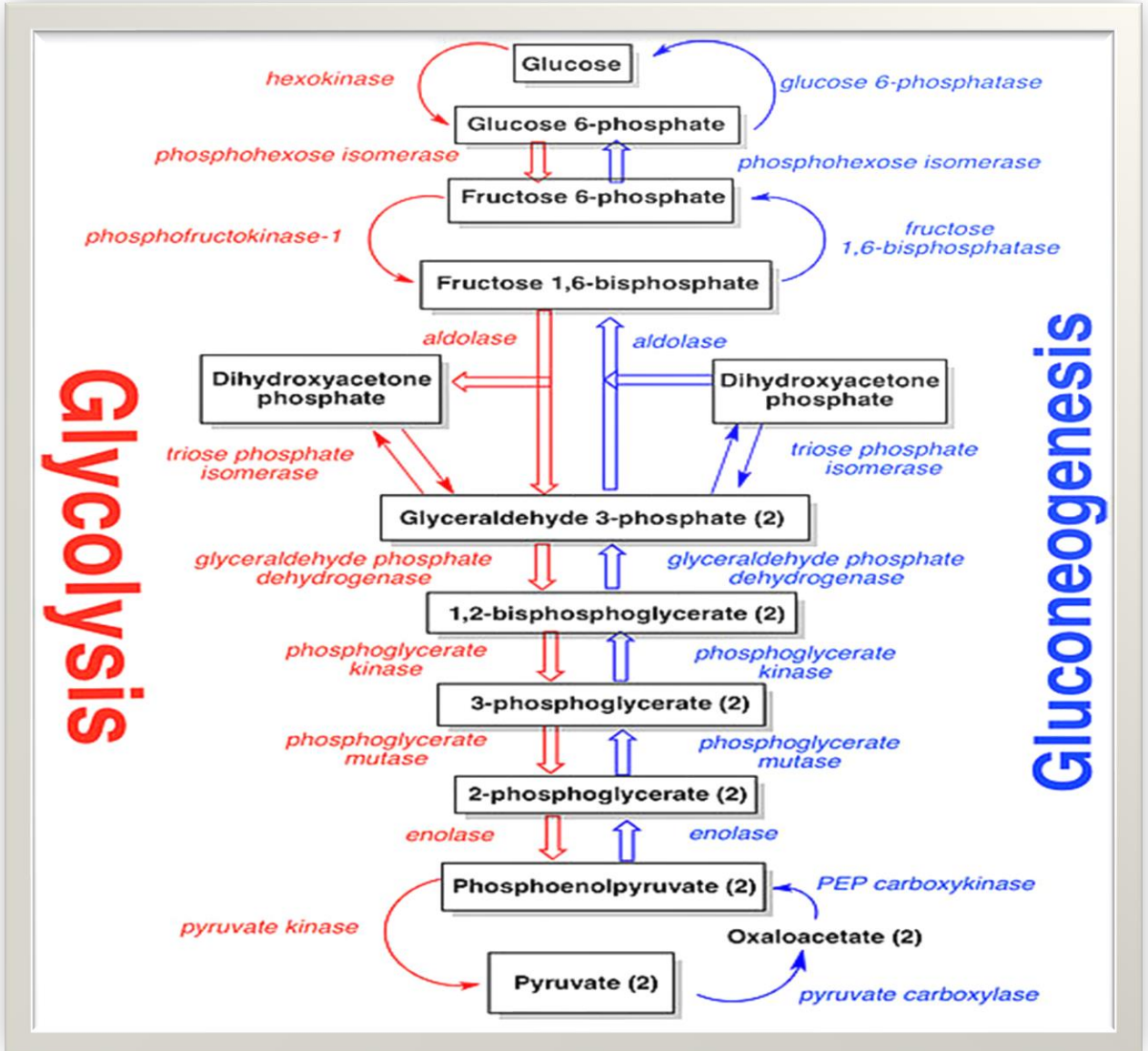






Gluconeogenesis: Steps
Reversal of Glycolysis?

- 7 of the reactions of glycolysis are reversible & are shared between glycolysis and gluconeogenesis
- However 3 of the reactions of glycolysis are irreversible

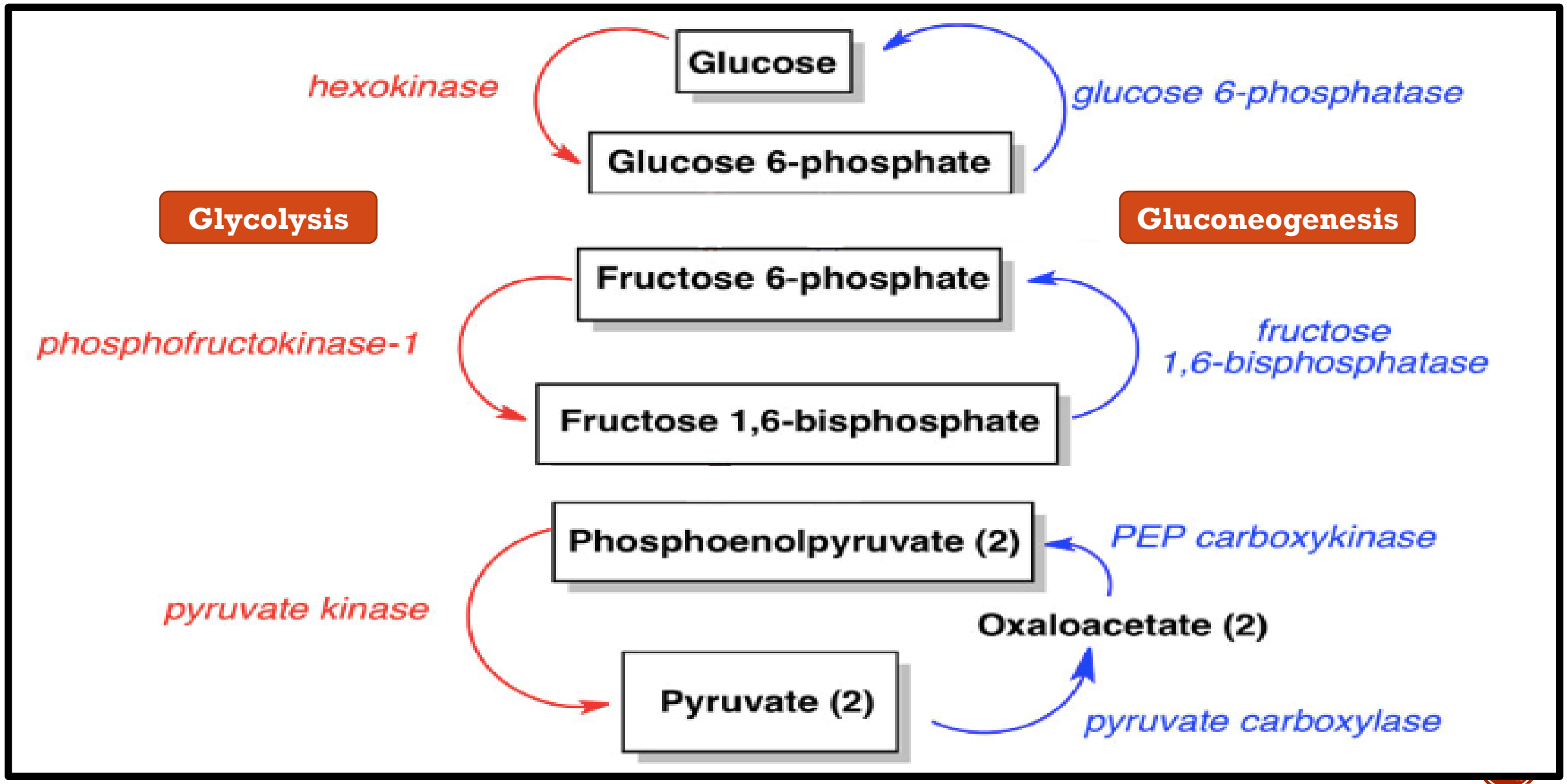


Idea of gluconeogenesis

- Gluconeogenesis is the **reversal of glycolysis**
- Except for the **three irreversible kinases**.
  - **1- Pyruvate Kinase**
  - **2- Phosphofructokinase-1**
  - **3- Glucohkinase (Hexokinase).**

The three irreversible enzymes of glycolysis are overcome in gluconeogenesis by 4 enzymes as follow

Glycolysis (3 steps, 3 enzymes)	Overcome by	Gluconeogenesis (4 steps, 4 enzymes)
1- Glucokinase	→	Glucose-6-phosphatase
2- Phosphofructokinase- 1	→	Fructose 1,6 bisphosphatase
3- Pyruvate kinase	→	1- Pyruvate carboxylase 2- Phosphoenol pyruvate carboxykinase (Dicarboxylic acid shuttle)


Glucose
hexokinase
glucose 6-phosphatase
Glucose 6-phosphate
Glycolysis
Gluconeogenesis
Fructose 6-phosphate
phosphofructokinase-1
fructose
1,6-bisphosphatase
Fructose 1,6-bisphosphate
Phosphoenolpyruvate (2)
PEP carboxykinase
pyruvate kinase
Oxaloacetate (2)
Pyruvate (2)
pyruvate carboxylase

Dicarboxylic acid shuttle

Cytoplasm

Pyruvate

❑ Pyruvate carboxylase is a mitochondrial enzyme, while other enzymes of gluconeogenesis are cytoplasmic.

Mitochondrial membrane

Pyruvate

Pyruvate carboxylase

Oxalacetate

- Malate
- Aspartate

❑Malate (Aspartate) shuttle help transport OAA outside the mitochondria

Cytoplasm

- Malate
- Aspartate

Oxalacetate

PEP carboxykinase

Phosphoenol pyruvate (PEP)

Substrates (sources) for gluconeogenesis

1- Glucogenic amino acids eg. **Alanine: (via Glucose alanine cycle)**

2- Lactate: (via Cori's cycle).

3- Propionate

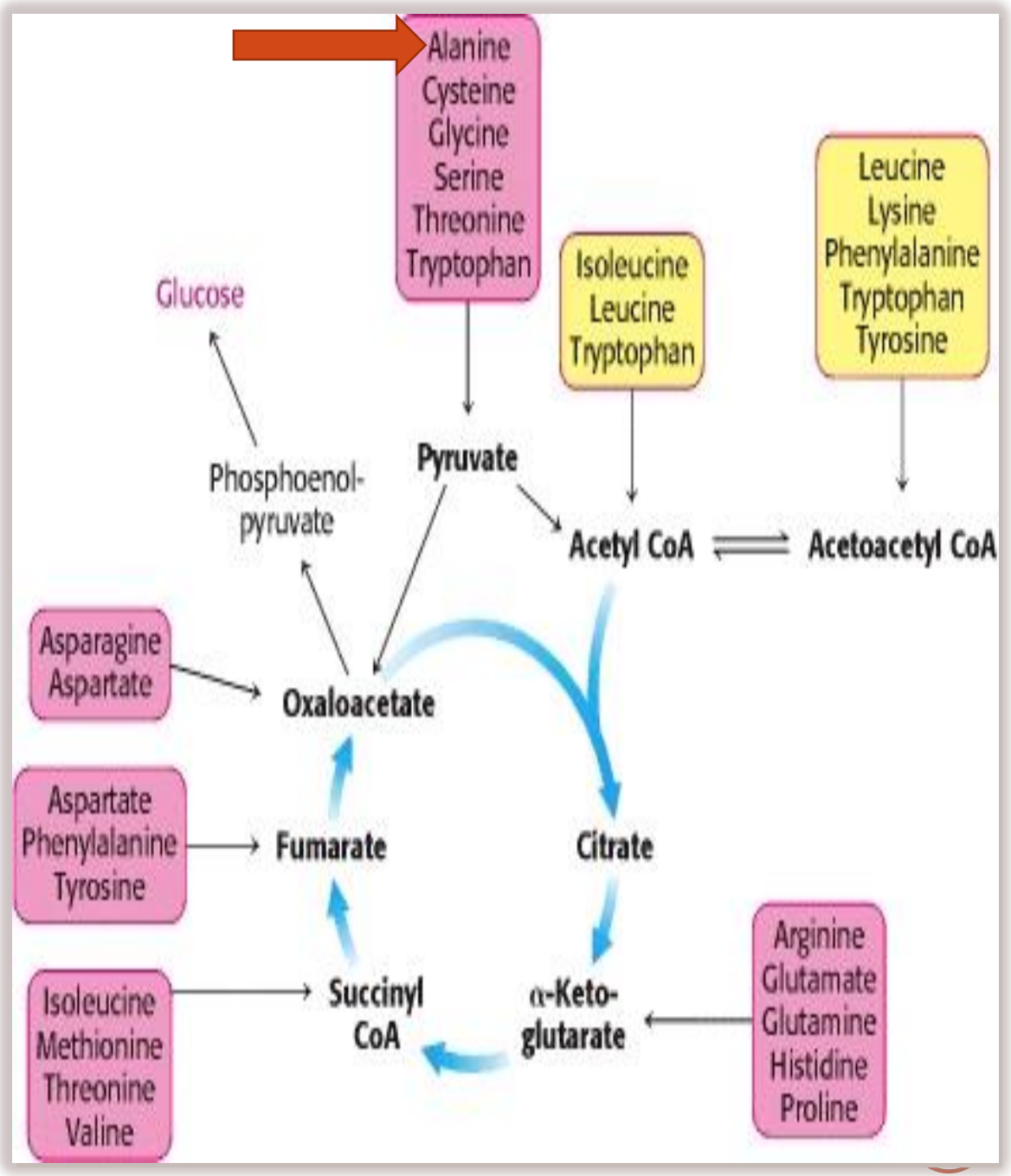
4- Glycerol

1.Glucogenic amino acids

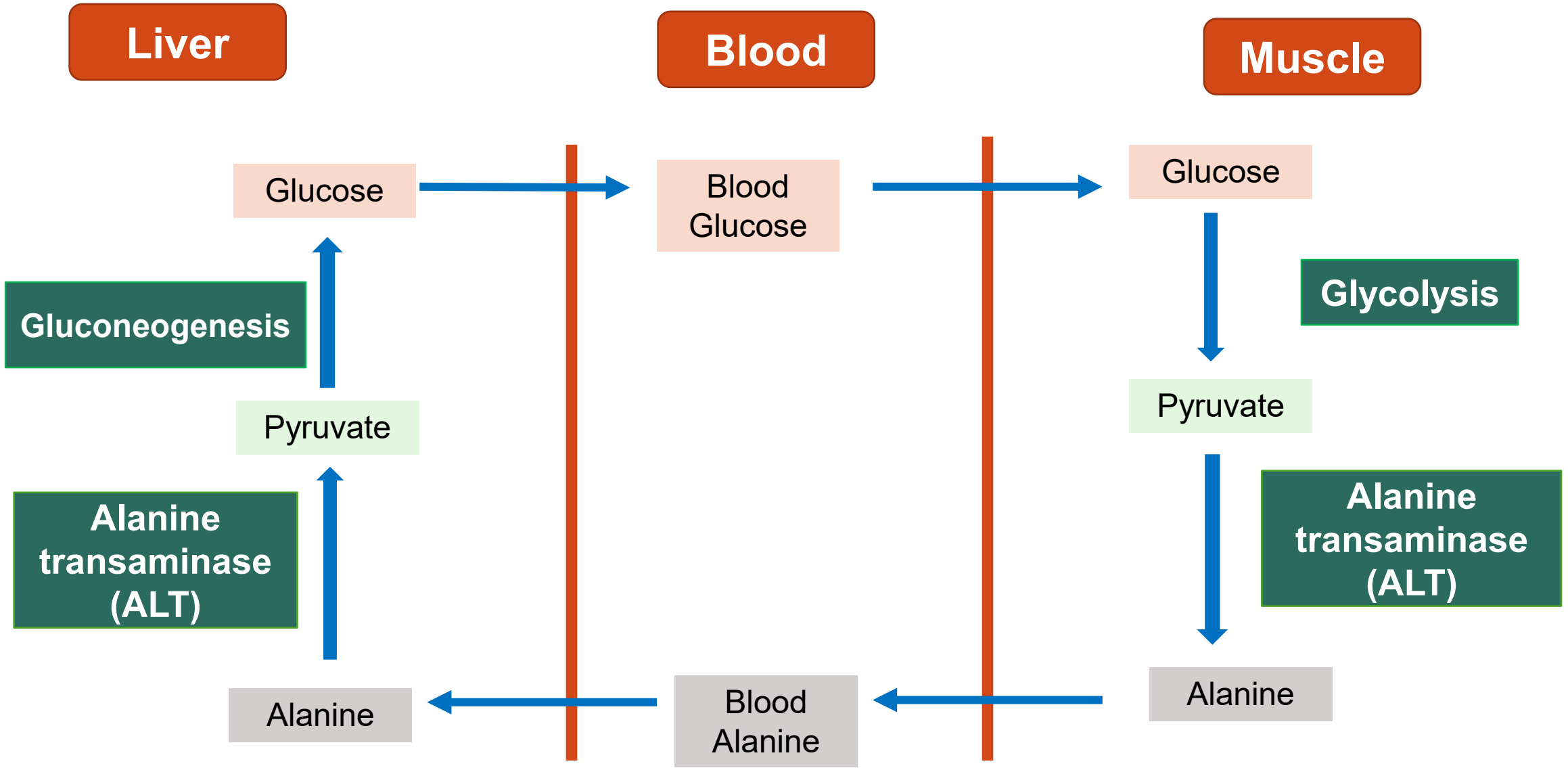
All amino acids are glucogenic (gives pyruvate or oxalacetate or other intermediates of Krebs' cycle) **except lysine and leucine**

After 18 hours fasting

(depletion of glycogen)→ protein degraded to give amino acids that become the main source of blood glucose.



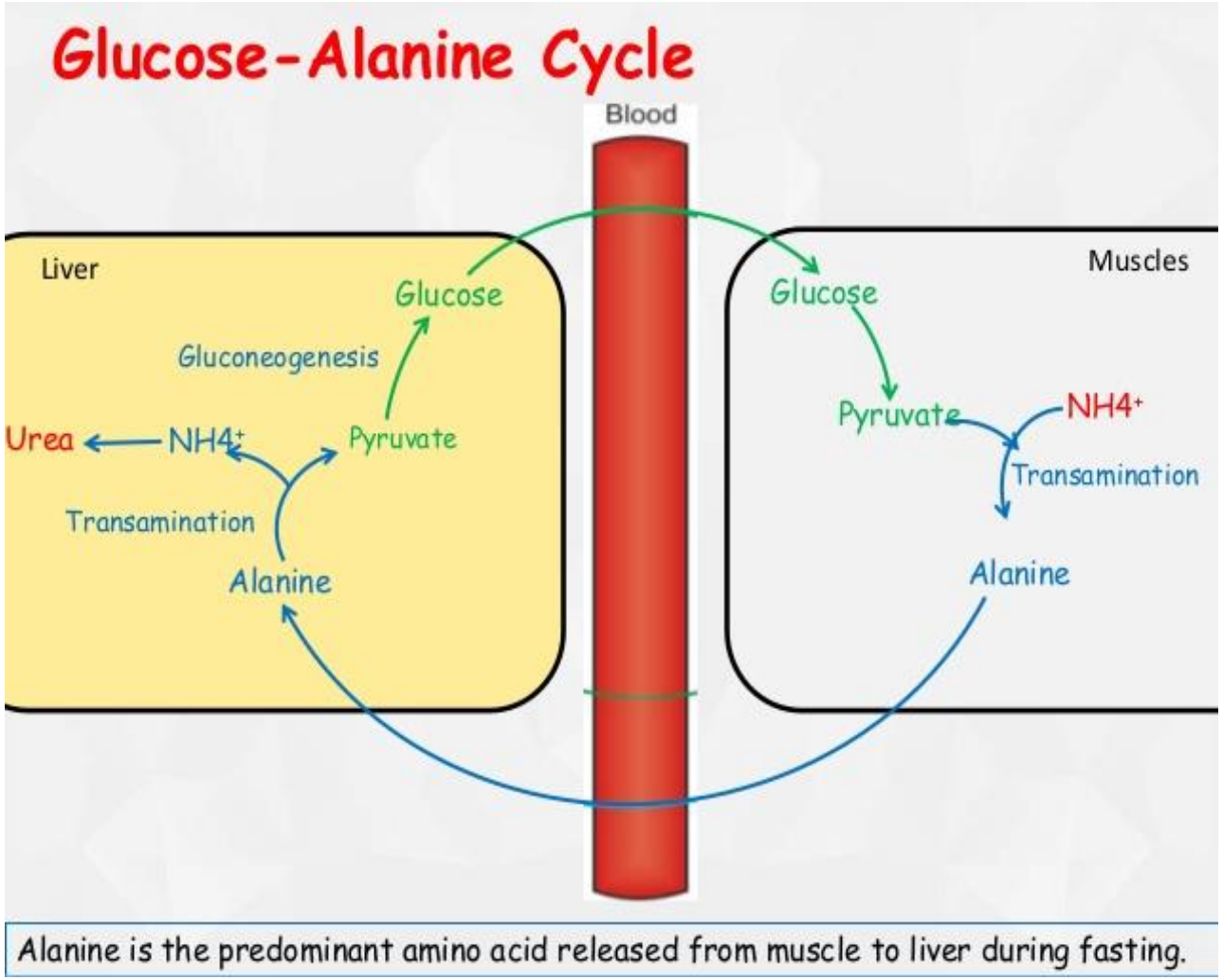
2.Alanin (Glucose-alanine cycle)



2.Alanin (Glucose-alanine cycle)

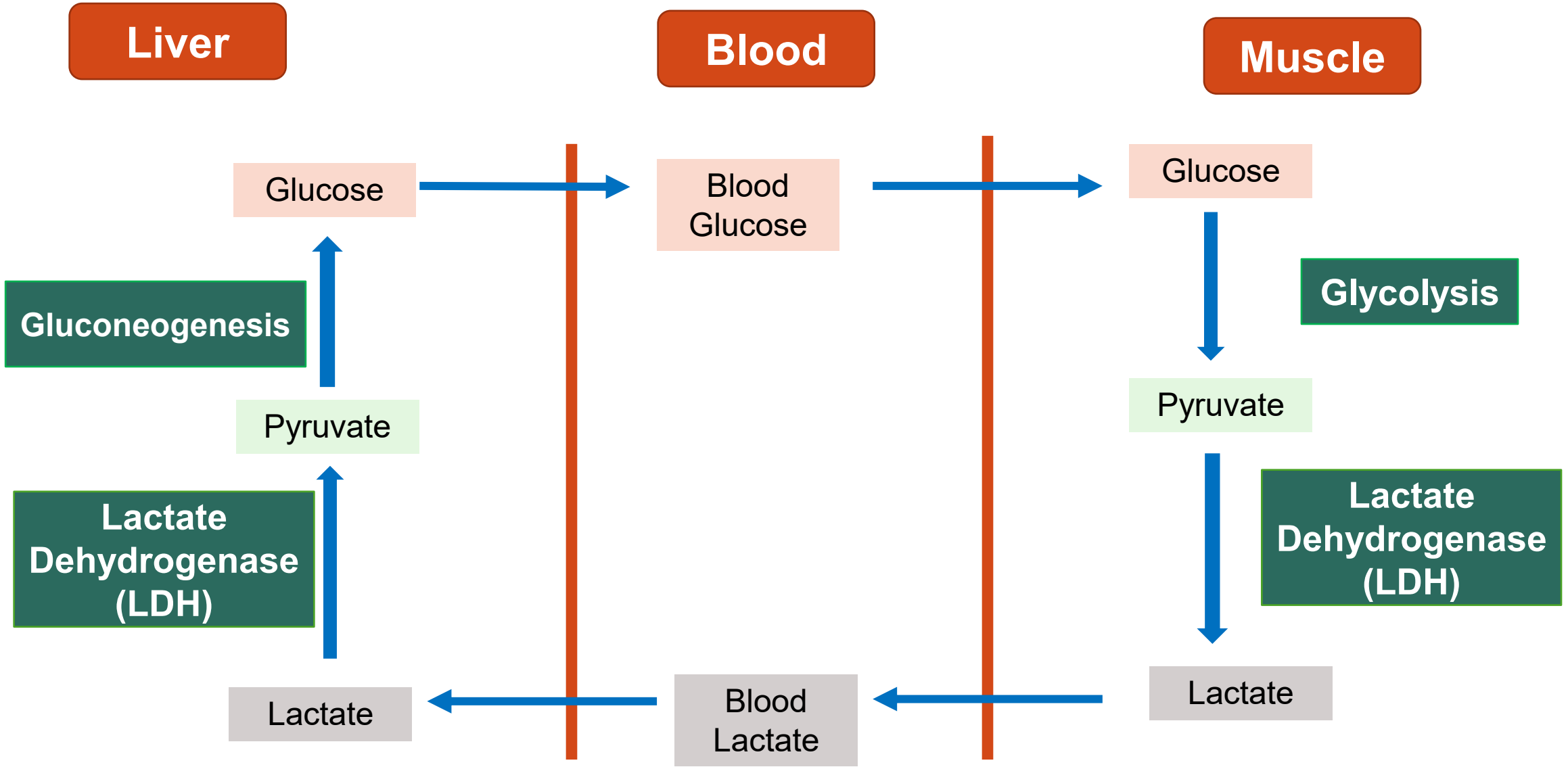
Biological significance:

- It acts as an alternative pathway for pyruvate other than lactate (prevent accumulation of lactate).
- It supplies contracting muscle with glucose for ATP production.
- Disposal of ammonia produced from protein catabolism through formation of urea which excreted in urine



3.Lactate (Cori cycle)

Lactic acids produced by RBCs & contracting muscles is recycled and used to synthesis glucose



3.Lactate (Cori cycle)

Biological significance:

- It supplies red cell and contracting muscle with glucose for ATP production.
- It remove lactate from the muscle (prevent lactic acidosis).
- Oxidation of reduced NAD.

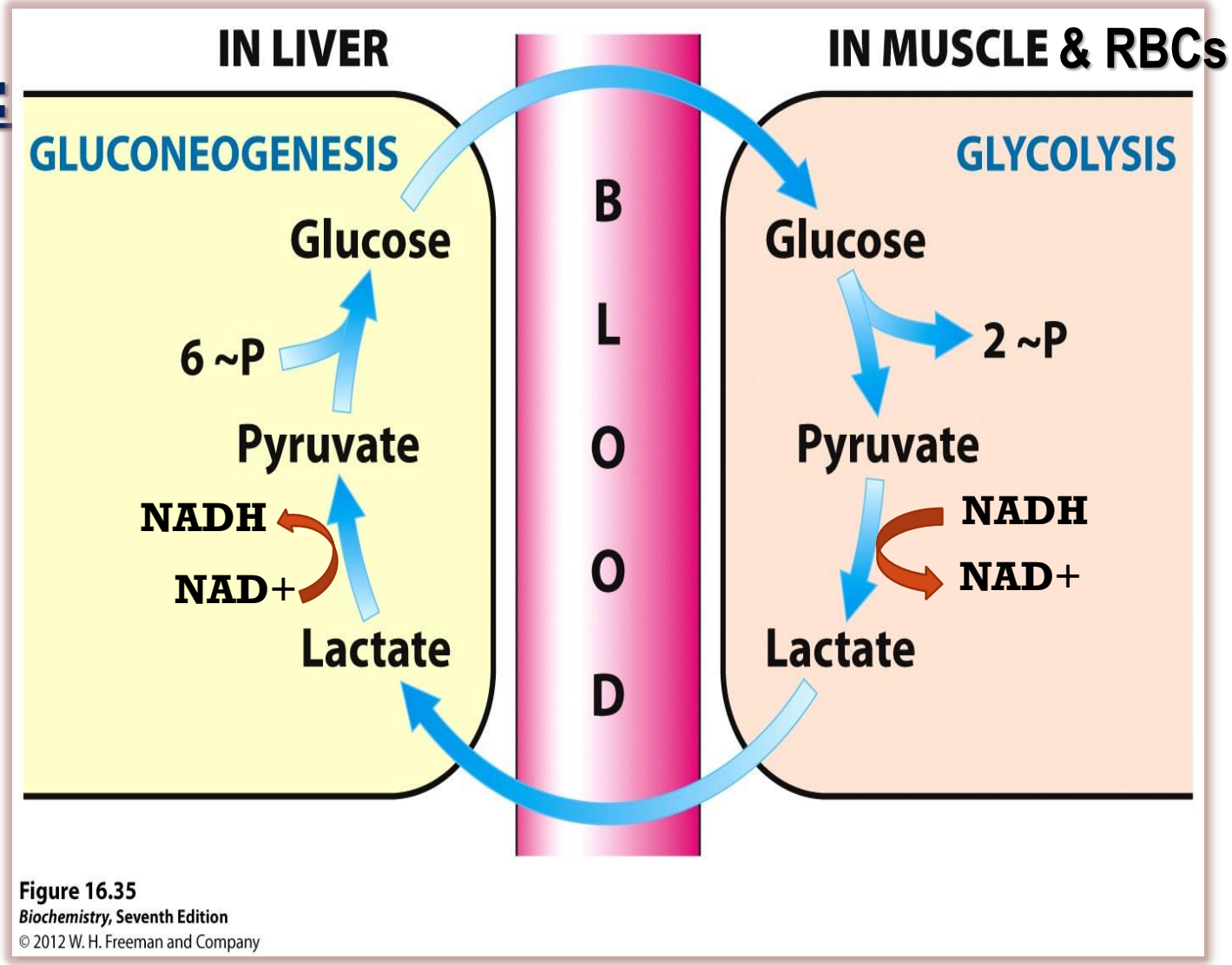


Figure 16.35
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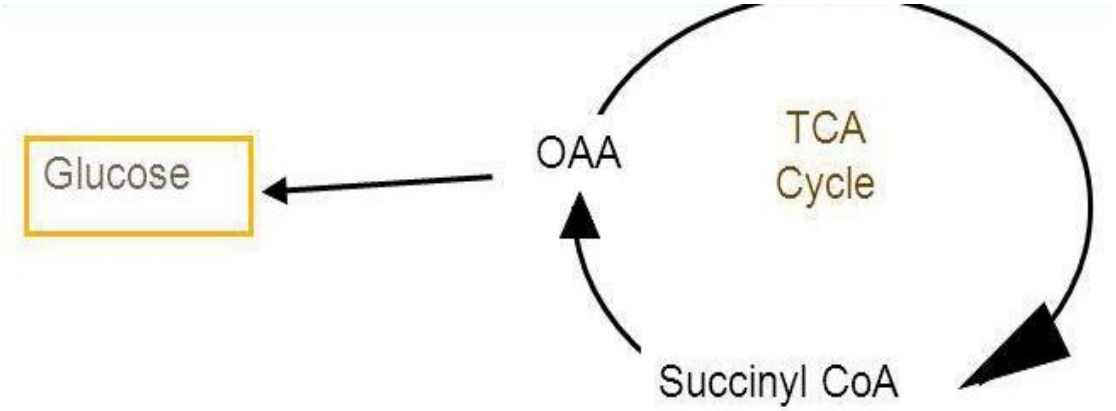
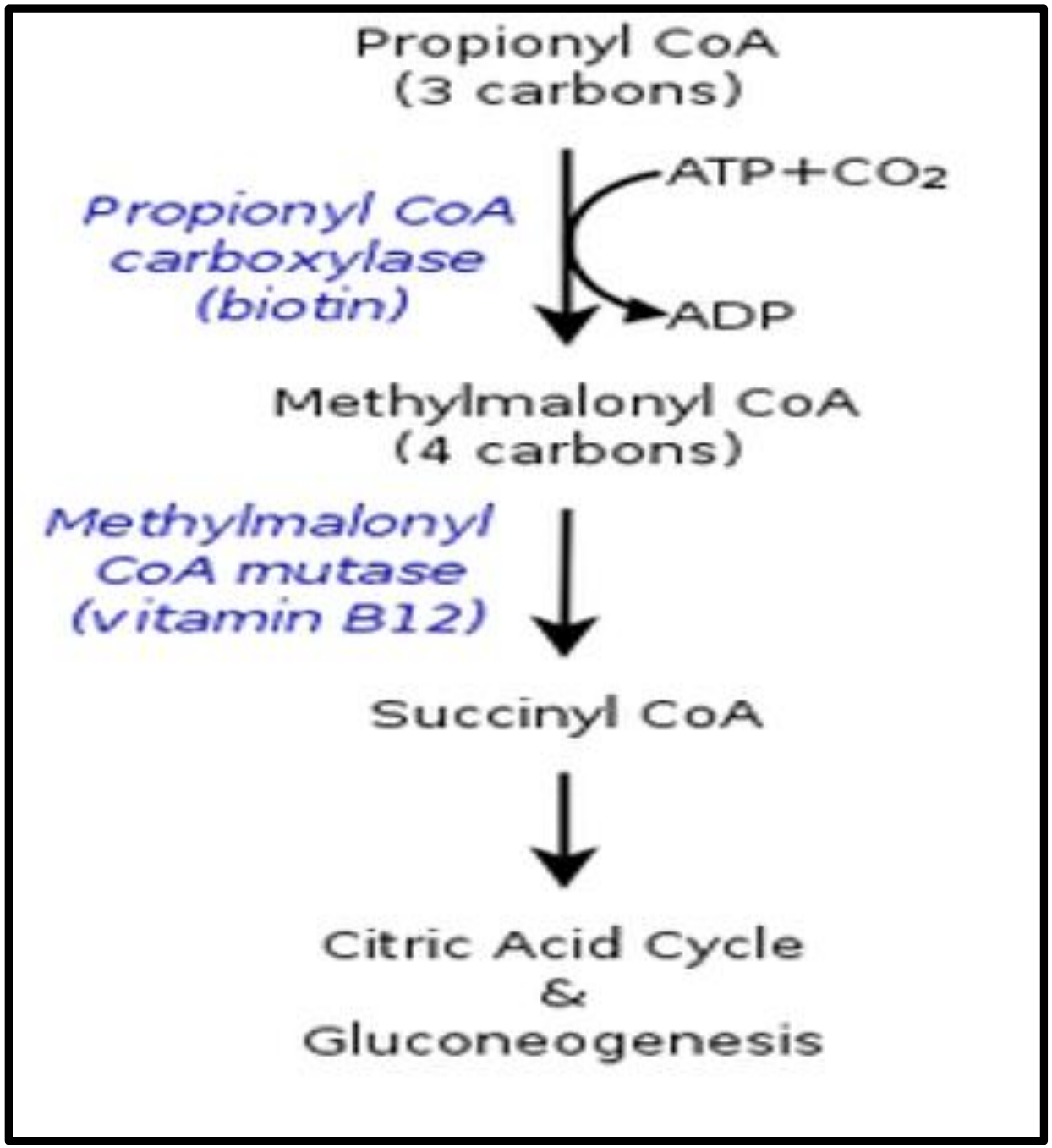
4. Propionate

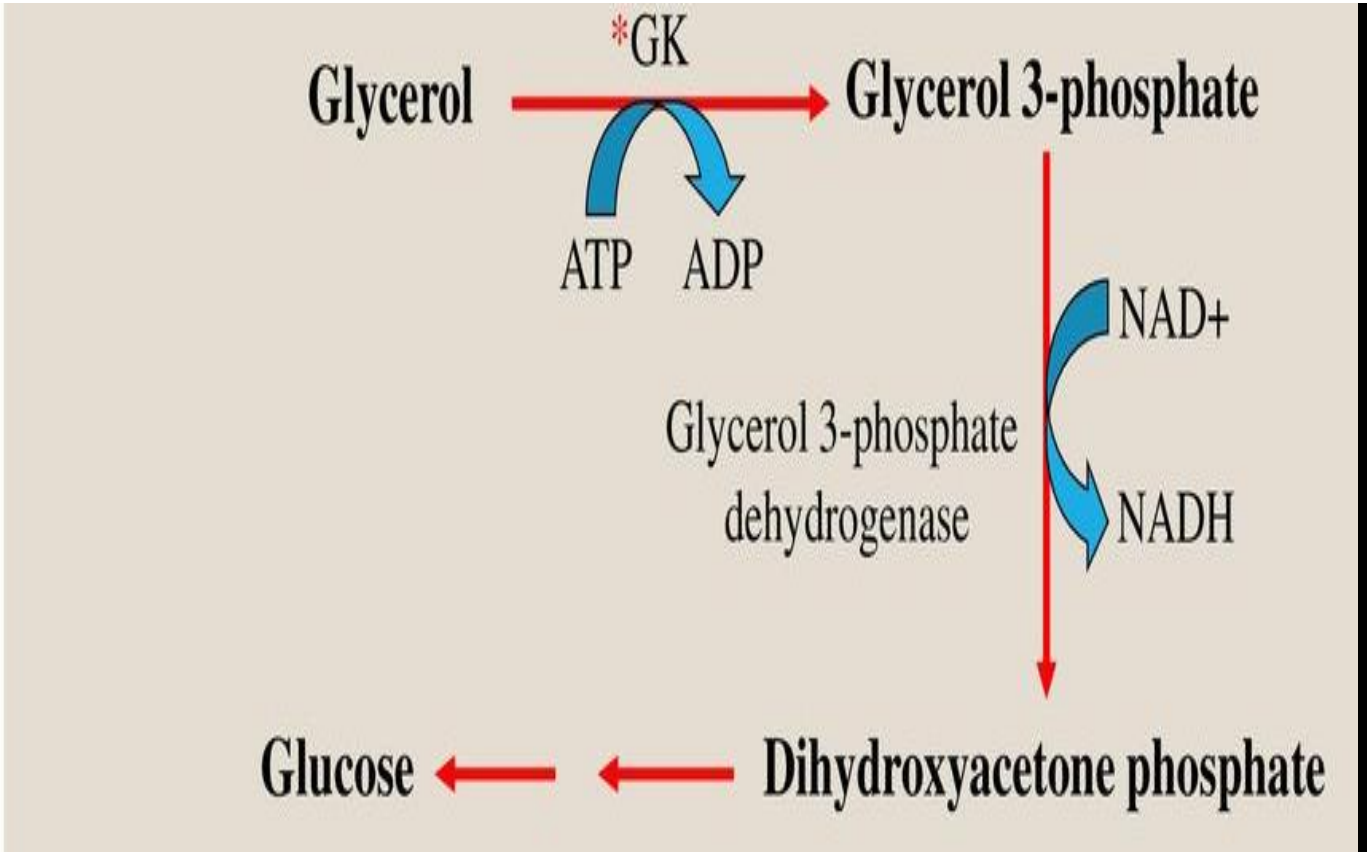
- Propionate is converted to **succinyl COA** → **Krebs** →OAA

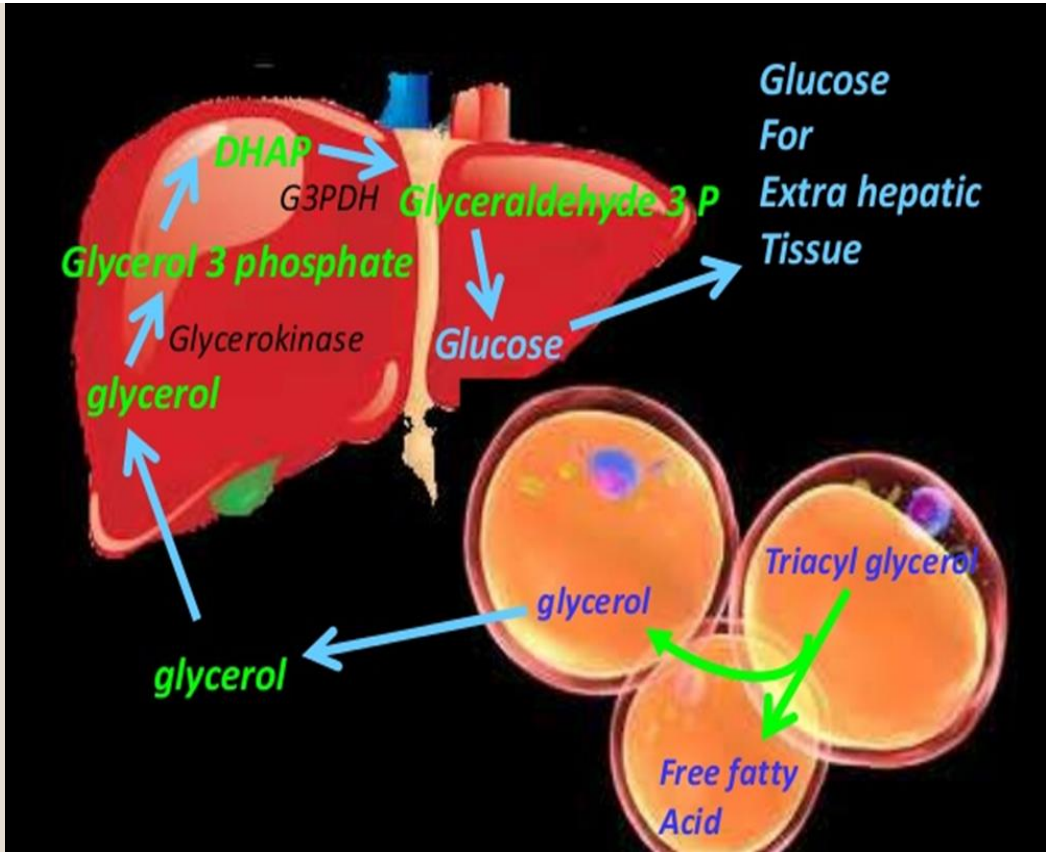




5. Glycerol

Glycerol is derived from **lipids**





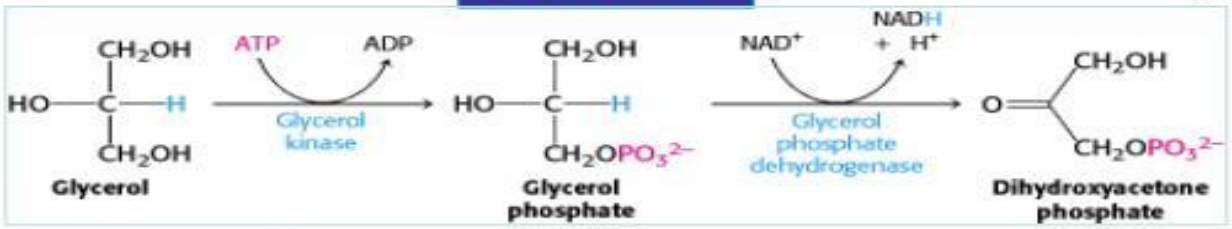
* GK= Glycerol kinase is present only in **liver and kidney**.

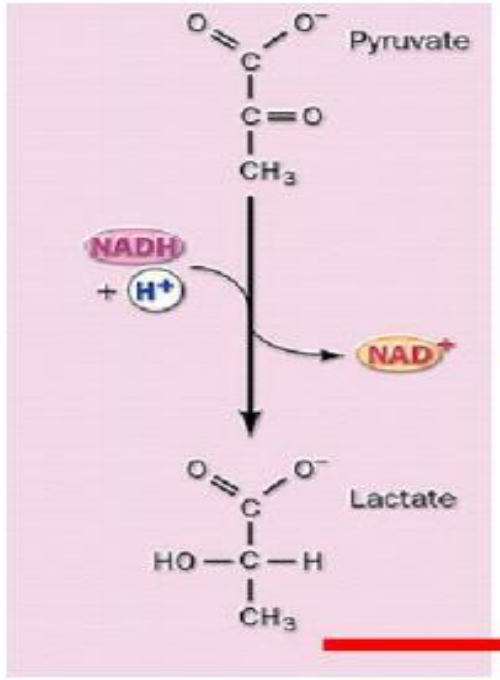
Noncarbohydrate precursors of glucose:

Triglycerols

Fatty acids

glycerol

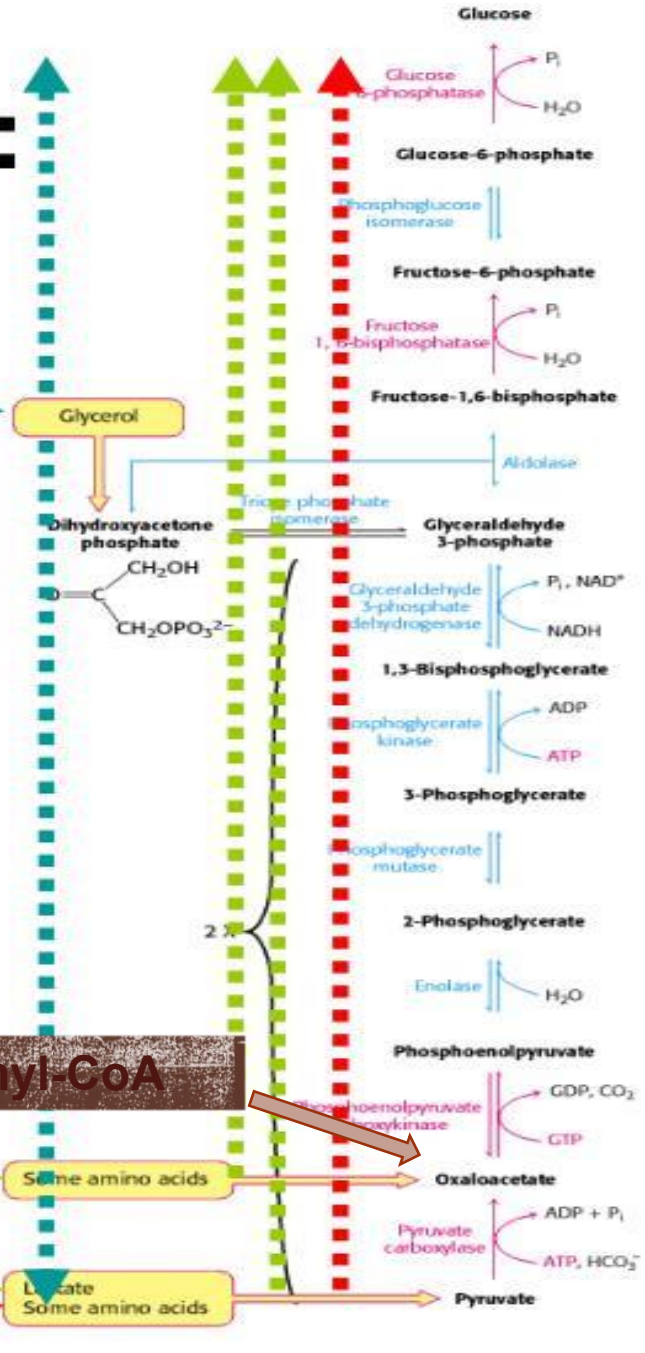


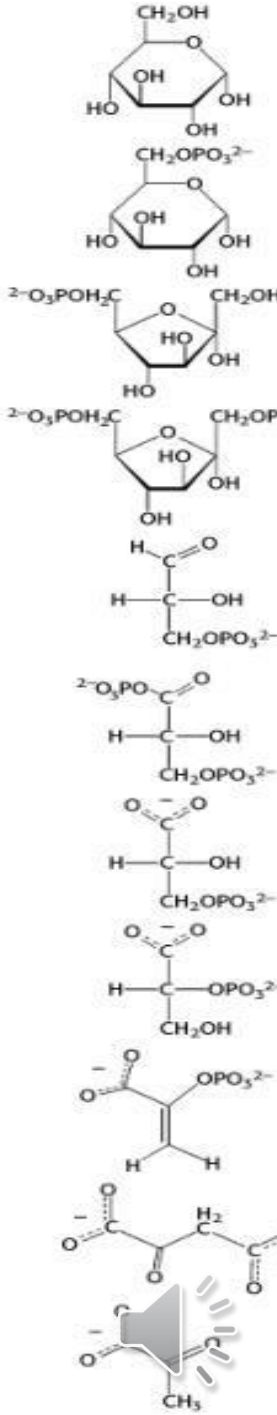


Dietary & muscle proteins

Amino acids

propoinyl-CoA





Regulation of gluconeogenesis

- ✓ **The key regulatory (rate limiting) enzymes of** gluconeogenesis are those used in the 3 **bypass steps.**
  1. **Pyruvate carboxylase**
  2. **Phosphoenolpyruvate carboxykinase**
  3. **Fructose 1,6 bisphosphatase**
  4. **Glucose 6 phosphatase**

- ✓ **Glycolysis and gluconeogenesis** are under **reciprocal regulation**

- ✓ When **glycolysis** is **turned on**, **gluconeogenesis** should be **turned off and vice versa.**

✓ The balance between glycolysis and gluconeogenesis is under both **hormonal (insulin/Glucagon ratio) and control according to energy level.**

I. Hormonal regulation of gluconeogenesis:

Insulin released **after carbohydrate meal or in (Hyperglycemia)** → **decreases** rate of synthesis of gluconeogenic key enzymes

(***at the same time increases the glycolytic key enzymes).***

Anti-insulin hormones (glucagon) released in case of **carbohydrate deficiency or Hypoglycemia→ increase** the rate of synthesis of gluconeogenic key enzymes

(at the same time decrease the glycolytic key enzymes).

II. Regulation according to the energy level

All rate-limiting enzymes are **regulated by "energy" signals** (ATP, AMP, etc.)

a) When **energy** status of cell is **high (high ATP)** → glycolysis **turned off** → **pyruvate is used for gluconeogenesis** → synthesis and storage of glucose.

a) When **energy** status is low **(high ADP)** → glycolysis **turned on** → glucose rapidly degraded (oxidized in glycolysis & TCA) to provide energy.

MCQs

Gluconeogenesis mainly takes place in:

a) Stomach
b) Liver
c) Heart
d) Intestine
e) spleen

MCQs

Which one of the following is a rate-limiting enzyme of gluconeogenesis?

a) Hexokinase
b) Phsophofructokinase 1
c) Pyruvate carboxylase
d) Pyruvate kinase
e) Enolase

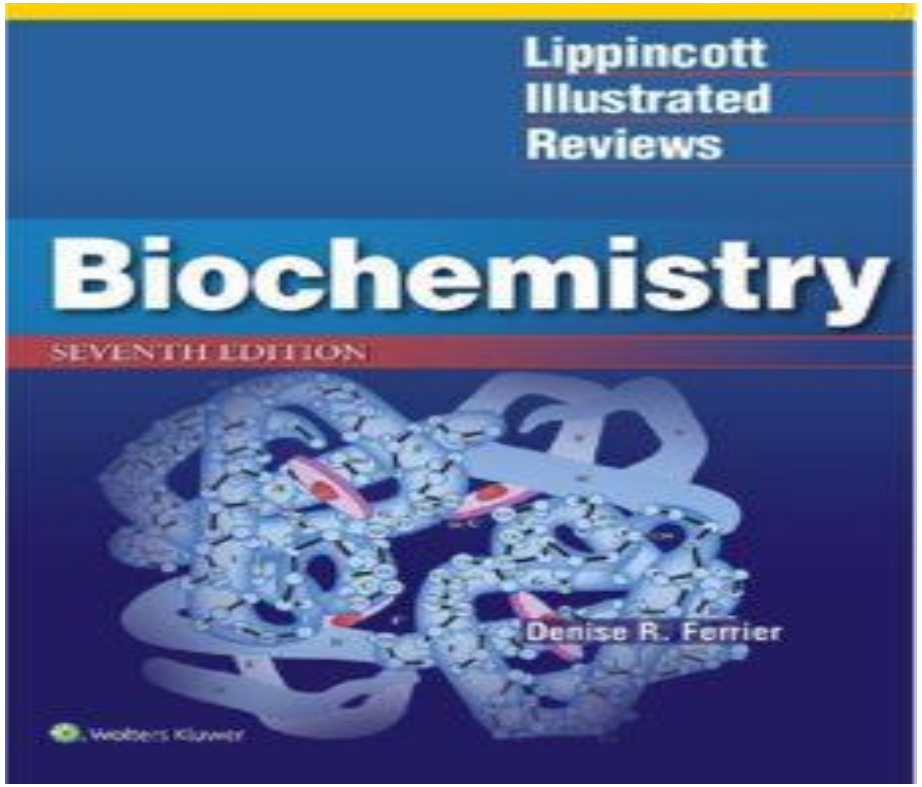
MCQs

The hormone responsible for stimulating gluconeogenesis is:

a) Glucagon
b) Insulin
c) Melatonin
d) TSH
e) Prolactin


Life
isn't about
finding yourself.
...
Life
is about
creating yourself.

References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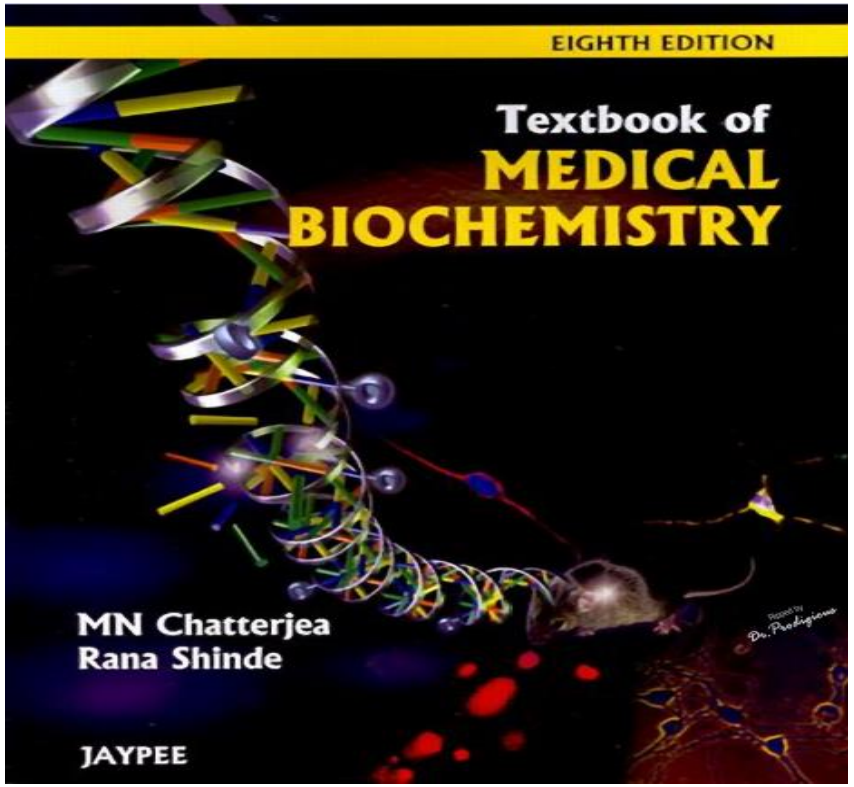
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