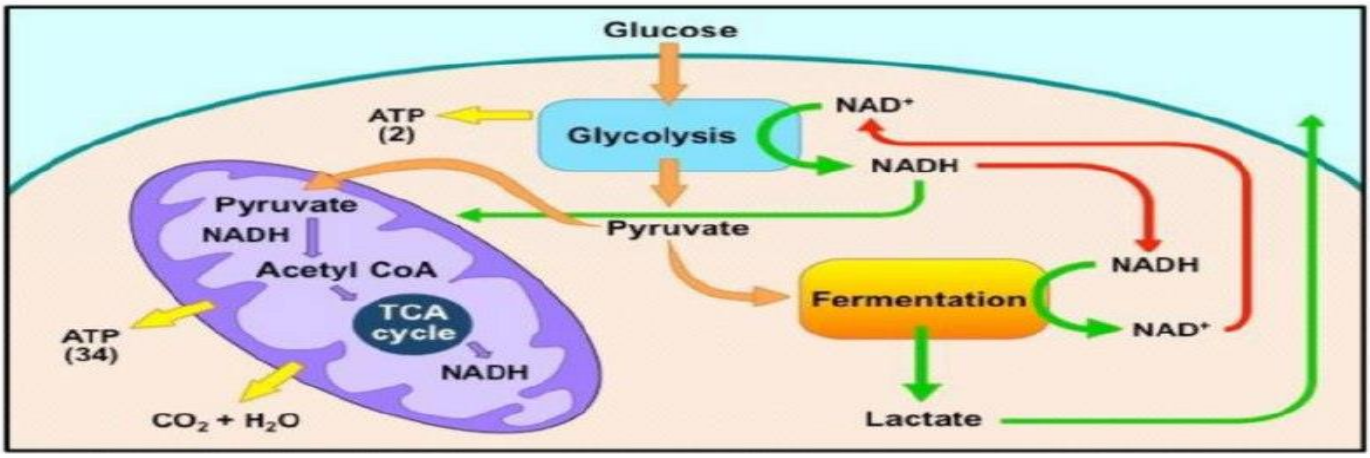
Glucose Oxidation I

▪ Pathways for glucose oxidation:

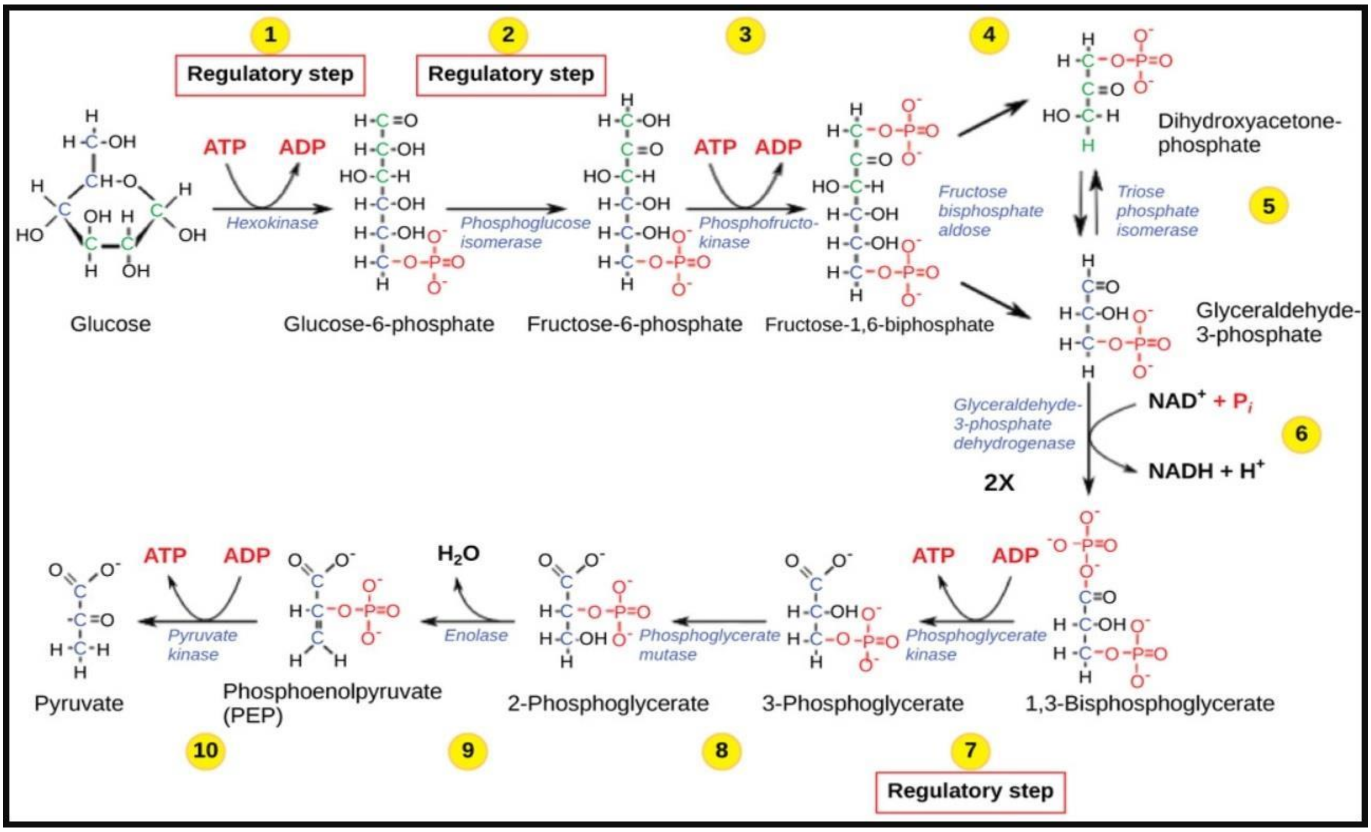
Major pathways	Minor pathways
• ***For Energy production***	• ***Not for energy*** *production, but for production of* ***certain substances.***
• ***Include:*** ➢ *Glycolysis* ➢ *Oxidative decarboxylation.* ➢ *Kreb's cycle*	• ***Include :*** ➢ ***Pentose shunt:*** *production of pentoses and NADPH*



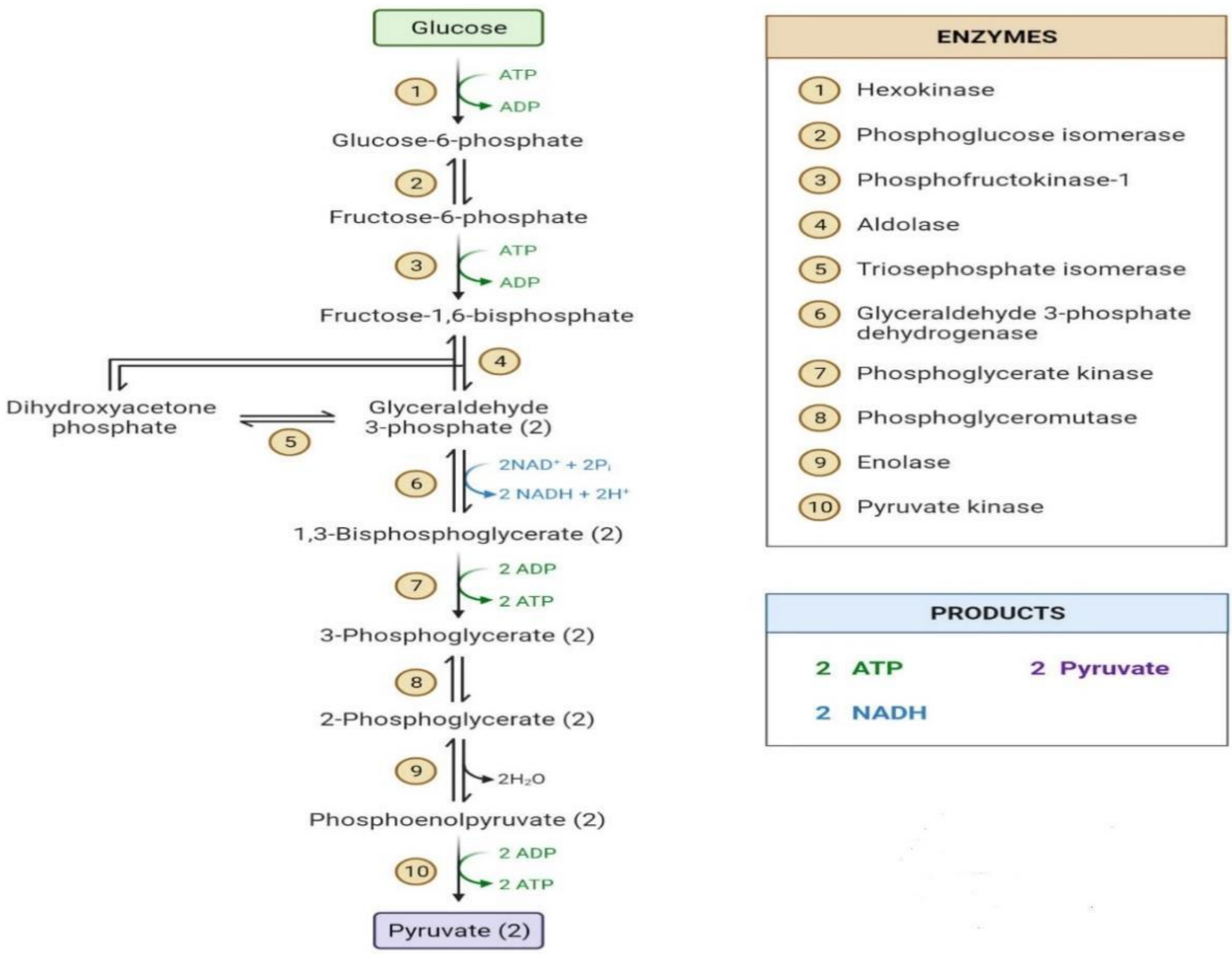
1- Glycolysis (Glyco = sugar, lysis = breakdown)

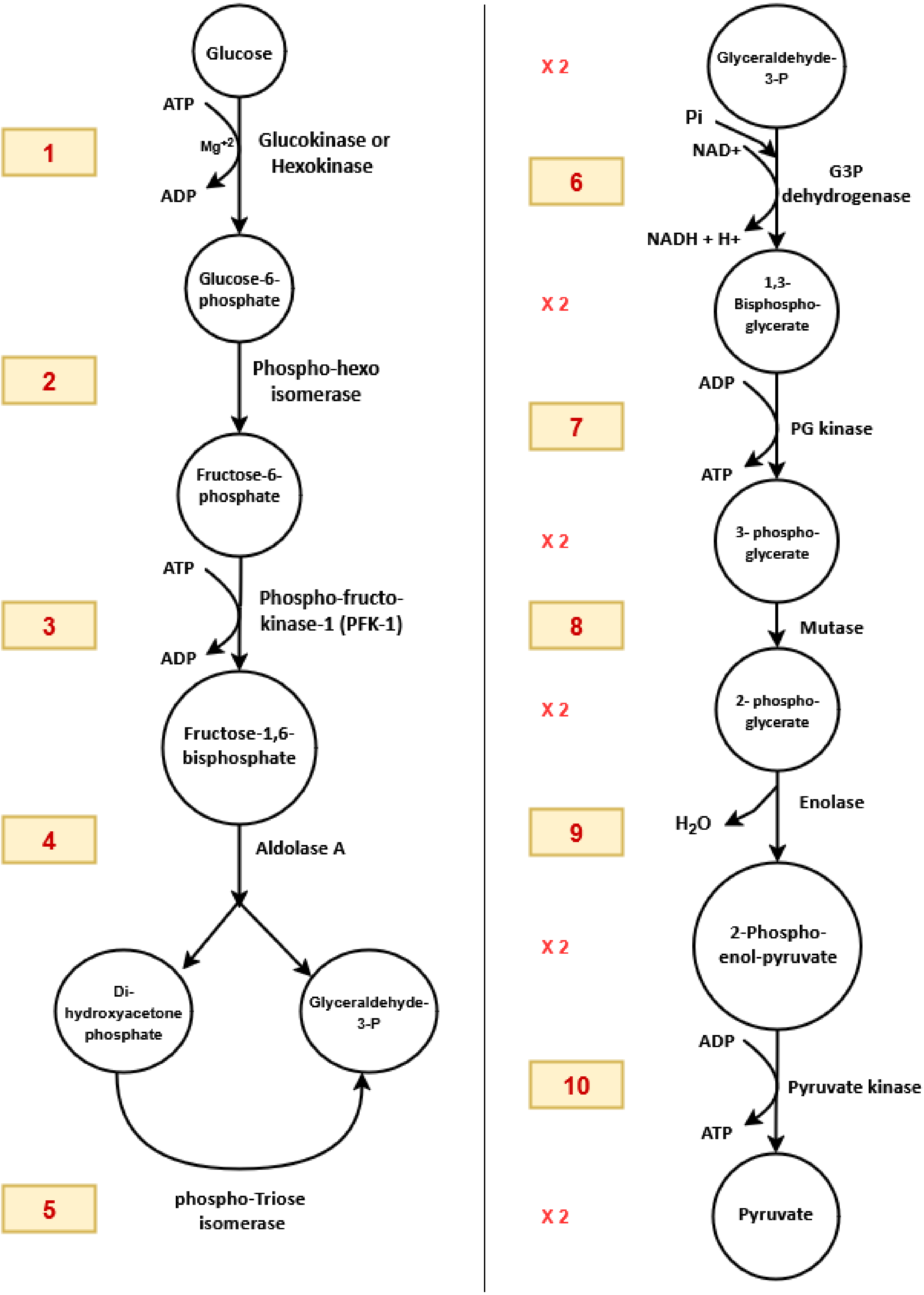
Definition: **Written Q**	• *It is the* ***first stage*** *in cellular respiration.* • *It is a series of* ***biochemical reactions*** *that converts:* ➢ ***Glucose*** → ***Pyruvate*** *(**aerobic** condition)* ➢ ***Glucose*** → ***Lactate*** *(**anaerobic** condition) and (in RBCs = No mitochondria)*
Site:	• *Cytoplasm of* ***all cells.***
Steps	• ***10 steps***

1) in presence of oxygen (glycolysis is aerobic)



Glycolysis and Glycolytic Enzymes





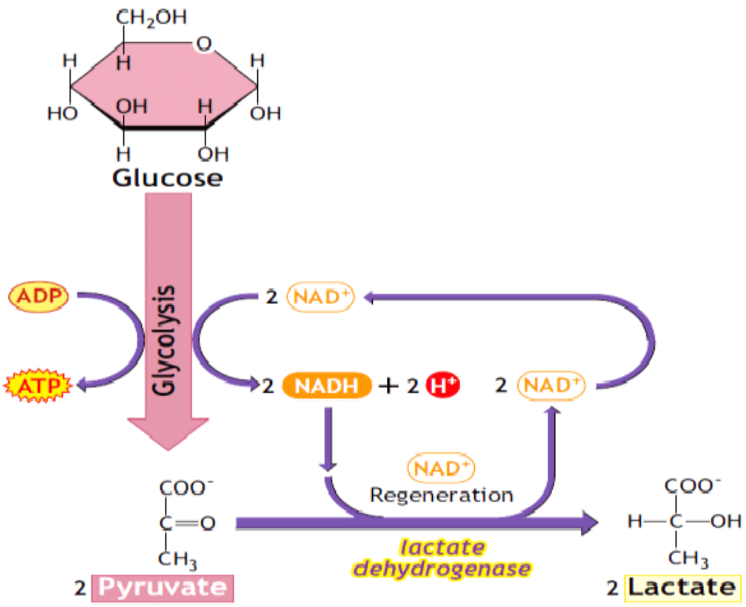
1
Glucose
ATP
Mg+2
ADP
Glucokinase or Hexokinase
Glucose-6-phosphate
2
Phospho-hexo isomerase
Fructose-6-phosphate
3
ATP
ADP
Phospho-fructo-kinase-1 (PFK-1)
Fructose-1,6-bisphosphate
4
Aldolase A
Di-hydroxyacetone phosphate
Glyceraldehyde-3-P
5
phospho-Triose isomerase
X 2
Glyceraldehyde-3-P
6
Pi
NAD+
NADH + H+
G3P dehydrogenase
X 2
1,3-Bisphospho-glycerate
7
ADP
ATP
PG kinase
X 2
3- phospho-glycerate
8
Mutase
X 2
2- phospho-glycerate
9
H_2O
Enolase
X 2
2-Phospho-enol-pyruvate
10
ADP
ATP
Pyruvate kinase
X 2
Pyruvate

NB:

- *Steps 1, 2 and 3 together are called as the* ***preparatory phase of glycolysis.***
- *Steps 4 and 5 are together called the* ***splitting phase of glycolysis.***
- *Steps 6, 7, 8, 9 & 10 are together called the* ***energy generating phase of glycolysis.***
- *Step 7,10 are* ***substrate level phosphorylation steps***

2) Under anaerobic conditions

- ***Glycolysis is anaerobic:***
  - ***Pyruvate*** *is reduced by lactate dehydrogenase to* ***lactate.***
- ***Examples:***
  - *Exercising muscles.*
  - *in cells lacking mitochondria (RBCs).*



- ***Significance of lactate production in anaerobic glycolysis:*** **written Q**
  - ***Regeneration of NAD+*** *in the cytoplasm.*
  - *This helps* ***continuity*** *of glycolysis , NAD+ is needed for* ***step 6*** *(glyceraldehyde-3-phosphate dehydrogenase)*

Importance of glycolysis:

1) **Energy production** during aerobic and anaerobic conditions:

	1- Under aerobic condition:	2- Under anaerobic condition:
Energy gain	**Glucose → 2 pyruvate + 8 ATP**	**Glucose → 2 lactate + 2 ATP**
How calculated	• 2 NADH+H+ = **6 ATP (produced** by ETC in the mitochondria). • **4 ATP** are **produced** by substrate level phosphorylation. • **2 ATP consumed** by hexokinase &phosphofructokinase-1= **-2** So, the net energy gain = **10 – 2 = 8 ATP / 1 Glucose molecule.**	• **4 ATP formed** by substrate level phosphorylation. • **2 ATP utilized** by hexokinase & phosphofructokinase-1= **-2** So, the net energy gain **= 2 ATP/1 molecule of Glucose.**

2) Glycolysis is the only source of **energy** in **erythrocytes**.

3) Anaerobic glycolysis forms the **major source of energy for muscles** during strenuous exercise, when muscle tissue lacks enough oxygen.

4) The glycolysis provides **carbon skeletons** used for **synthesis of non-essential amino acids** (serine from 3-phosphoglycerate, alanine from pyruvate) as well as **glycerol** part of triacylglycerols and phospholipids. **Written Q**

5) Most of the reactions of the glycolytic pathway are reversible, which are also used for **gluconeogenesis**.

Comparison between aerobic and anaerobic glycolysis: written Q

	Aerobic glycolysis	Anaerobic glycolysis
Site	Cytoplasm of **all cells**	Cytoplasm of **RBCs and skeletal muscles** during strenuous exercise
End products	2 Pyruvic acid 2 NADH+ 2H+	2 Lactic acid 2 NAD+
Regeneration of NAD+	Through **respiratory chain in mitochondria**	Through **lactate formation in cytoplasm**
Energy production	**8 ATP**	**2 ATP**

Rate limiting (key regulatory) enzymes of glycolysis:

- ***The three enzymes which catalyze the three irreversible reactions in the glycolytic pathway :*** **MCQ**

  1) Hexokinase/Glucokinase (step 1)

  2) ***Phospho-Fructo-Kinase-1 (PFK-1) (step 3):*** *most important rate limiting enzyme*

  3) Pyruvate kinase (step 10)

Regulation of key glycolytic enzymes' activity:

1) PFK-1:

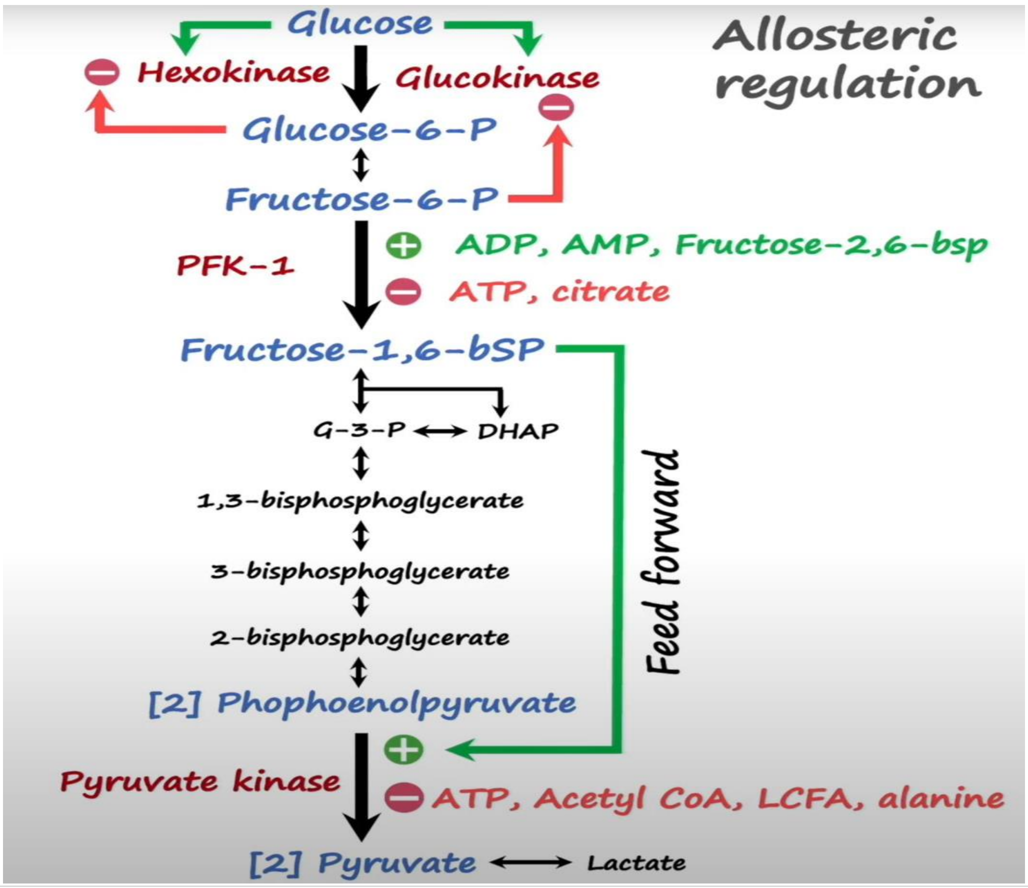
- *is allosterically inhibited by* ***ATP and citrate*** *and activated by* ***ADP, AMP and fructose 2,6-bisphosphate*** *which is the most potent allosteric activator.*

2) Pyruvate kinase:

- *is allosterically activated by* ***fructose 1,6-bisphosphate*** *and inhibited by* ***alanine, ATP and acetyl COA***

3) Hexokinase/Glucokinase: written Q

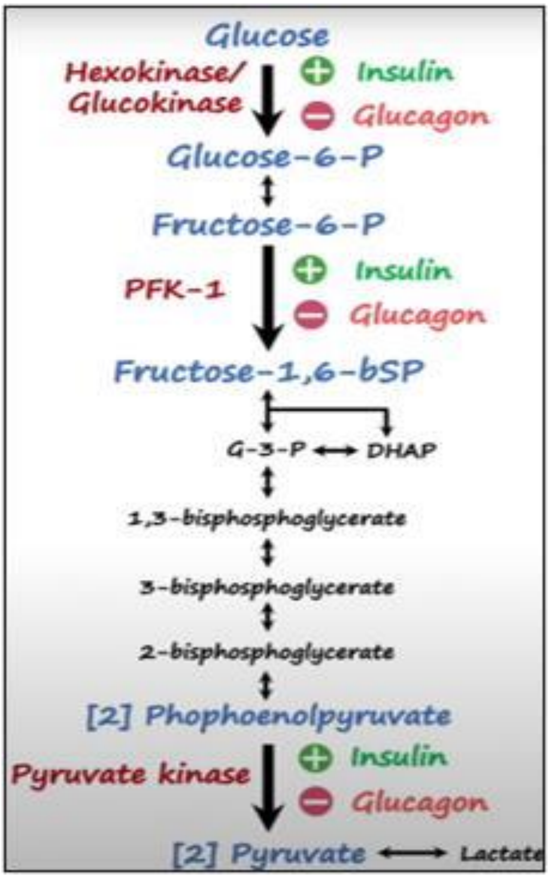
	Hexokinase	Glucokinase
Site	**Most tissues**	**Liver** and **pancreatic β cells**
Affinity to glucose	**High affinity** (low Km)	**Low affinity** (high Km)
Activity	It acts even in the presence of **low blood glucose** levels (**fasting state**)	It acts **only** in the presence of **high blood glucose** levels (**fed state**)
Effect of insulin	**No effect**	**Induce** its synthesis
Effect of glucose-6-P	**Inhibits** its activity	**No effect**
Effect of fructose-6-P	**No effect**	**Inhibits** its activity



Hormonal Regulation of glycolysis

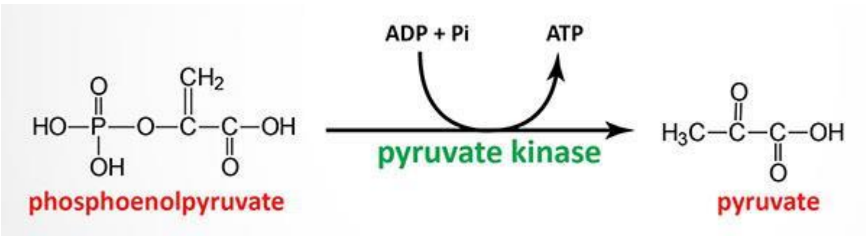
- **Insulin/glucagon ratio are the main hormonal regulator of glucose utilization:** **written Q**

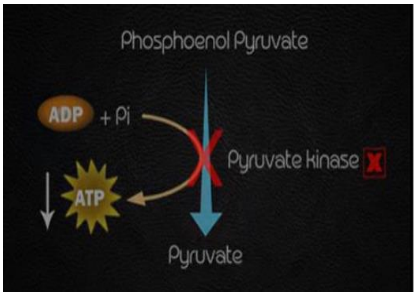
	Insulin:	**Glucagon:**
Nature	• ***The only hypoglycemic hormone.***	• ***Hyperglycemic*** *hormone*
Secretion	• *Secreted after feeding of carbohydrates or in response to high blood glucose level (**hyperglycemia**).*	• *Secreted in case of carbohydrate deficiency or in response to low blood glucose level (**hypoglycemia**).*
Function MCQ	• *Insulin generally **stimulates** all the pathways of glucose utilization, including glycolysis (induction of glycolytic enzymes).*	• *Glucagon **inhibits** glycolysis (inhibits the activity of key glycolytic enzymes).*

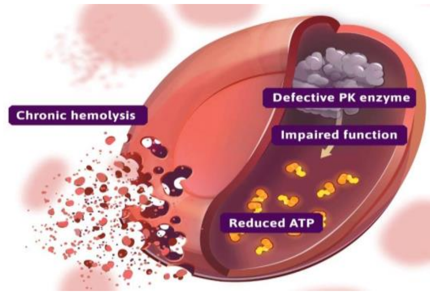


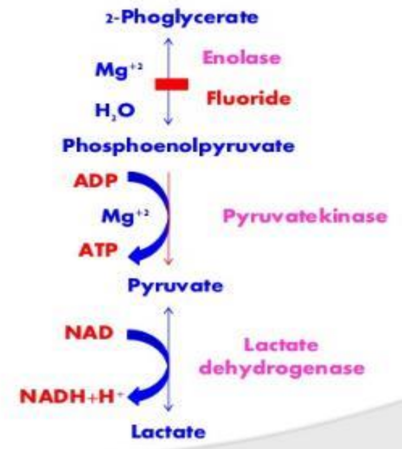
Biomedical importance (clinical aspects) of glycolysis:

Pyruvate kinase	• *Inherited deficiency of **pyruvate kinase** leads to **hemolytic anemia** due to decreased ATP production from glycolysis.* **MCQ**
Fluoride:	• *It removes **Mg+2 ions** and so will inhibit **enolase enzyme** → inhibition of glycolysis in bacteria → no production of **lactic acid** produced by bacteria which cause **dental caries.*** **MCQ** • ***Fluoride is added to blood, when taking a blood sample for glucose estimation (Why??)*** ➢ *Fluoride is added to irreversibly inhibit **enolase enzyme**. Thus, fluoride will stop the **whole glycolysis** in order not to lower blood glucose values are obtained.*



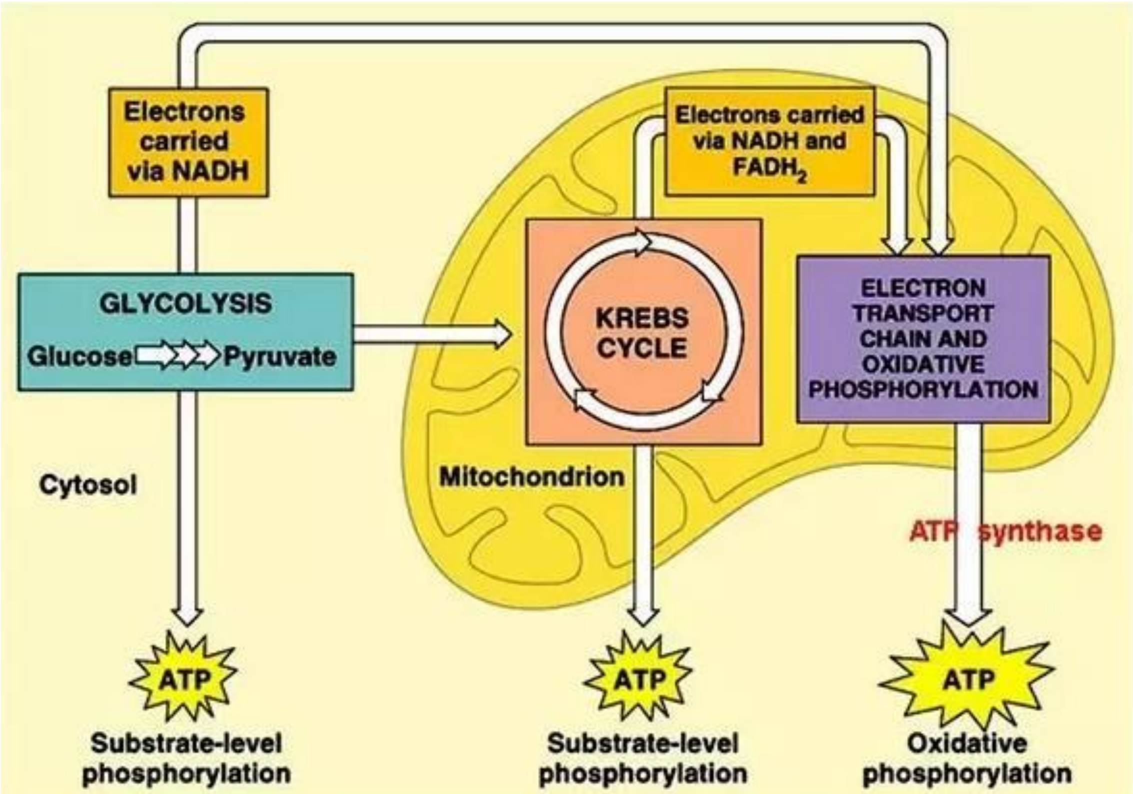


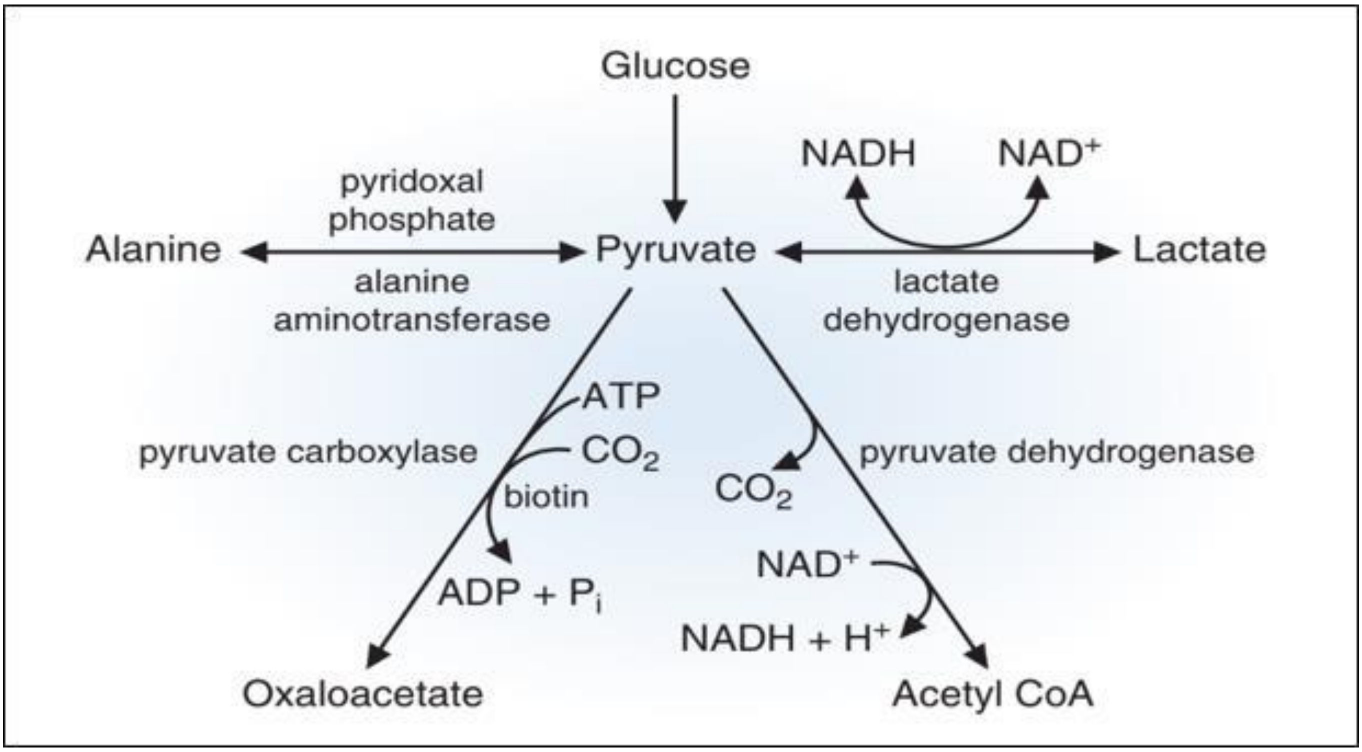




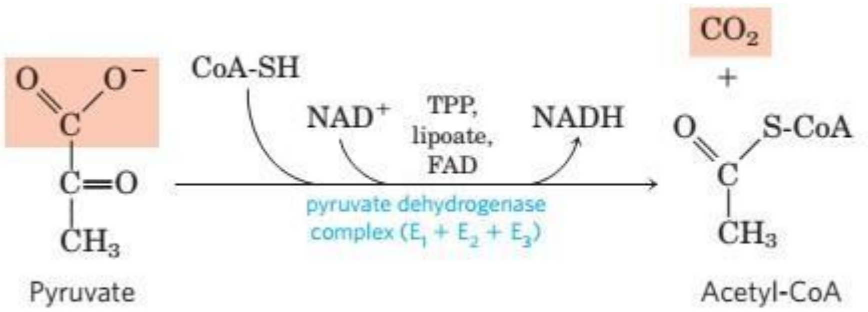
Metabolic fates of pyruvate

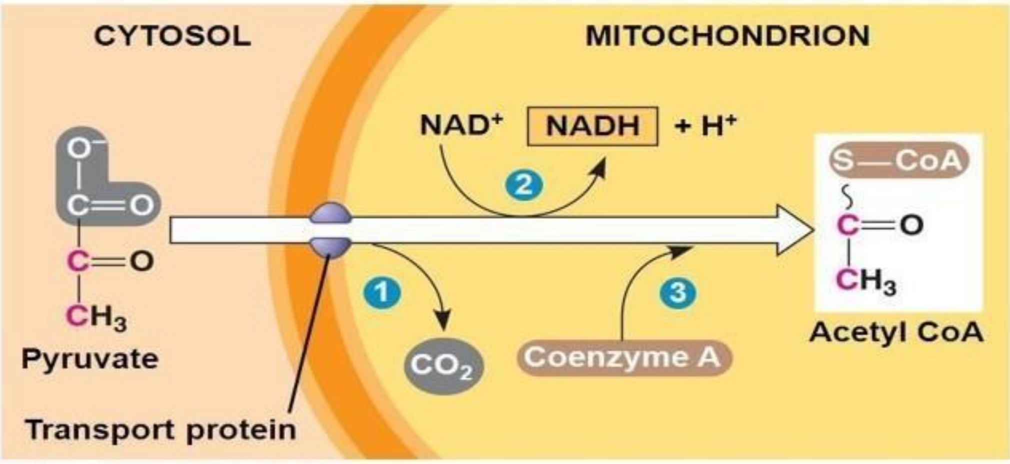
- *Conversion to **lactate, Acetyl CoA, oxaloacetate or alanine.***
- ***Under aerobic conditions:***
  - ***2 pyruvate** will be transported into mitochondria and converted into **2 active acetate (2 acetyl CoA)** for oxidation through Krebs cycle.*

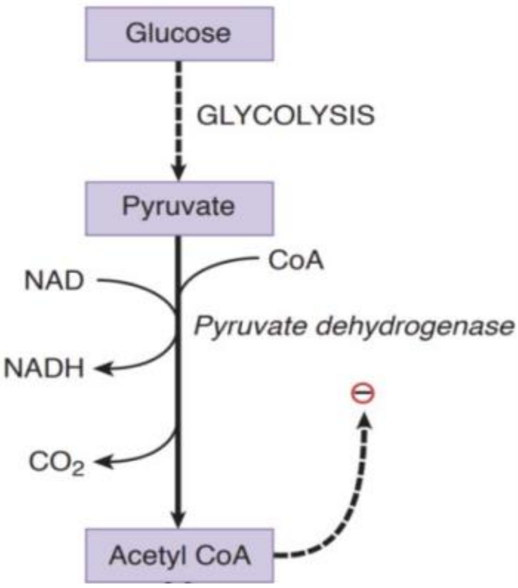


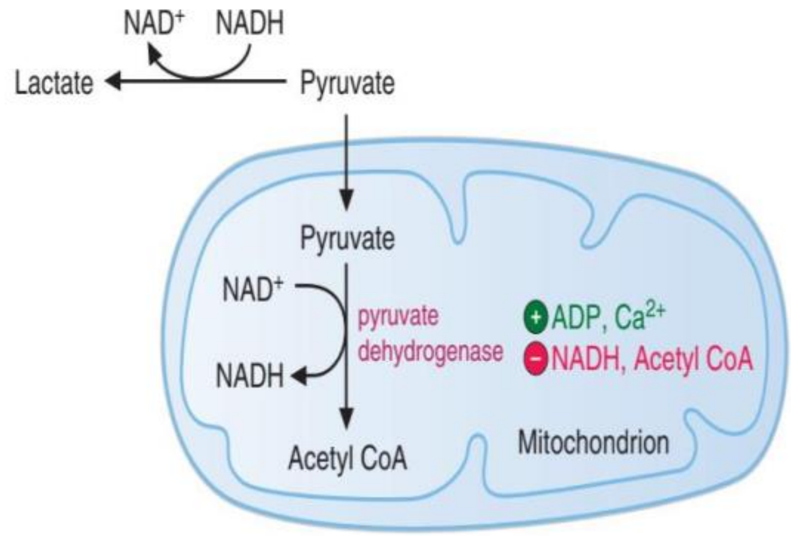


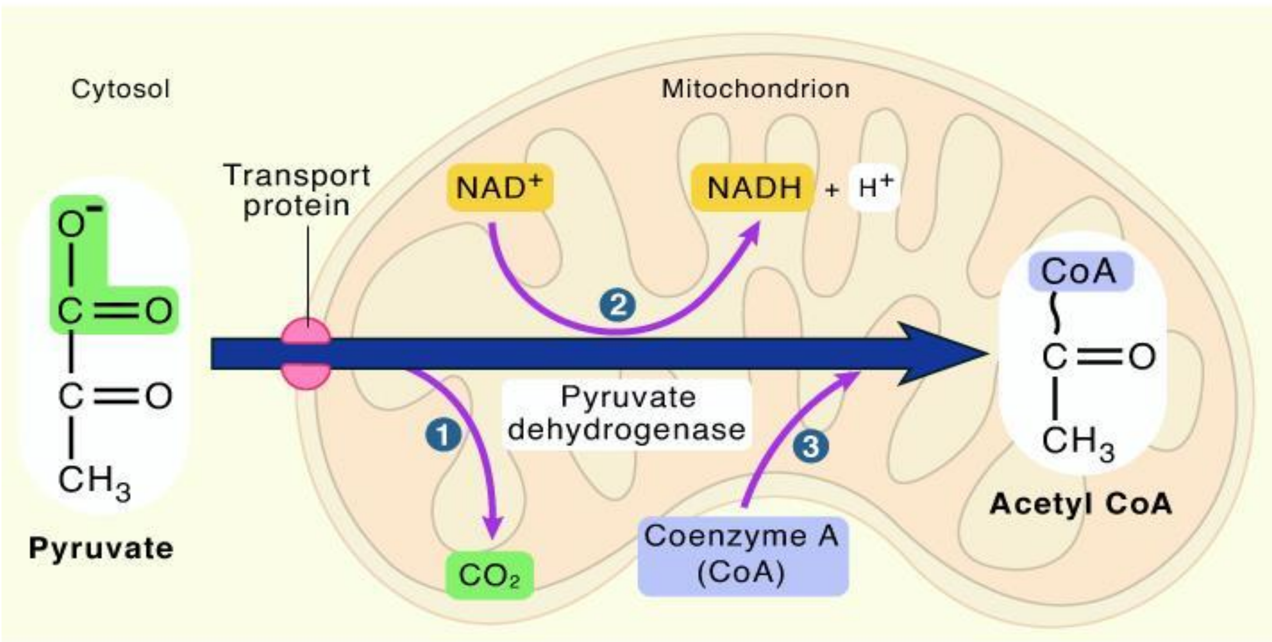
Oxidative decarboxylation of pyruvic acid:

Def:	• *It is conversion of pyruvic acid into acetyl CoA (**The link reaction between Glycolysis and Citric acid cycle**).*
Site:	• *In mitochondrial matrix of **all tissues except RBCs.***
Steps:	• *Conversion of pyruvic acid into acetyl CoA is catalyzed by a multi-enzyme complex called **pyruvate dehydrogenase complex**, which is composed of **3 Enzymes requiring 5 Cofactors:*** 1. ***TPP; Thiamine pyrophosphate** (Vit B1).* ***MCQ*** 2. ***Lipoic acid*** 3. ***CoASH** (Vit B5, pantothenic acid)* 4. ***FAD** (Vit B2, riboflavin)* 5. ***NAD+** (Vit B3, niacin)*  ***2 Pyruvate → 2 acetyl CoA + 2 CO2 + 2 NADH+H***
Energy production:	• ***6 ATP** formed by oxidation of **2 NADH+H⁺** by the electron transport chain.* ***MCQ***
Regulation:	• ***Pyruvate dehydrogenase is inhibited by:*** ➢ *Its product acetyl-CoA, NADH and ATP* • ***Pyruvate dehydrogenase is activated by:*** ➢ *COA, NAD+, ADP and insulin.*









1 Carboxyl group gets removed, forming CO_2

2 NAD^+ gets reduced to NADH

3 Coenzyme A gets attached to acetate, forming acetyl CoA

Clinical aspects (Thiamine deficiency)

- *Thiamine deficiency, which is common in **alcoholics**, **decreases** pyruvate dehydrogenase (**PDH**) activity causing pyruvate to accumulate in tissues and form **lactate**.* ***MCQ***
- *High NADH levels from alcohol metabolism decrease PDH activity and increase the conversion of pyruvate to lactate resulting in **high levels of blood lactate → lactic acidosis which may lead to coma.***

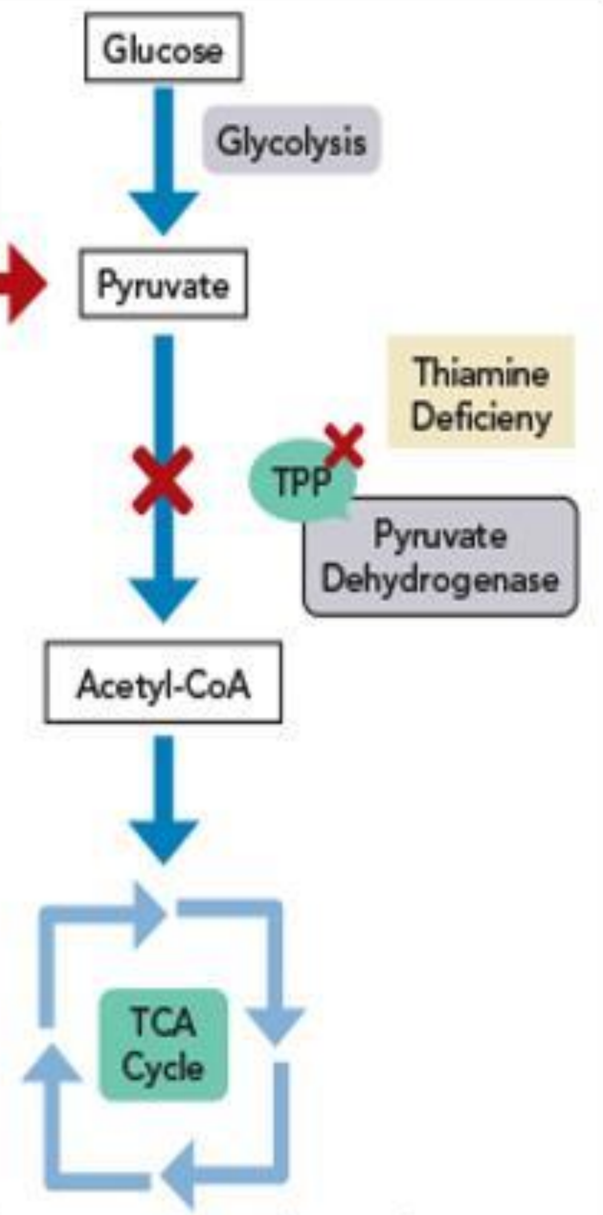


Figure 1
Thiamine is an essential cofactor in the conversion of pyruvate to acetyl-CoA. In the setting of thiamine deficiency, the pathway is instead shunted toward lactate.[9] Abbreviations: Co-A, Co-factor A. TCA, Tricyclic acid cycle. TPP, Thiamine pyrophosphate