CARBOHYDRATE METABOLISM CONTINUE LECTURE 2

Third year-biochemistry subject – laboratory science departments -Alzahraa university

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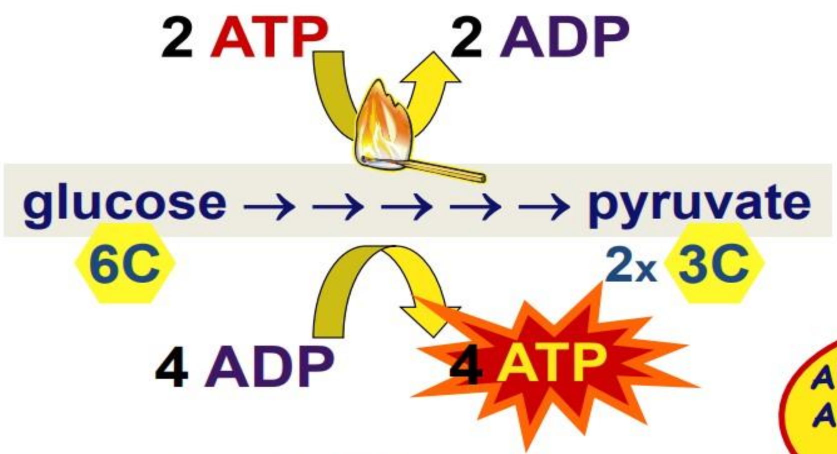
Learning objectives

1. Understand the overall purpose of the citric acid cycle in cellular respiration:
2. Describe the key steps and intermediates in the citric acid cycle
3. Identify the key enzymes involved in the citric acid cycle
4. Understand the purpose of the electron transport chain
5. Understand the overall purpose of gluconeogenesis
6. Understand the major steps in gluconeogenesis
7. Describe the key enzymes and regulation of gluconeogenesis

Summary for the previous lecture

Energy accounting of glycolysis



- Net gain = 2 ATP
  - some energy investment (-2 ATP)
  - small energy return (+4 ATP)
- 1 6C sugar → 2 3C sugars

. What is substrate level phosphorylation?

- Substrate level phosphorylation is a process by which ATPs are formed directly without going through electron transport chain
- Eg direct generation of ATP in step 7 (conversion of 1,3-bisphosphoglycerate to 3 phosphoglycerate)
- &step 10 (conversion of phosphoenolpyruvat to pyruvate) in glycolysis

- **Notes:** Cellular respiration is a collection of three unique metabolic pathways: glycolysis, the citric acid cycle, and the electron transport chain

METABOLIC FATE OF PYRUVATE

- Inside the mitochondria, pyruvate is oxidatively
- decarboxylated to acetyl CoA by pyruvate dehydrogenase (PDH) enzyme complex
- **Site of this enzyme mitochondrial matrix**
- **Structure of 5 enzyme & need 5 co enzyme**
- **Function :- oxidation decarboxylation**
- **Reaction type :- irreversible**
- **This pyruvate dehydrogenase complex require 5 coenzyme**
- The co enzymes needed are: (TFLN-CO)

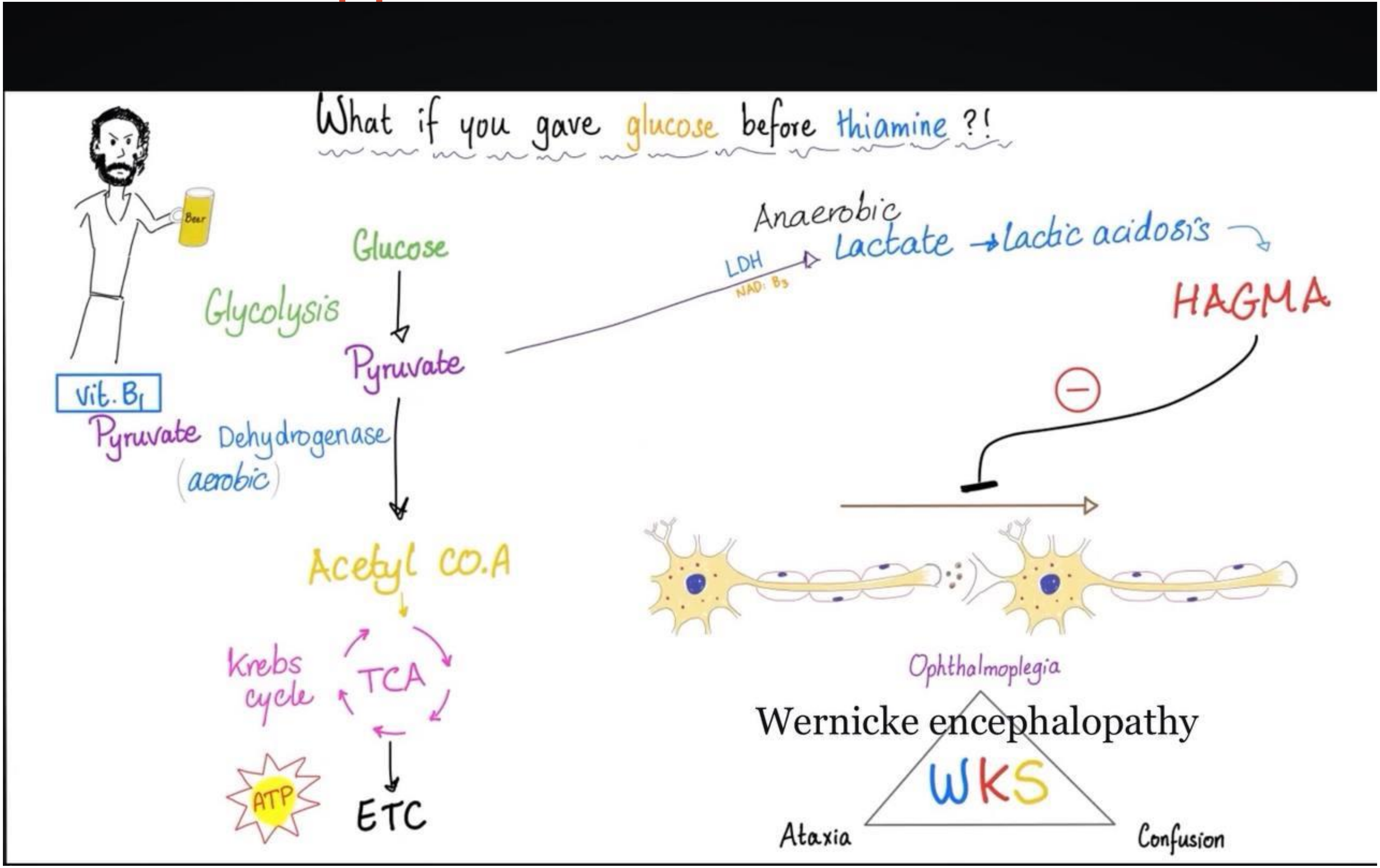
1. . Thiamine pyrophosphate (TPP) VITAMIN B1
2. FAD (ribofalvin vit B2)
3. NAD+ (niacin vit B3)
4. Lipoic acid
5. Co-enzyme A (CoA)

5 enzyme in the pyruvate dehydrogenase complex

1. Pyruvate dehydrogenase
2. Dihydrolipoyl transacetylase
3. Dihydrolipoyl dehydrogenase

- **Regulators**
- Pyruvate dehydrogenase kinase (inhibiter)
- Pyruvate dehydrogenase phosphatase (stimulator)

Clinical application



Citric acid cycle also known as Tricarboxylic acid (TCA) and Krebs cycle

- It is a chain of reactions occurring in the mitochondria, through which almost all living cells produce energy in aerobic respiration.
- It uses oxygen and gives out water and carbon dioxide as products. In which ADP is converted into ATP
- It is part of the larger glucose metabolism where by glucose is oxidized to form pyruvate, which is then oxidized to acetyl-CoA and enters the TCA cycle producing nicotinamide adenine dinucleotide NADH
- Kreps cycle occur in mitochondrial matrix

- The regulated enzymes of the citric acid cycle are

1. **citrate synthase**
2. **isocitrate dehydrogenase,**
3. **alpha-ketoglutarate dehydrogenase.**

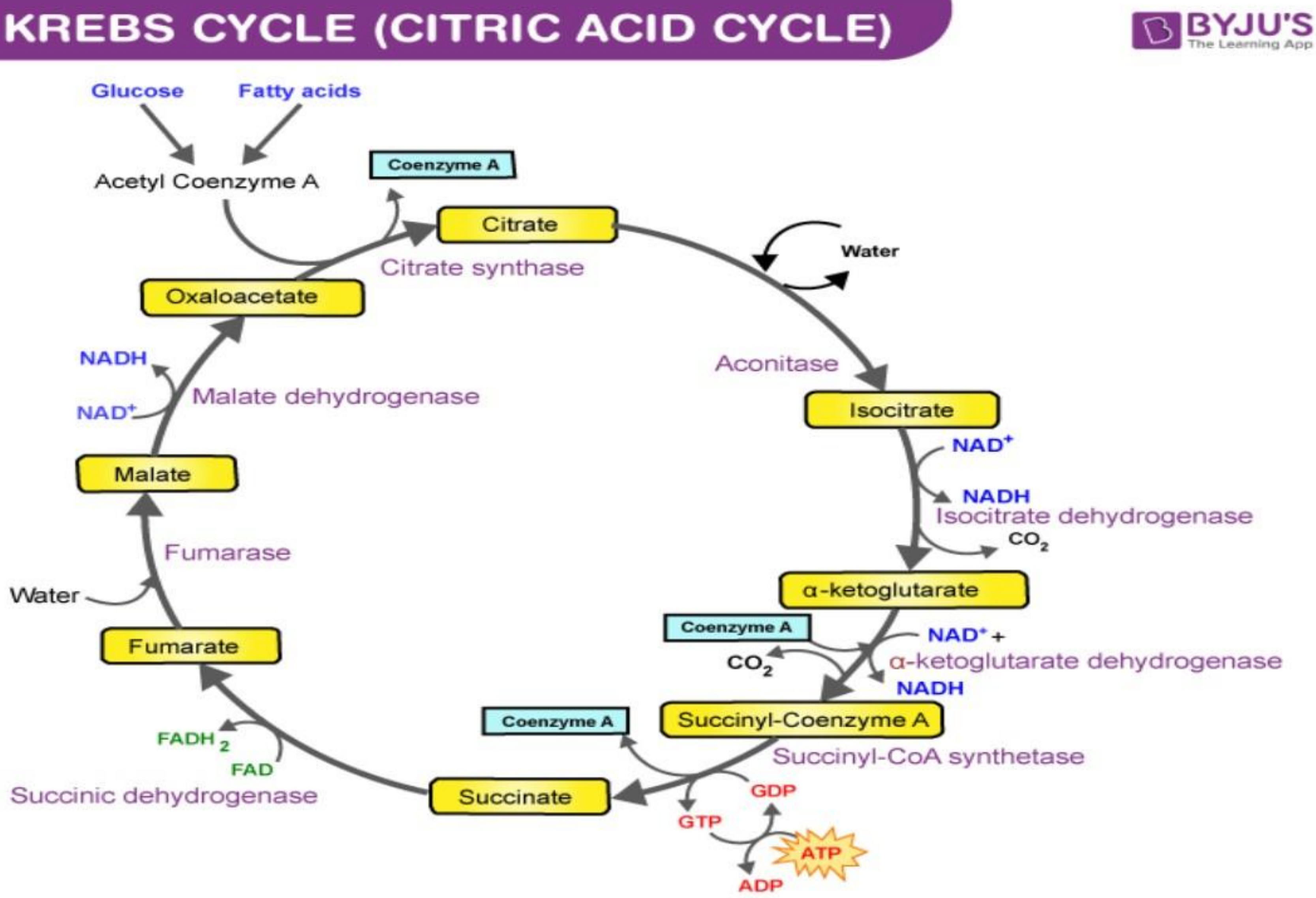
- **Regulation of TCA cycle**

❖ **NADH inhibits all the regulatory enzymes in the TCA cycle**

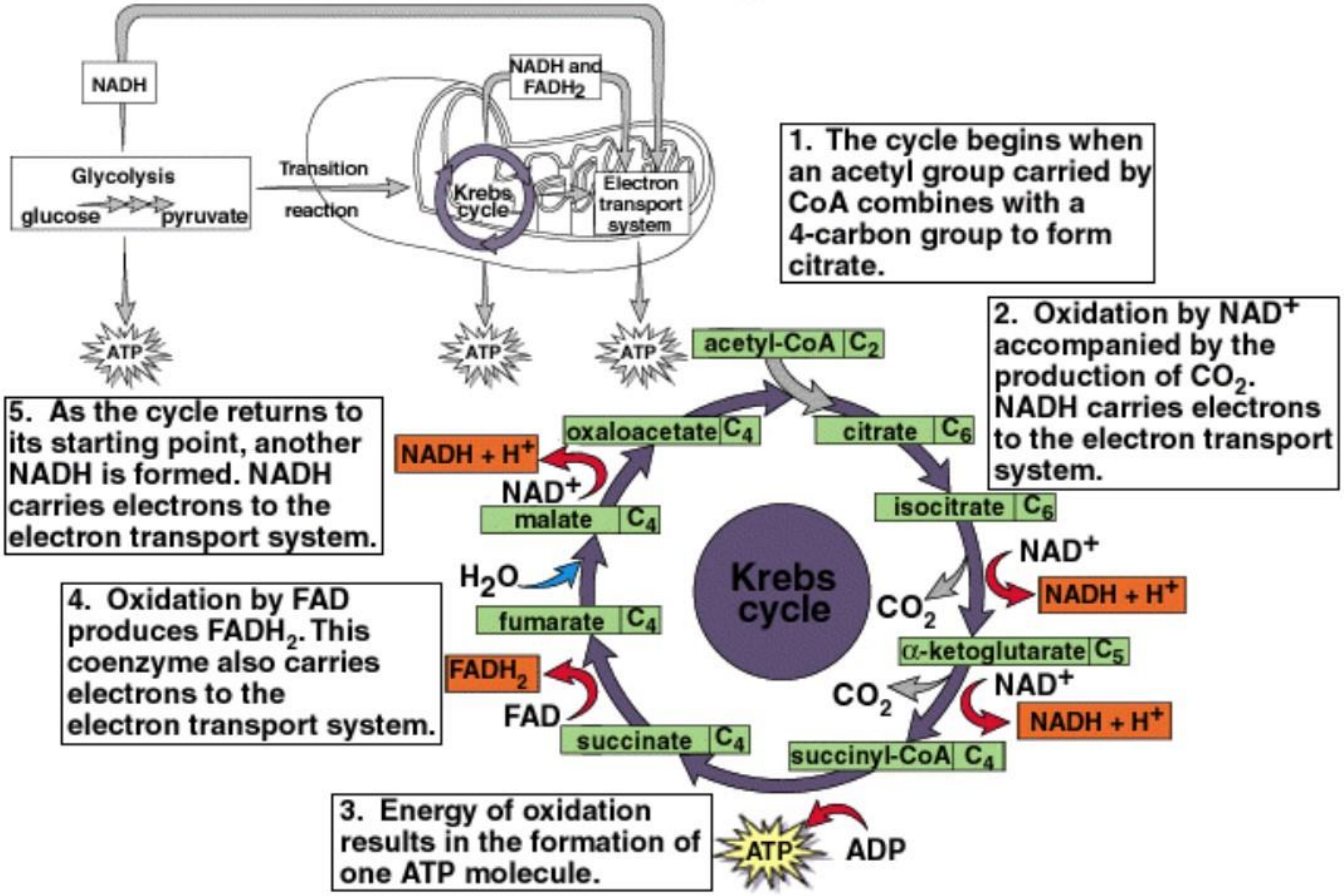
❖ Calcium ions regulate the citric acid cycle by activating pyruvate dehydrogenase

- **the first component of the pyruvate dehydrogenase complex reaction that forms acetyl-Co**

KREBS CYCLE (CITRIC ACID CYCLE)

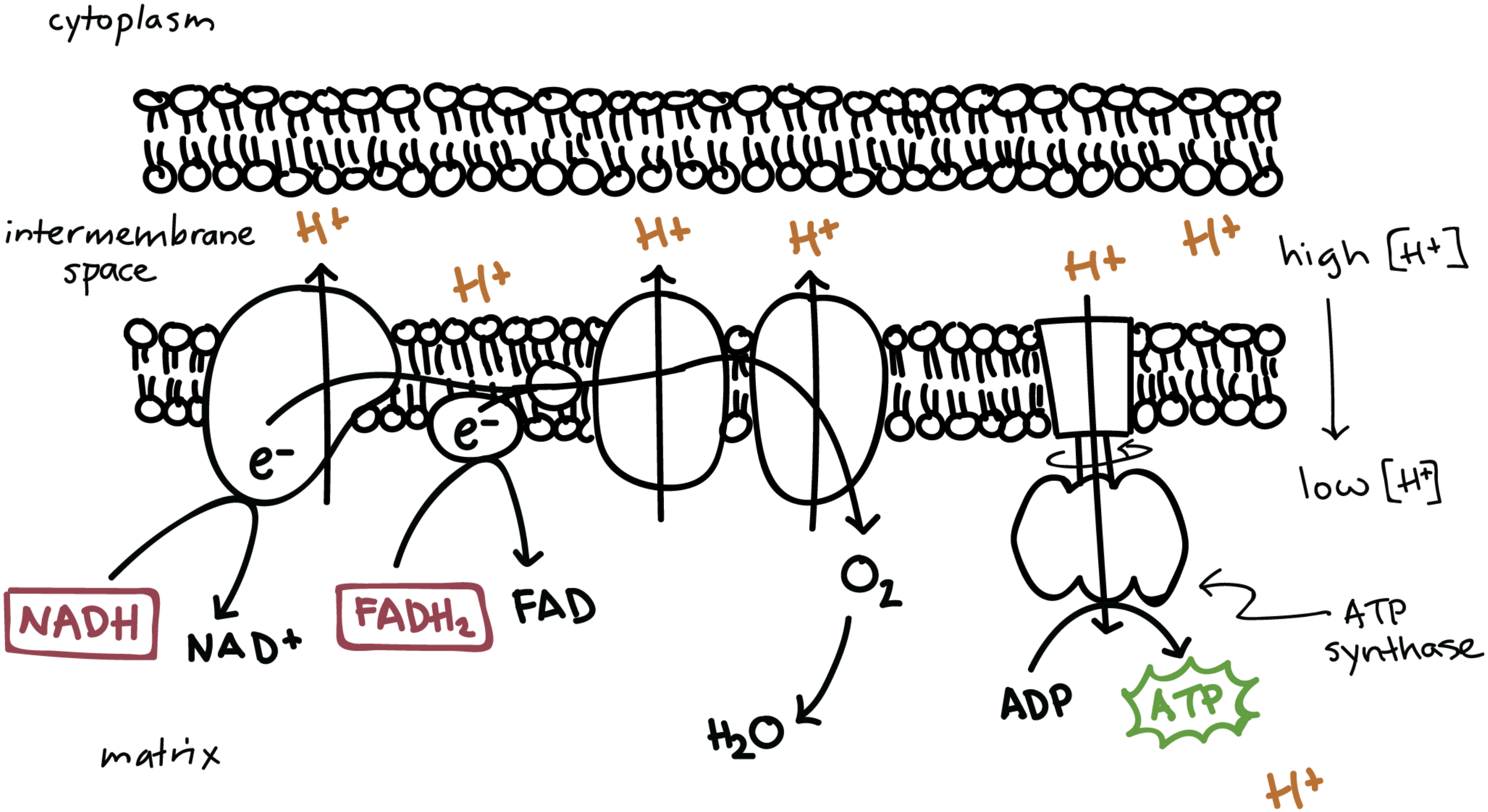


Kreb's cycle


NADH
NADH and FADH2
Glycolysis
glucose
pyruvate
Transition reaction
Krebs cycle
Electron transport system
ATP
ATP
ATP
1. The cycle begins when an acetyl group carried by CoA combines with a 4-carbon group to form citrate.
2. Oxidation by NAD+ accompanied by the production of CO2. NADH carries electrons to the electron transport system.
3. Energy of oxidation results in the formation of one ATP molecule.
4. Oxidation by FAD produces FADH2. This coenzyme also carries electrons to the electron transport system.
5. As the cycle returns to its starting point, another NADH is formed. NADH carries electrons to the electron transport system.
acetyl-CoA C2
citrate C6
isocitrate C6
NAD+
NADH + H+
CO2
α-ketoglutarate C5
CO2
NAD+
NADH + H+
succinyl-CoA C4
ATP
ADP
succinate C4
FAD
FADH2
fumarate C4
H2O
malate C4
NAD+
NADH + H+
oxaloacetate C4
Krebs cycle

Electron transport chain

this occur in the inner mitochondrial membrane



electron Transport Chain (ETC):

- \- NADH and FADH2 produced in glycolysis and the citric acid cycle are used in the electron transport chain to produce ATP through oxidative phosphorylation.

Each NADH can yield about 2.5 ATP

Each FADH2 can yield about 1.5 ATP.

- Therefore, from the NADH and FADH2 produced, the total ATP yield can be calculated.

- **<u>Summary of Net Energy Gain from Carbohydrate Metabolism:</u>**
- **- Glycolysis: 2 ATP (net) + 2 NADH**
- **From pyruvate to acetyl-COA : 2 NADH**
- **- Krebs Cycle: 2 ATP + 6 NADH + 2 FADH2**

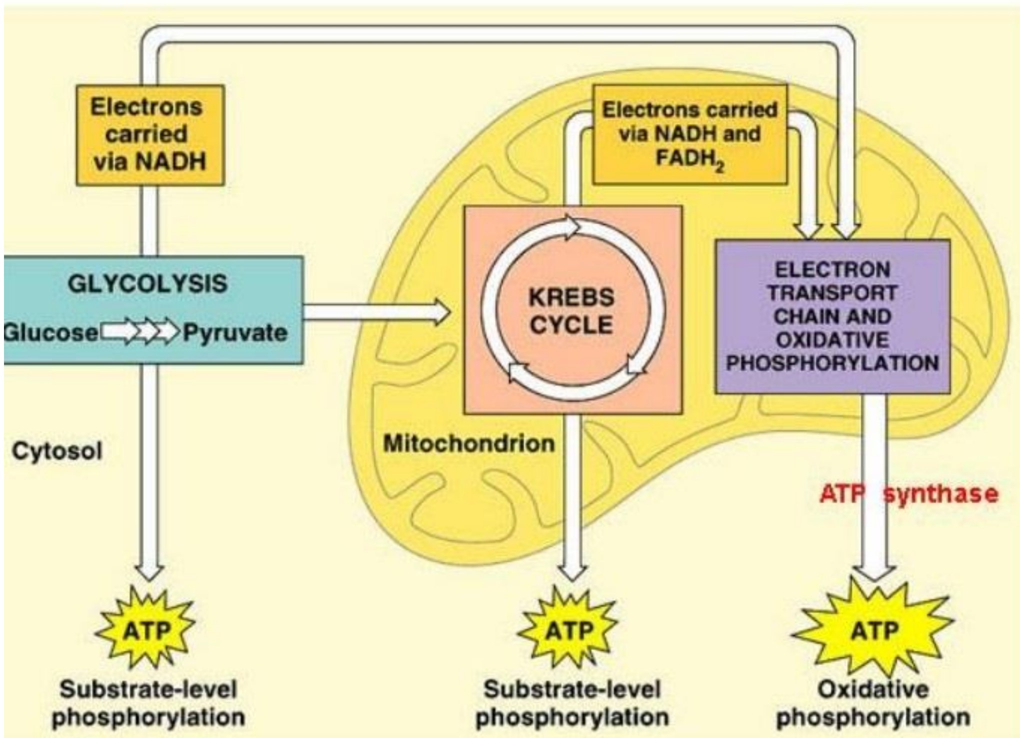
- **- Total ATP Yield:**
- **- From glycolysis (2 ATP, 2 NADH): 2 + (2 x 2.5) = 7 ATP**
- **From pyruvate to acetyl-COA : 2 NADH = 2 * 2.5 = 5 ATP**
- **From Krebs Cycle (2 ATP, 6 NADH, 2 FADH2): 2 + (6 x 2.5) + (2 x 1.5) = 20 ATP**
- **- Overall Total: Approximately 30-32 ATP per glucose molecule, depending on the cell type and conditions.**

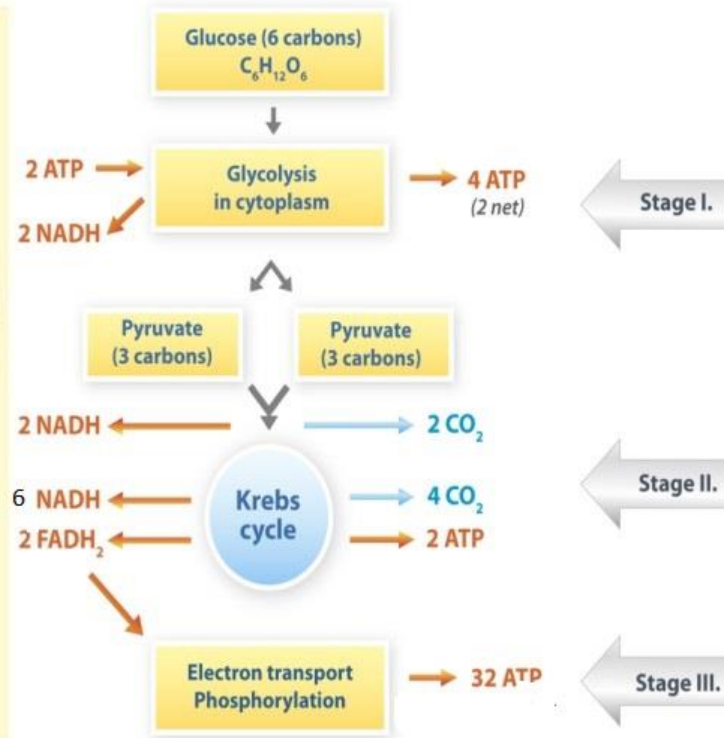
Glycolysis	KREPS CYCLE
It is the first step of respiration	Krebs cycle is the second step of aerobic respirations
Anaerobic break down of glucose molecule in a set of enzymatic processes into 2 pyruvate	**Aerobic** oxidation of acetyl COA into co2 and water
Occur in cytoplasm (no o2 needed)	Occur in mitochondria (need o2)
Occur in linear sequence	Occur in cyclic sequence
Consumes 2 molecules of ATP in the **phosphorylation steps**	Don’t consume ATP
Net gain of energy 2 ATP 2 NADH	Net gain of energy 2 ATP 6 NADH 2 FADH2
4 ATP generated by substrate level phosphorylation	2 GTP (equivalent to 2 ATP)generated by substrate level phosphorylation

Overview of Cellular Respiration

In **presence of oxygen** (aerobic) glycolysis is followed by: ___Krebs Cycle___

___Electron Transport Chain___





GLUCONEOGENESIS

- When blood glucose is low and no further ATP is available as in fasting or starvation, glucose is produced from non-carbohydrate precursors like lactate, pyruvate, glycerol, and amino acids (except leucine and lysine).
- . **Site** Gluconeogenesis occurs mainly in the liver, and to a lesser extent in the renal cortex
- The pathway is partly mitochondrial and partly cytoplasmic

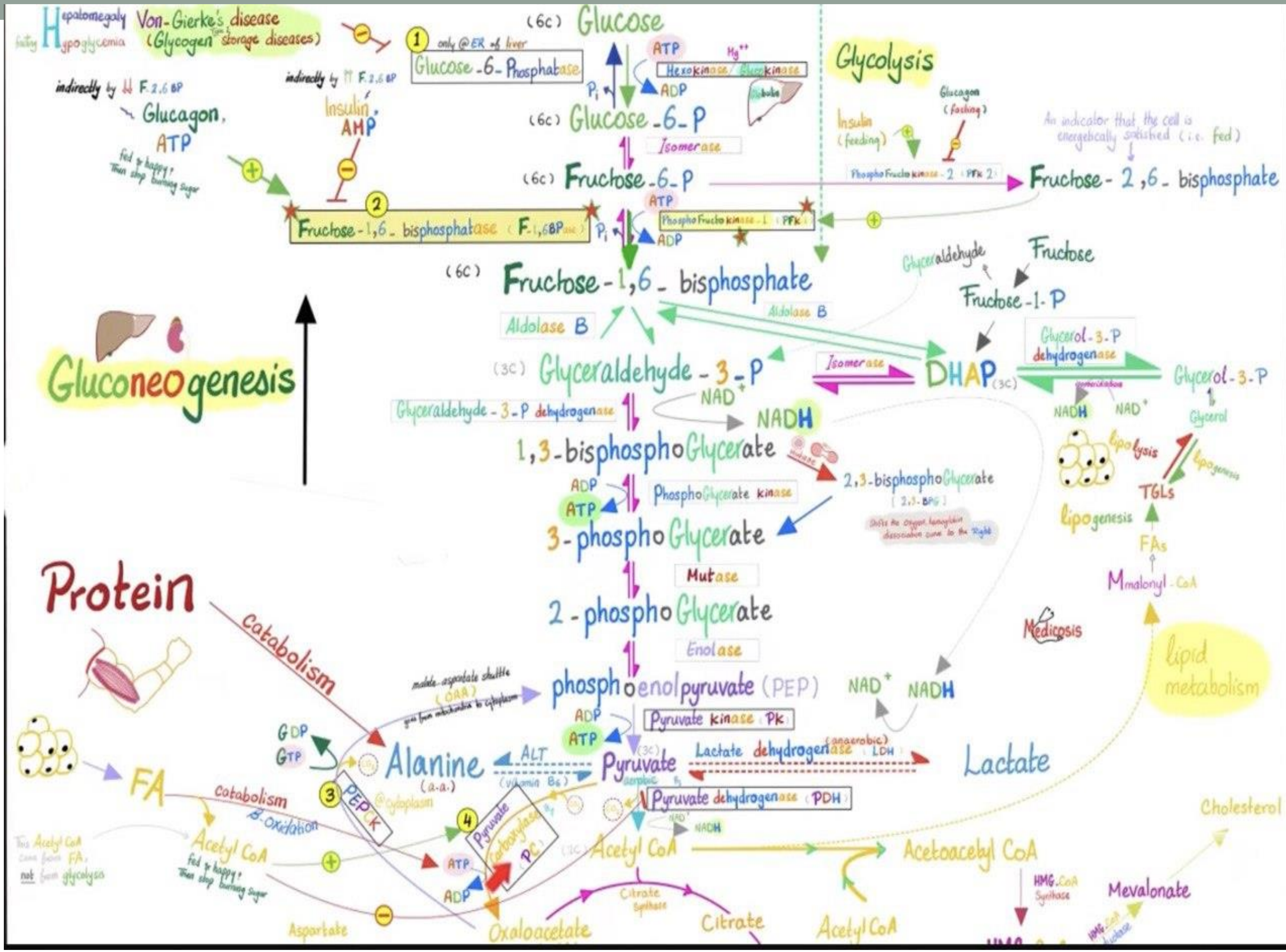
Regulation of Gluconeogenesis

It is stimulated by

- Glucagon
- growth hormone
- epinephrine
- cortisol

inhibited by insulin.

Gluconeogenesis supply energy for 24 hours to two days after beginning fasting. This process does not require oxygen.



Hepatomegaly
Hypoglycemia
Von-Gierke's disease
(Glycogen storage diseases)
only @ER of liver
Glucose-6-Phosphatase
(6c) Glucose
ATP
Mg++
Hexokinase/ Glucokinase
ADP
Pi
(6c) Glucose-6-P
Isomerase
Glycolysis
indirectly by ↓↓ F.2,6 BP
indirectly by ↑↑ F.2,6 BP
Glucagon,
ATP
Insulin,
AMP
Fed & happy? Then stop burning sugar
Insulin (feeding)
Glucagon (fasting)
An indicator that the cell is energetically satisfied (i.e. fed)
(6c) Fructose-6-P
PhosphoFructokinase-2 (PFK 2)
Fructose-2,6-bisphosphate
Fructose-1,6-bisphosphatase (F.1,6BPase)
PhosphoFructokinase-1 (PFK)
(6C) Fructose-1,6-bisphosphate
Aldolase B
Glyceraldehyde
Fructose
Fructose-1-P
Gluconeogenesis
(3C) Glyceraldehyde-3-P
Isomerase
DHAP (3C)
Glycerol-3-P dehydrogenase
Glycerol-3-P
NAD+
NADH
Glycerol
Glyceraldehyde-3-P dehydrogenase
1,3-bisphosphoGlycerate
2,3-bisphosphoGlycerate [2,3-BPG]
lipolysis
lipogenesis
TGLs
ADP
ATP
PhosphoGlycerate kinase
3-phosphoGlycerate
Mutase
2-phosphoGlycerate
Enolase
FAs
Mmalonyl-CoA
Protein
Catabolism
Medicosis
lipid metabolism
malate-aspartate shuttle
(OAA)
goes from mitochondria to cytoplasm
phosphoenolpyruvate (PEP)
NAD+
NADH
ADP
ATP
Pyruvate kinase (Pk)
GDP
GTP
Alanine (a.a.)
ALT
(vitamin B6)
(3C) Pyruvate
aerobic
Lactate dehydrogenase (anaerobic) (LDH)
Lactate
PEPCK
@cytoplasm
Pyruvate dehydrogenase (PDH)
NADH
FA
Catabolism
β-oxidation
Pyruvate Carboxylase (PC)
ATP
ADP
This Acetyl CoA came from FA, not from glycolysis
Acetyl CoA
Fed & happy? Then stop burning sugar
(2C) Acetyl CoA
Acetoacetyl CoA
Cholesterol
HMG.CoA Synthase
Mevalonate
Citrate Synthase
Citrate
Acetyl CoA
Aspartate
Oxaloacetate

- **Glucose is made from pyruvate in gluconeogenesis at the cost of 4 ATP, 2 GTP, and 2 NADH.**
- Energy must supply brain and RBCs which utilize glucose only
- **Phosphoenol pyruvate carboxy kinase catalyzes the rate limiting reaction in gluconeogenesis**

"circumvent" How do we bypass them in Gluconeogenesis ?! (4)		Irreversible enzymes in glycolysis (3)
only @ ER of liver (1) Glucose - 6 - Phosphatase (G6Pase)	⟷	(1) Hexokinase / Glucokinase
(2) Fructose - 1,6 - bisphosphatase (F-1,6BPase)	⟷	(2) Phospho Fructo kinase - 1 (PFK-1)
(3) PEP Carboxykinase (PEPCK) & (4) Pyruvate Carboxylase (PC) B_7	⟷	(3) Pyruvate kinase (PK)

There are three irreversible steps

- (1) conversion of pyruvate to PEP via oxaloacetate, catalyzed by pyruvate carboxylase and **Phosphoenol pyruvate carboxy kinase** ;
- (2) dephosphorylation of fructose 1,6- bisphosphate by fructose 1,6- bisphosphatase
- (3) dephosphorylation of glucose 6- phosphate by glucose 6- phosphatase.

STEPS OF GLUCONEOGENESIS

- Starting from pyruvate, In the mitochondria
- pyruvate is carboxylated to form **oxaloacetate via the enzyme pyruvate carboxylase**
- **This oxaloacetate has to be transported from mitochondria to cytosol, because further reactions of gluconeogenesis are taking place in cytosol**
- Because oxaloacetate cannot pass through the mitochondrial membranes it must be first converted into **malate by malate dehydrogenase**.
- Malate can then cross the mitochondria membrane into the cytoplasm where it is then converted back into oxaloacetate with another **malate dehydrogenase**.
- Lastly, oxaloacetate is converted into **Phosphoenol pyruvate** via PEP carboxykinase

- The next several steps are exactly the same as glycolysis only the process is in reverse
- **The second step that differs from glycolysis is the conversion of fructose-1,6-bisphosphate to fructose-6-P with the use of the enzyme fructose-1,6-phosphatase.**

- The last step that differs from glycolysis is the conversion of glucose-6-P to glucose with the enzyme glucose-6-phosphatase.
- **This enzyme is located in the endoplasmic reticulum of the liver cells**


THANK
YOU