UNIVERSITY OF BASRAH

AL-ZAHRAA MEDICAL COLLEGE

MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

The module: Metabolism

Session 3, Lecture 2

Duration : 1 hr

Tricarboxylic acid cycle and gluconeogenesis

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Marks Essentials of Medical Biochemistry.
Ganong's Review of Medical Physiology .
For more discussion, questions or cases need help please post to the session group

Learning outcomes

- Describe the Role of TCA in metabolism (LO 1)
- Explain How TCA is regulated (LO 2)
- Explain WHY and HOW glucose is produced from non carbohydrate sources (LO 3)

Citric acid cycle (LO1)

- Also known as Krebs cycle, or tricarboxylic acid cycle.
- TCA cycle essentially involves the oxidation of acetyl CoA to CO2 and H2O.
- TCA cycle is the most important central pathway connecting almost all the individual metabolic pathways.
- The TCA cycle is the final common oxidative pathway for carbohydrates, fats, amino acids.

Citric acid cycle (LO1)

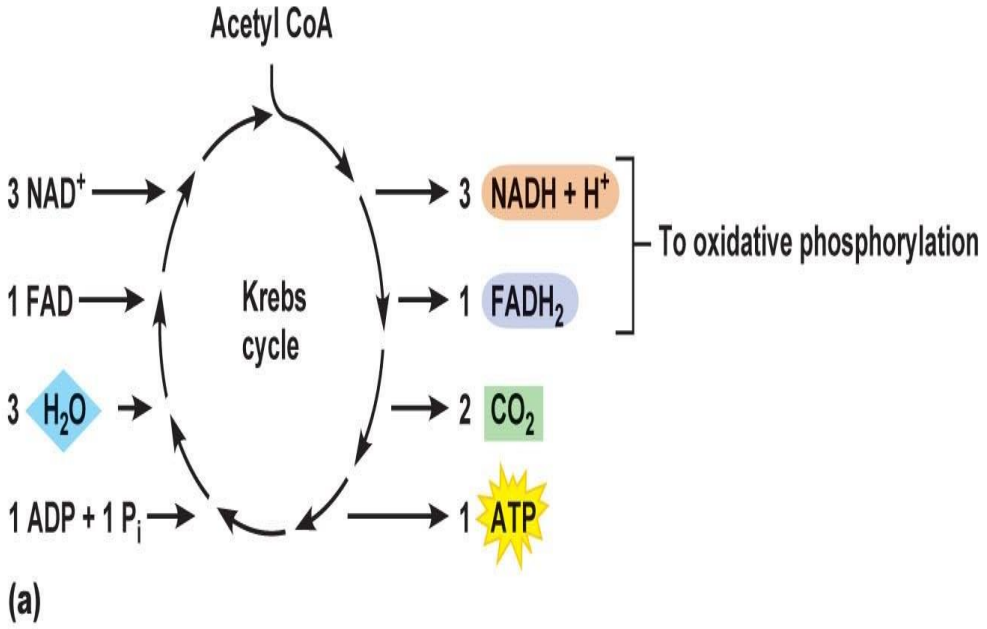
- TCA cycle supplies energy & also provides many intermediates required for the synthesis of amino acids, glucose, heme etc.

- the reactions of the citric acid cycle take place inside mitochondria, in contrast with those of glycolysis, which take place in the cytosol.
- Any genetic defect in the reactions of TCA would be lethal ??

Krebs cycle products (LO1)

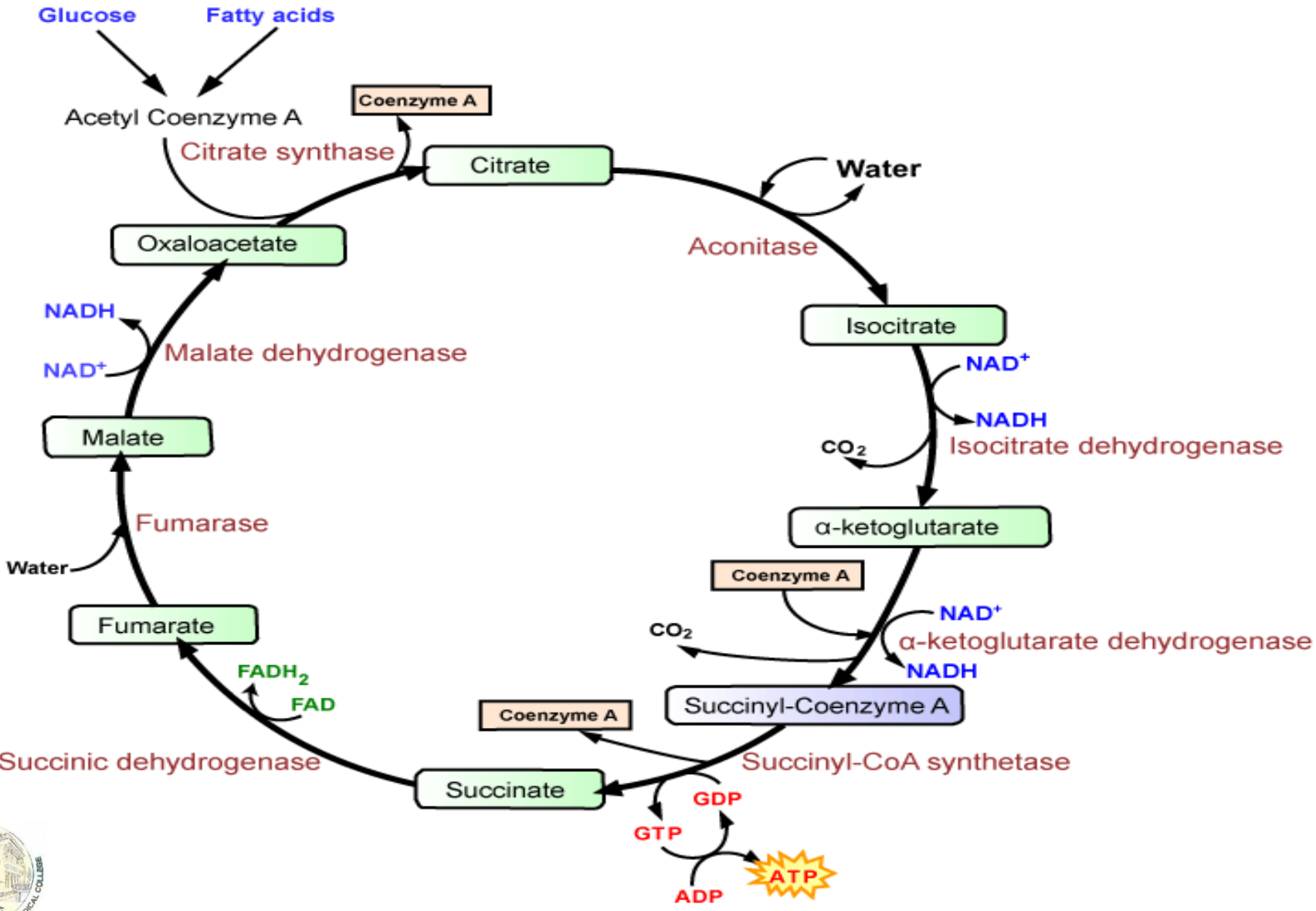
- **In a single turn of the cycle (for one molecule of acetyl CoA):**

- **1 GTP or ATP**
- **3 NADH.**
- **1 $FADH_2$.**
- **2 CO_2 (carbon dioxide)**



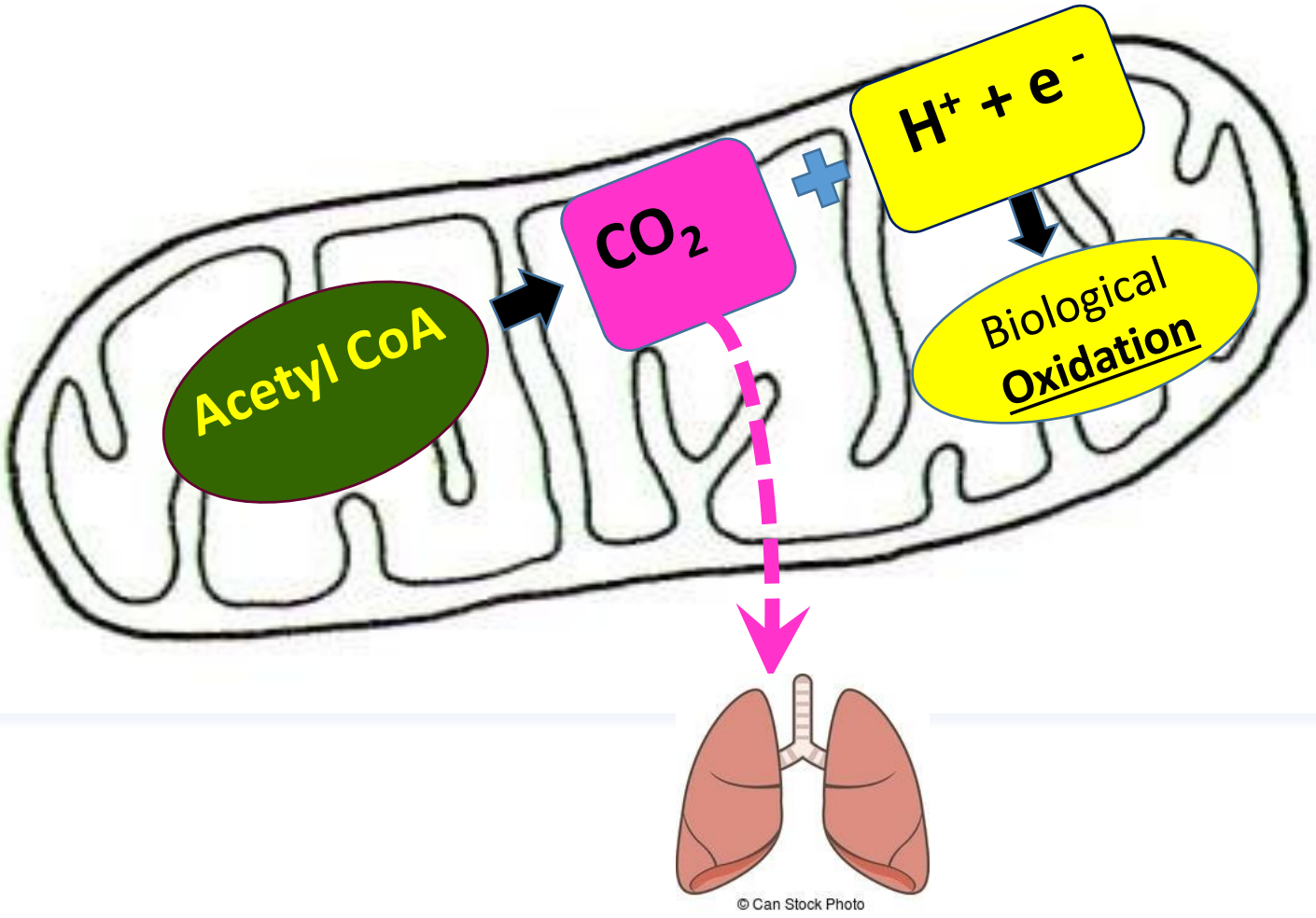
LO1

KREBS CYCLE (CITRIC ACID CYCLE)



Net reaction

$$\text{Acetyl CoA} + 3NAD^+ + FAD \longrightarrow 2CO_2 + CoASH + 3NADH + 3H^+ + GDP + P_i + 2H_2O \quad + FAD\,(2H) + GTP$$



Energy yield per Acetyl co A per turn of cycle (LO1)

- It's true that the citric acid cycle doesn't produce much ATP . However, it can make a lot OF {ATP} *indirectly*, by way of the NADH and FADH2 it generates. These electron carriers will connect with the last portion of cellular respiration, depositing their electrons into the electron transport chain(ETC) to drive synthesis of ATP molecules through oxidative phosphorylation.

Energy yield per Acetyl co A per turn of cycle (LO1)

- Oxidation of 3 NADH by ETC coupled with oxidative phosphorylation results in the synthesis of 9ATP.
- 1FADH2 leads to the formation of 2ATP.
- 1 ATP or GTP
- Thus, a total of 12 ATP are produced from one acetyl CoA.

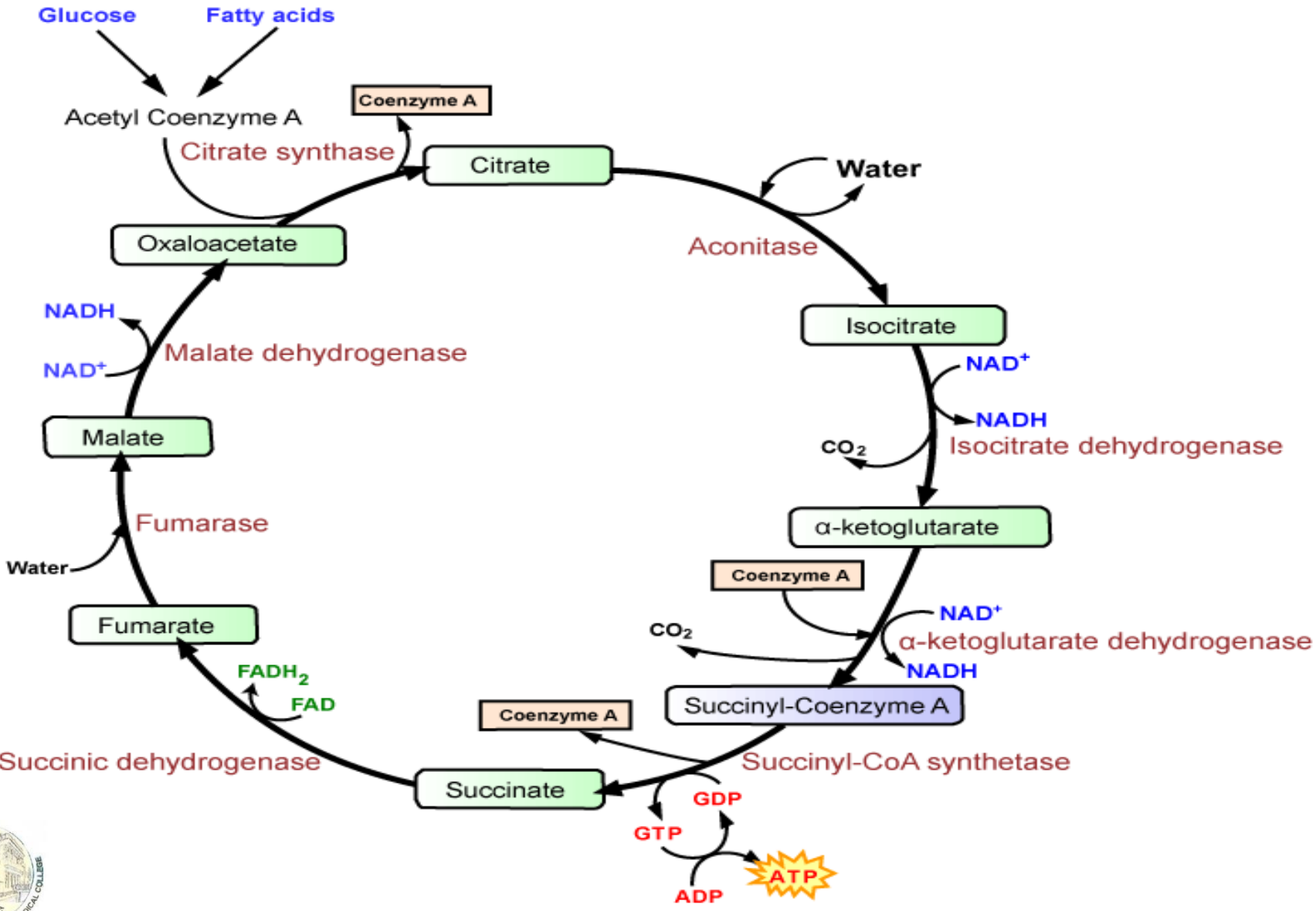
Regulation of TCA Cycle (LO2)

- **Three regulatory enzymes**

1. **Citrate synthase**
2. **Isocitrate dehydrogenase**
3. **α-ketoglutarate dehydrogenase**

LO1

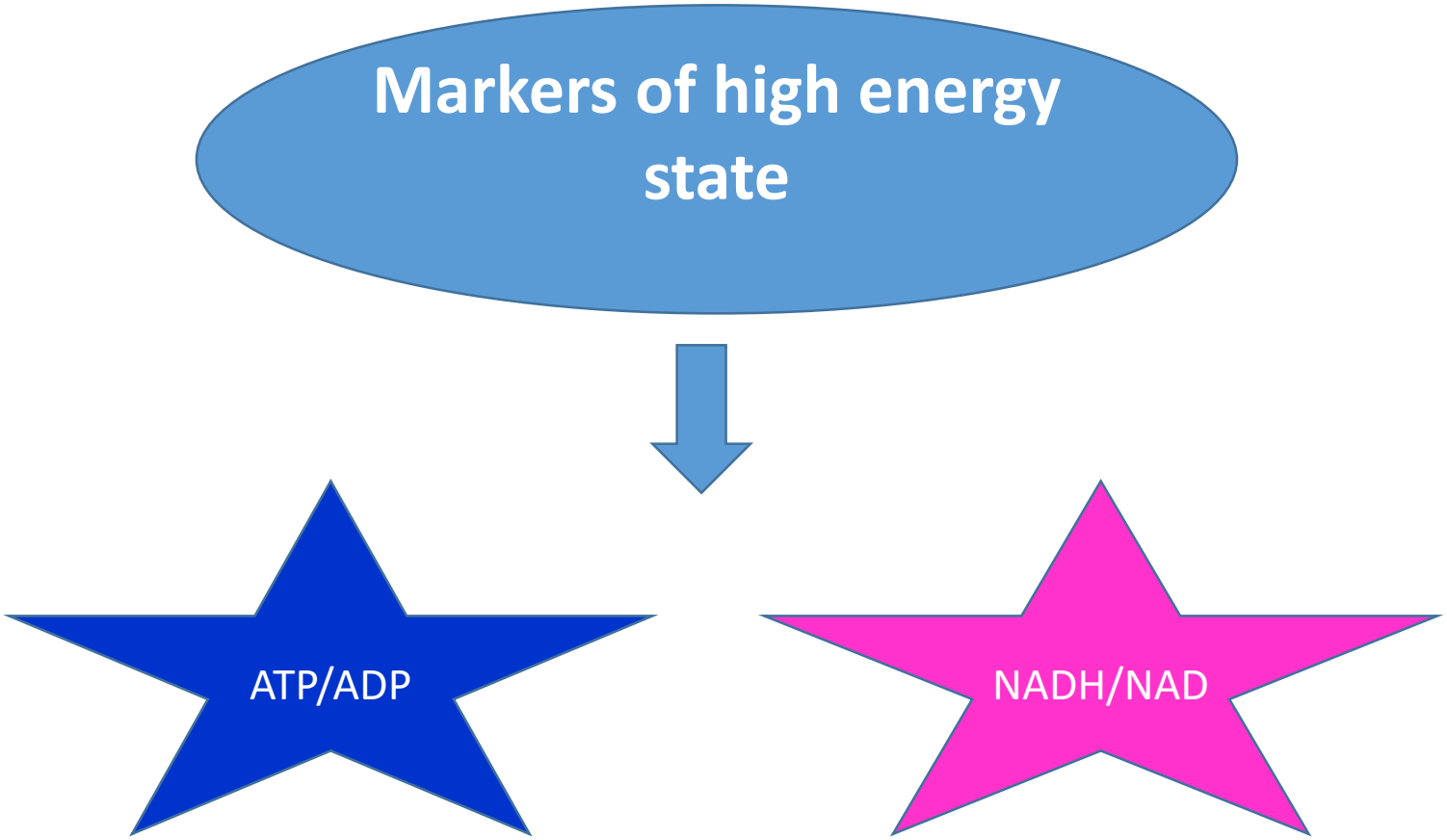
KREBS CYCLE (CITRIC ACID CYCLE)



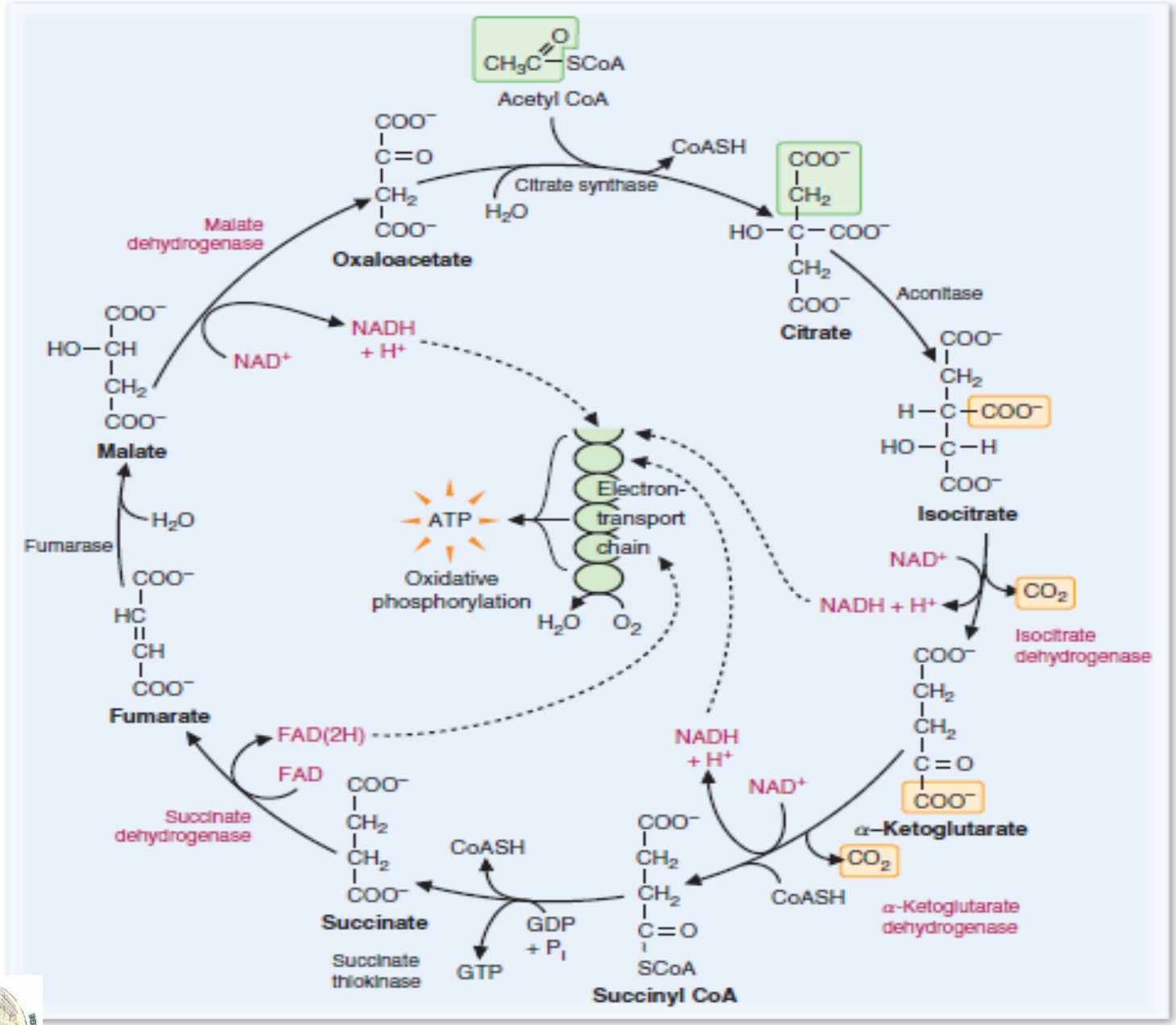
Regulation of TCA Cycle (LO2)

- **Citrate synthase is inhibited by ATP, NADH.**
- **Isocitrate dehydrogenase(allosteric enzyme), is activated by ADP & inhibited by ATP and NADH**
- **α-ketoglutarate dehydrogenase(allosteric enzyme), is inhibited by succinyl CoA & NADH.**
- **Availability of ADP is very important for TCA cycle to proceed.**

LO2



LO 2


Acetyl CoA
CoASH
Citrate synthase
H_2O
Oxaloacetate
Citrate
Aconitase
Isocitrate
Malate dehydrogenase
NAD+
NADH + H+
Malate
Fumarase
H_2O
Fumarate
ATP
Oxidative phosphorylation
Electron-transport chain
H_2O
O_2
NAD+
NADH + H+
CO_2
Isocitrate dehydrogenase
α–Ketoglutarate
NADH + H+
NAD+
CO_2
CoASH
α-Ketoglutarate dehydrogenase
FAD(2H)
FAD
Succinate dehydrogenase
Succinate
CoASH
GDP + P_i
GTP
Succinate thiokinase
Succinyl CoA

Significance of TCA Cycle (LO1)

- TCA cycle function in both oxidative and synthetic processes, it is amphibolic.
- A) Catabolic role OF TCA Cycle (LO1)

The citric acid cycle is the final common pathway for the oxidation of carbohydrate, lipid, and protein because glucose, fatty acids, and most amino acids are metabolized to acetyl-CoA or intermediates of the cycle.

B) Anabolic role of TCA cycle (LO1)

1- Role in Gluconeogenesis- All the intermediates of the cycle are potentially glucogenic, since they can give rise to oxaloacetate.

2- synthesis of nonessential amino acids, Alanine, aspartate, Asparagine, Glutamate , glutamine etc.

B) Anabolic role of TCA cycle (LO1)

3- Role in fatty acid synthesis:

- **Citrate is transported out of the mitochondrion when Aconitase is saturated with its substrate.**
- **This ensures that citrate is used for fatty acid synthesis only when there is an adequate amount to ensure continued activity of the cycle..**

B) Anabolic role of TCA cycle (LO1)

4- Role in Haem synthesis

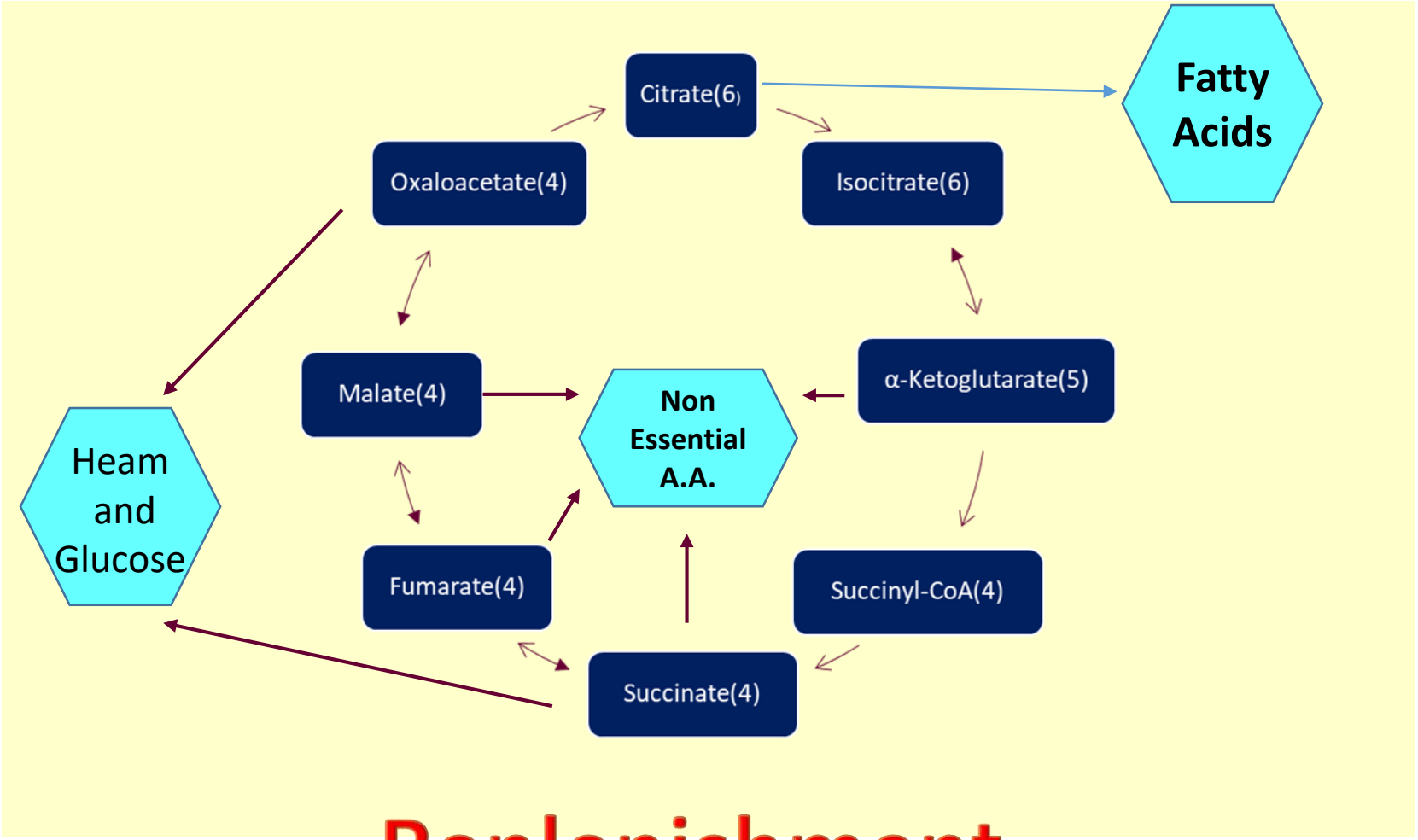
Succinyl Co A condenses with amino acid Glycine (is the first step of haem biosynthesis).

5- Role in purine and pyrimidine synthesis

Glutamate and Aspartate derived from TCA cycle are utilized for the synthesis of purines and pyrimidines.

LO 1

Anabolic Role of TCA



Replenishment

Gluconeogenesis (LO3)

- Gluconeogenesis is a metabolic pathway that results in the generation of glucose from non carbohydrates precursors.
- Liver and Kidney are the major gluconeogenic tissues
- But the small intestine may also be a source of the glucose in the fasting state

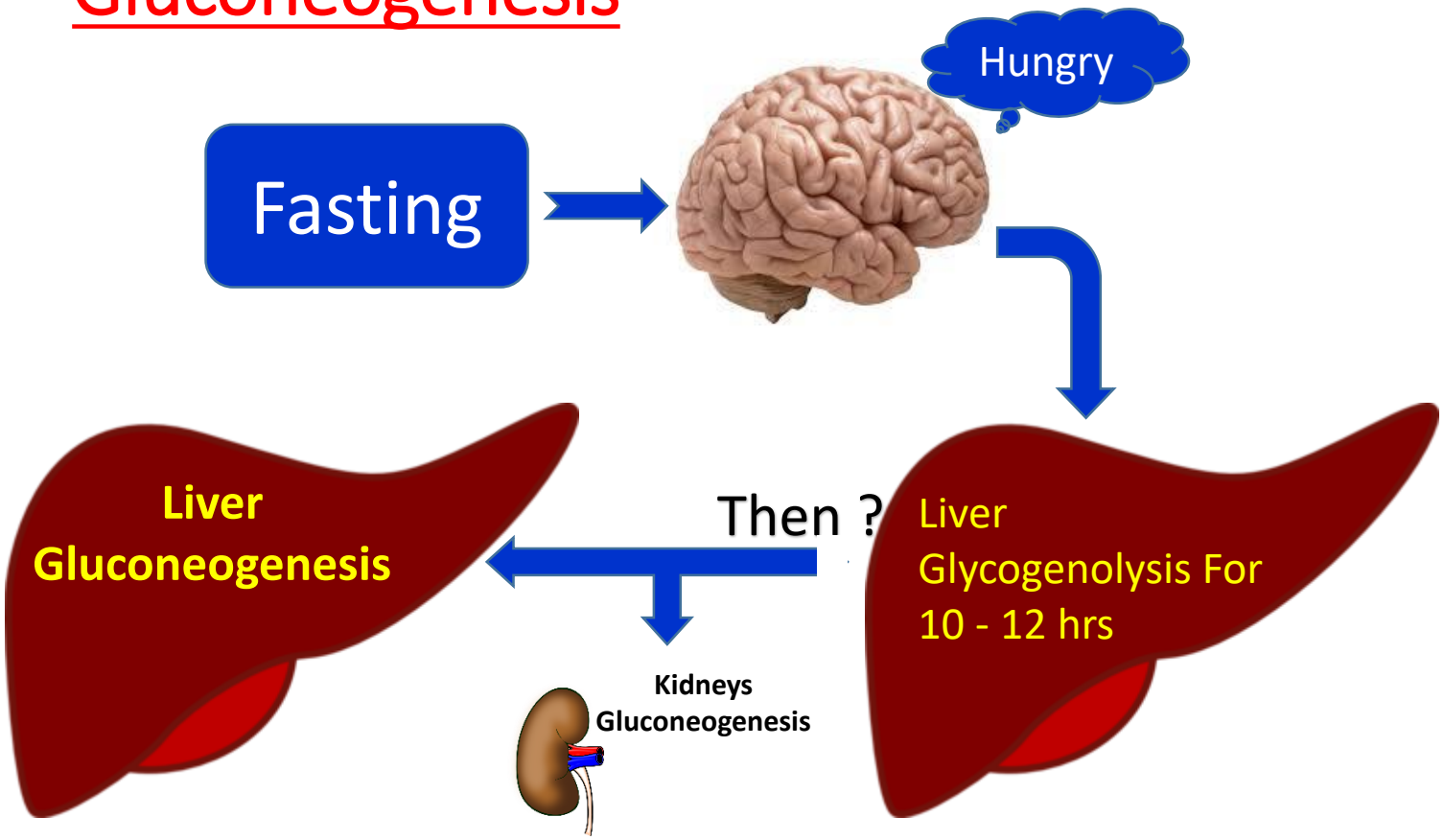
Importance of Gluconeogenesis (Lo3)

1- It provide a supply of glucose for the nervous system , erythrocytes , kidney medulla , lens , cornea of the eye and exercising muscle were in sufficient carbohydrates are available from the diet or glycogen reservoir.

2- Clears lactate produced by muscle and erythrocyte , formed during anaerobic glycolysis

3- Clears glycerol produced by adipose tissue

Gluconeogenesis



Gluconeogenisis

Substrates:

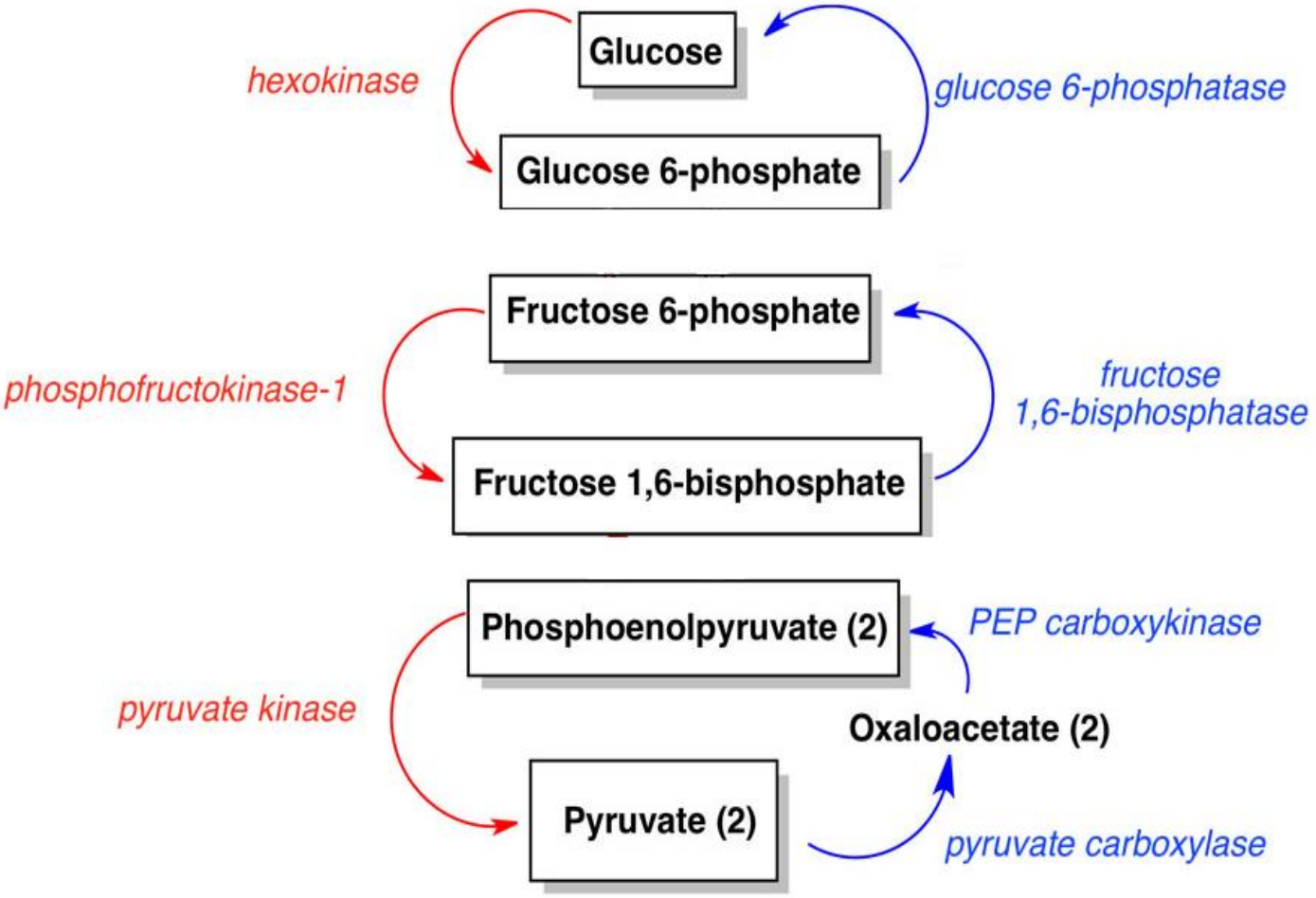
- Pyruvate
- Lactate
- Glycerol
- glucogenic amino acid e.g alanine,glutamate.

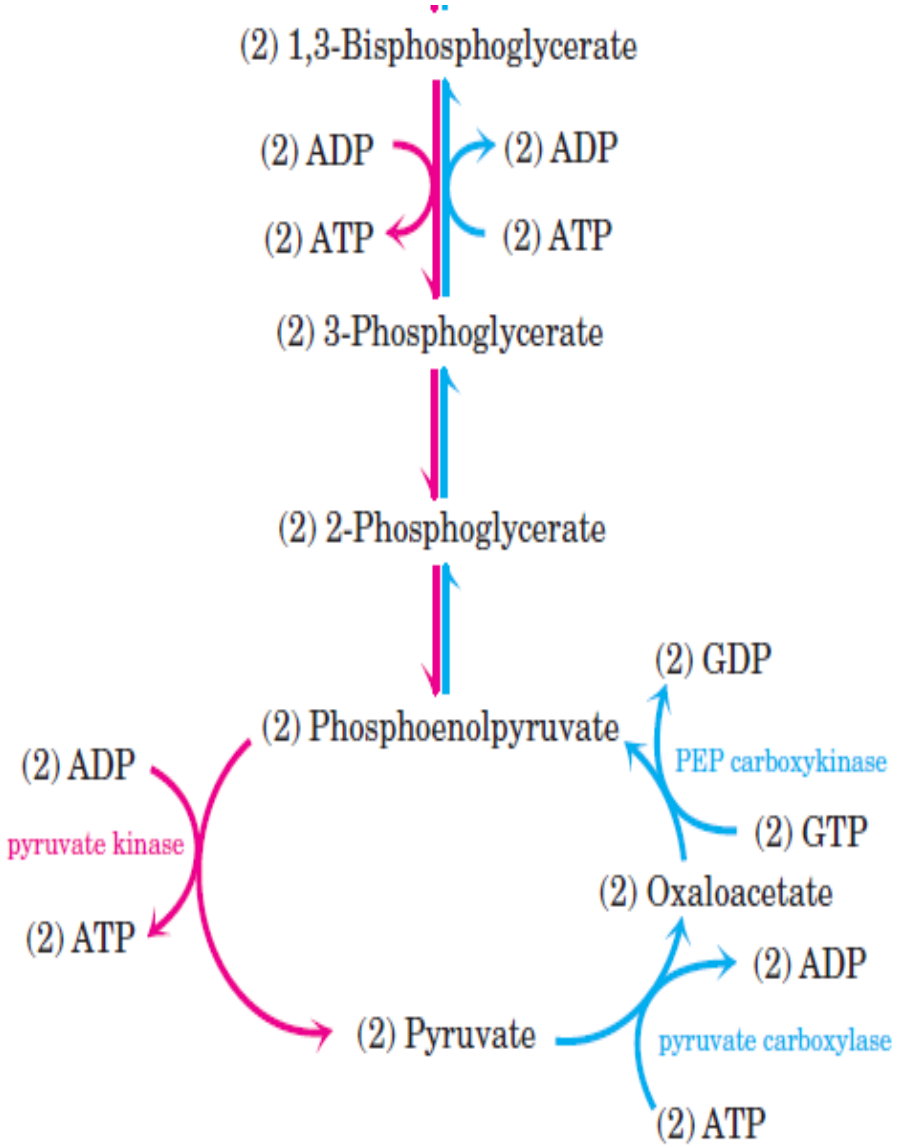
LO3

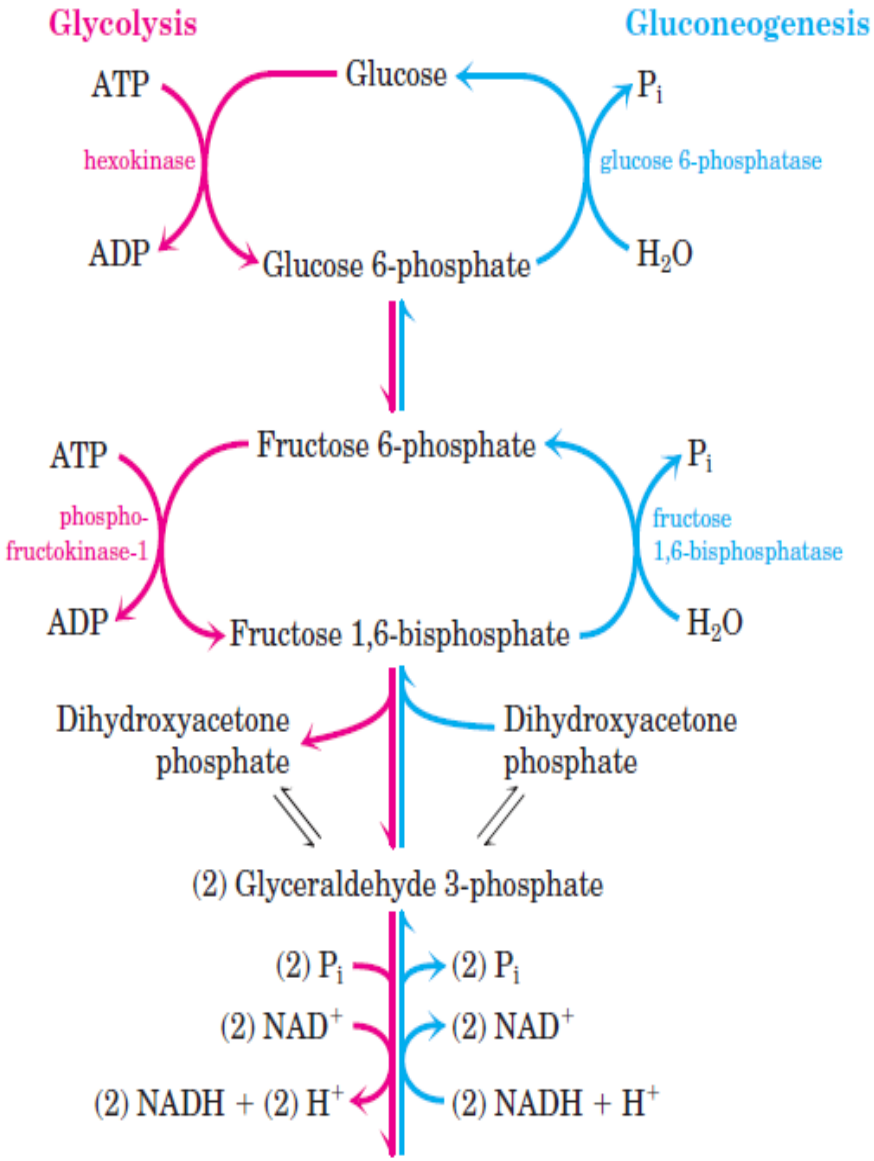
- **What about ketogenic amino acids**

LO 3

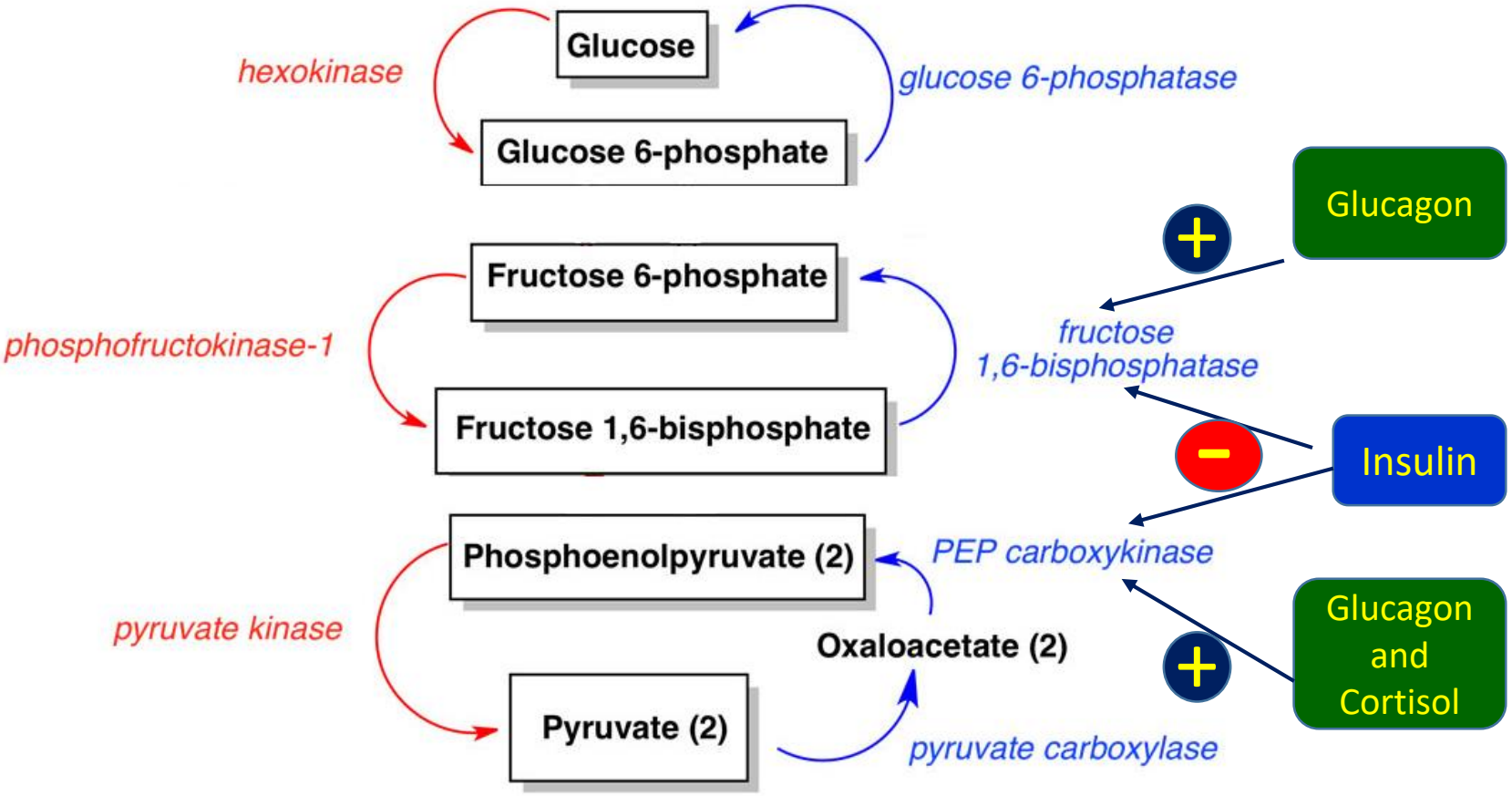
Gluconeogenisis




(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenolpyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) ADP
pyruvate kinase
(2) ATP
(2) Oxaloacetate
(2) ADP
(2) Pyruvate
pyruvate carboxylase
(2) ATP


Glycolysis
Gluconeogenesis
ATP
Glucose
P_i
hexokinase
glucose 6-phosphatase
ADP
Glucose 6-phosphate
H_2O
ATP
Fructose 6-phosphate
P_i
phospho-
fructokinase-1
fructose
1,6-bisphosphatase
ADP
Fructose 1,6-bisphosphate
H_2O
Dihydroxyacetone
phosphate
Dihydroxyacetone
phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) P_i
(2) NAD^+
(2) NAD^+
(2) NADH + (2) H^+
(2) NADH + H^+

Regulation of Gluconeogenisis



http://cdn1.teachmeseries.com/tmphysiology/wp-content/uploads/2017/07/22091125/3-Steps.png

Note:

- **In the absence of adequate levels of biologically effective insulin, such as occurs in diabetes, increased rates of gluconeogenesis contribute significantly to the hyperglycaemia.**


Thank You!