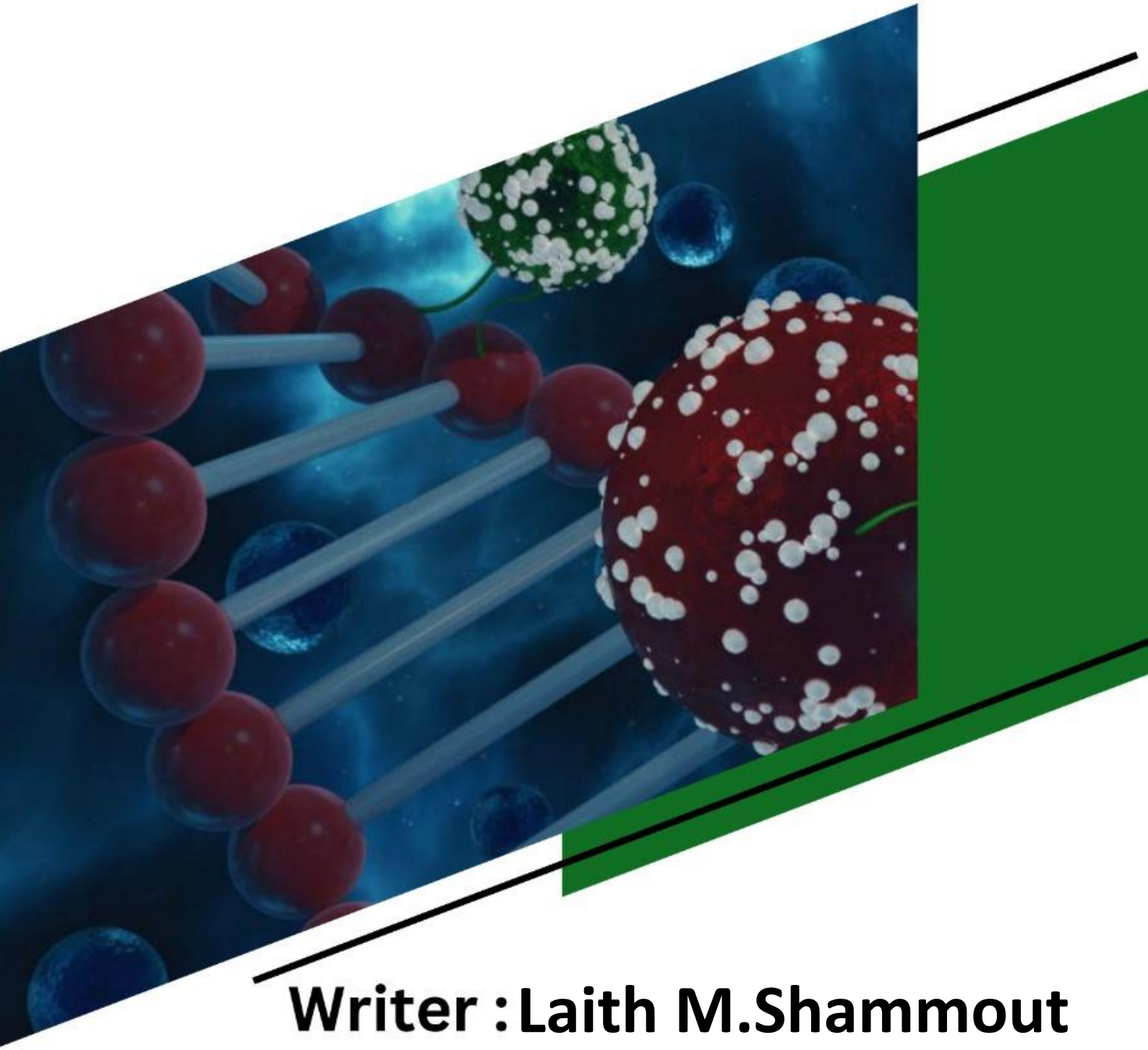
Doctor 021

METABOLISM

Sheet no. 11



Writer : Laith M.Shammout

Corrector : Mohammad Aladwi

Doctor : Diala abu hassan

The doctor started the lecture and asked what is the difference between digestion and metabolism?

She said that METABOLISM is a series of reactions that occur in cells

Digestion is based on how to break your food into small products and absorb it

When the product enters the cell regardless of the source it will go in metabolic pathways

The metabolic reactions could be (anabolic or catabolic)

Let's start with our first pathway which happens on sugars

GLYCOLYSIS REACTIONS AND REGULATION

- **Glycolysis is an example of a metabolic pathway**
- **The product of one reaction is the substrate of the next reaction**

glycolysis means breakdown of glucose into two pyruvates

it's a linear pathway (the product of a step is the reactant of the next step)

it consists of 10 steps we can classify them into:

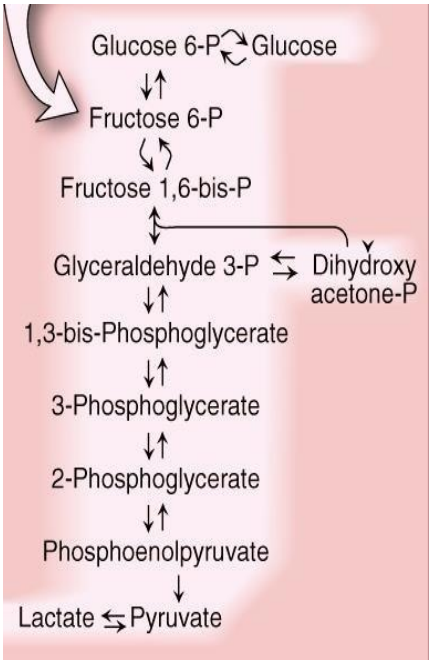
1-we want to modify glucose to make it a molecule which can be divided into two almost identical molecules(rearrangement).

2-the second phase we modify the products of the first phase, thus we extract energy and rearrange the molecules.

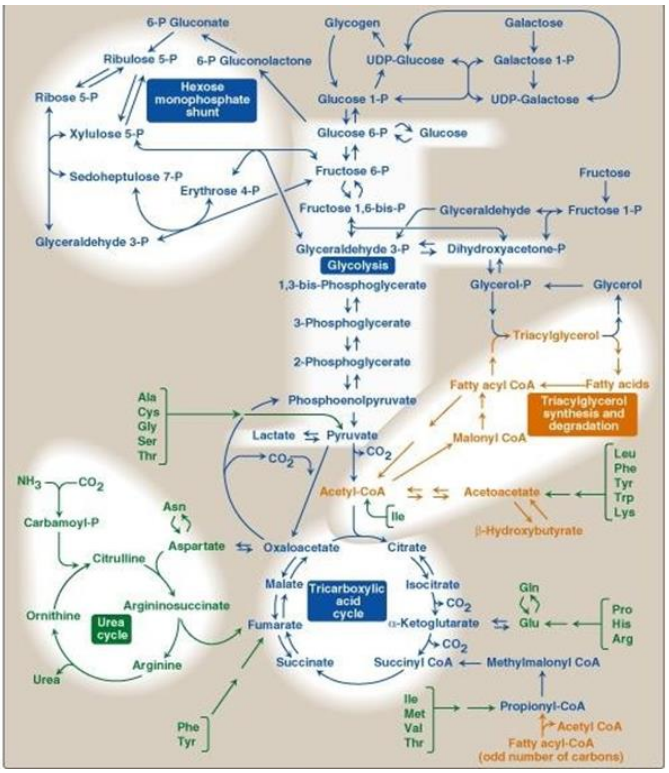
The steps of glycolysis:

Take a glimpse on the following steps

We will go into detail later



➢ Metabolic pathways intersect to form network of chemical reactions



Glycolysis is a part of a complex of pathways which meet at certain points

There are a lot of molecules which appear in different pathways (it's like a puzzle)

Take a look at this figure:

In the middle (the linear pathway to break glucose) it's the glycolysis

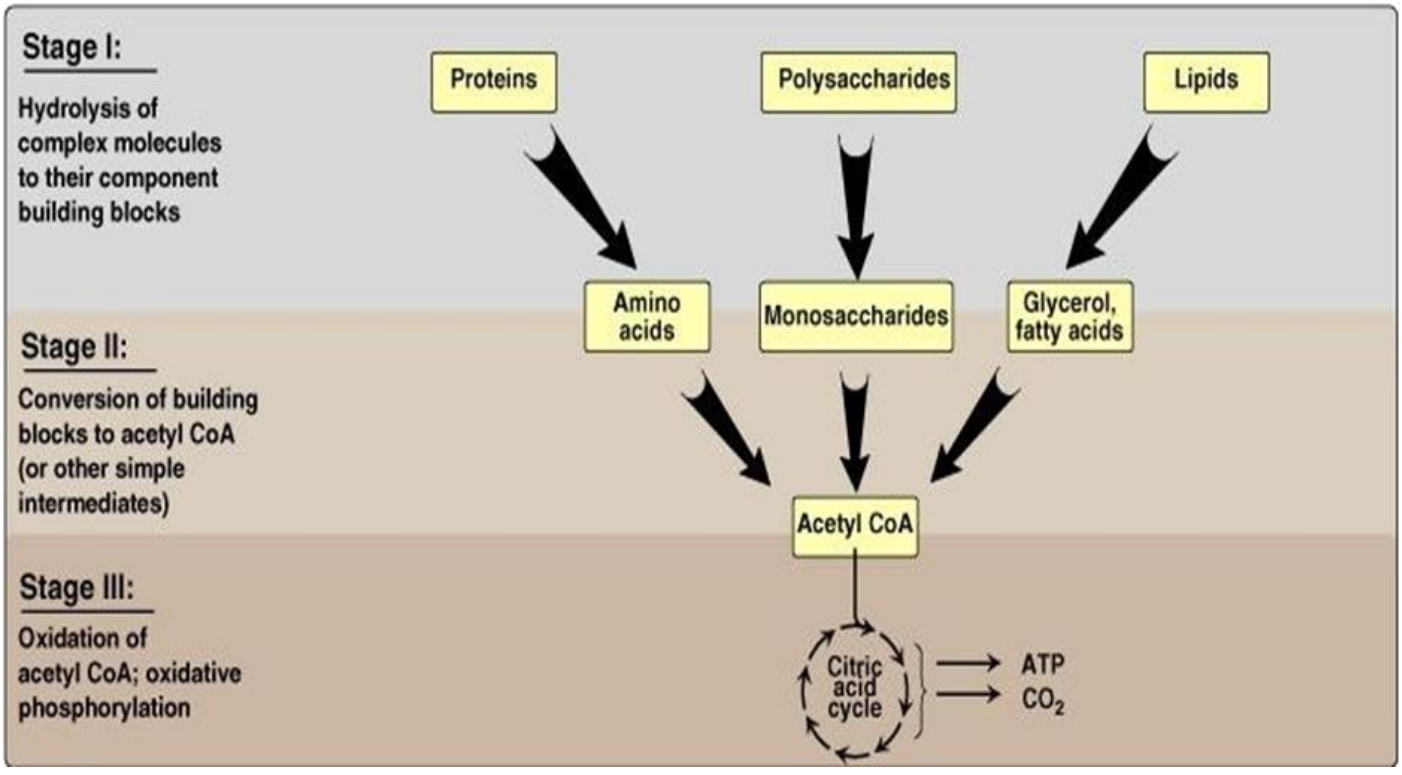
In the upper left it's the opposite pathway of glycolysis (glucogenesis).

In the upper right it's the pathway of production and degradation of glycogen.

The pathways usually meet at acetyl coa step

Kreps cycle is a universal pathway

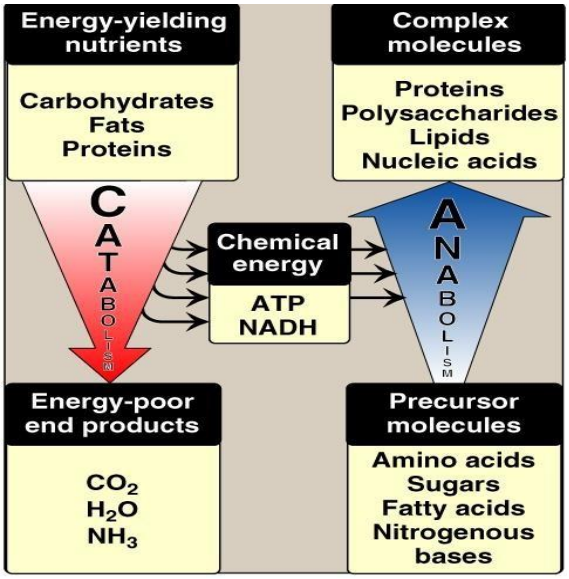
GENERAL STAGES OF METABOLISM



TYPES OF METABOLIC PATHWAYS

The catabolic pathways are degradative pathways to simplify the substrates into very small products even smaller than monomers energy is released in this pathway from breaking the bonds.

Anabolism is a building pathway it forms bonds, so it needs energy.



REGULATION OF METABOLISM

- **Signals from within the cell**

  Substrate availability (if cells don't have the substrate the enzyme will not work)

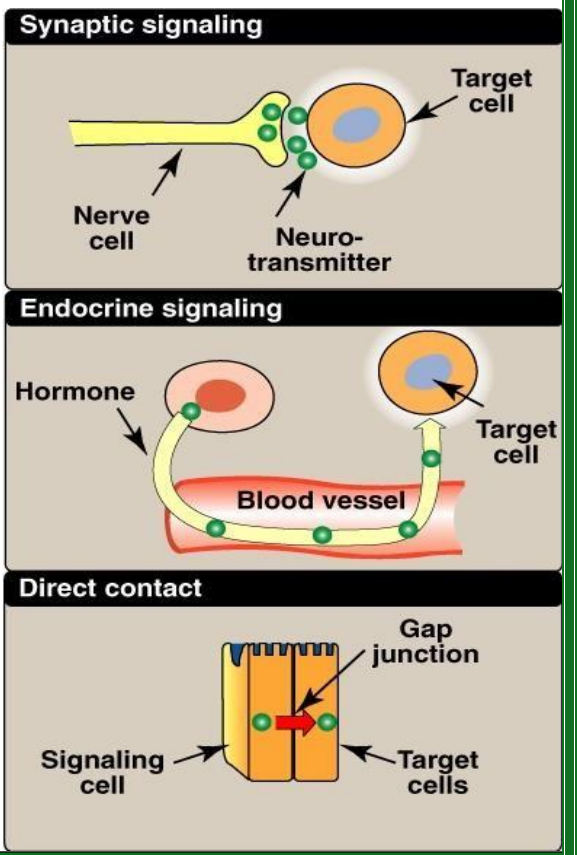
  product inhibition (feedback inhibition)

  allosteric (might be negative or positive regulation)

  - **Rapid response, moment to moment (because they are within the cell)**
- **Communication between cells (intercellular)**

Cell induces signal to effect on another cell
If they were adjacent, we call this effect paracrine effect.

- **Slower response, longer range integration**



Commonly used mechanisms of communication between cells

- **Second messenger**
  - The second messenger is used to transmit the signal from outside to inside.
  - Receptors in the membrane can't detach from the membrane so they need something to transmit the signal into the cell.

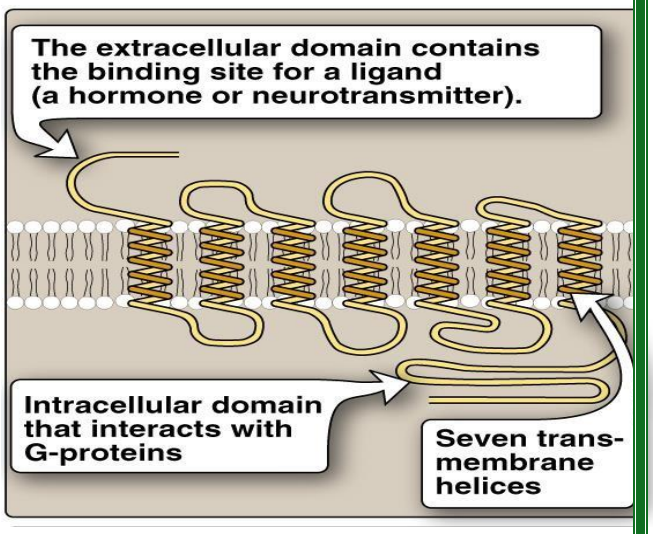
  Examples:

  – **Ca^{2+} / phosphatidylinositol system**

  – **Adenylcyclase system**

COMMUNICATION BETWEEN CELLS THROUGH RECEPTORS- GPCR

G Protein-Coupled Receptor of plasma membrane



- **the most abundant receptors in cells**
- **composed of 7 transmembrane helices, and this is shared with all GPCR**
- **the extracellular subunit is for ligand binding**
- **the intracellular is for interactions with G-protein**
- **G-protein is composed of 3 subunits (alpha, beta, gamma)**
- **Alpha subunit has the site for binding GDP or GTP, once it's bound to GDP it's in the inactive form**
- **When alpha subunit associates with the receptor, it activates the exchange (not phosphorylation) of GDP TO GTP**
- **The association of alpha subunit with the GTP make a conformational change thus alpha subunit dissociates from beta and gamma.**

the active alpha subunit can activate adenylyl cyclase (membrane bound enzyme) which is the enzyme that makes cAMP from ATP

cAMP is the first unbound membrane protein (so it's the second messenger)

cAMP can bind to protein kinase A which is composed of 4 subunits

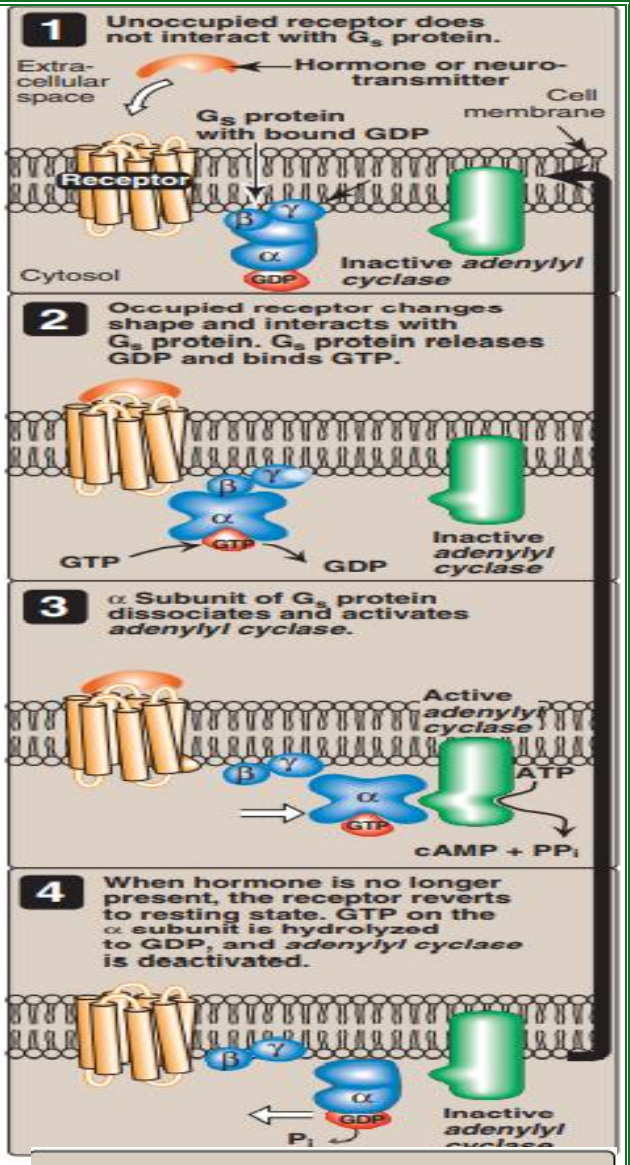
2 regulatory subunits (allosteric regulation)

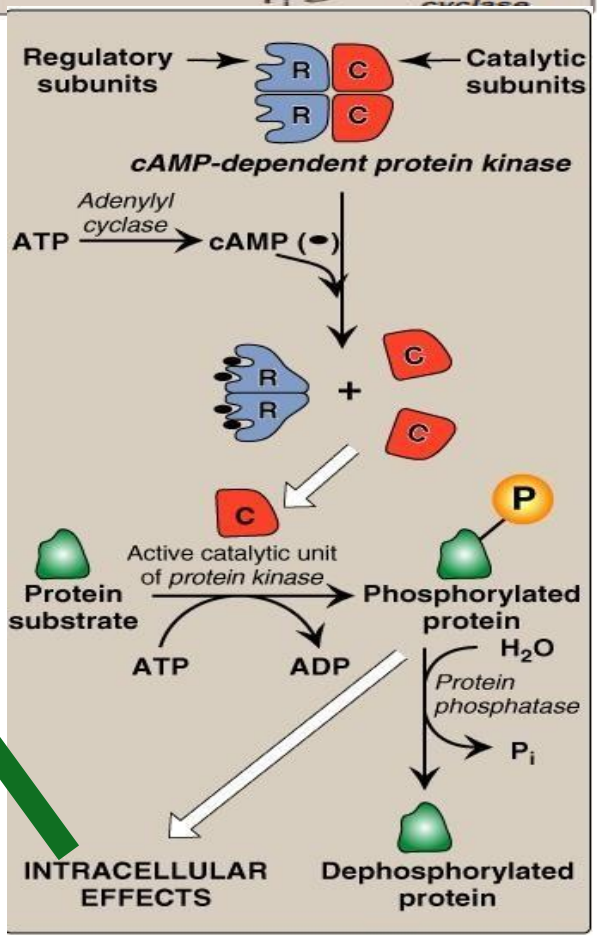
2 catalytic subunits(phosphorylation)

Each one of the regulatory subunits has locations for binding to two cAMP

When the cAMP associates with the regulatory subunits, it makes a conformational change, thus the catalytic subunits dissociate from the regulatory, then it phosphorylates any cellular protein, causing different responses.

The phosphate interacts with the protein via covalent bond but this bond is reversible and removed by phosphatase.
this phosphorylation can cause activation or inhibition of the pathway or the protein.





INTRACELLULAR EFEECTS

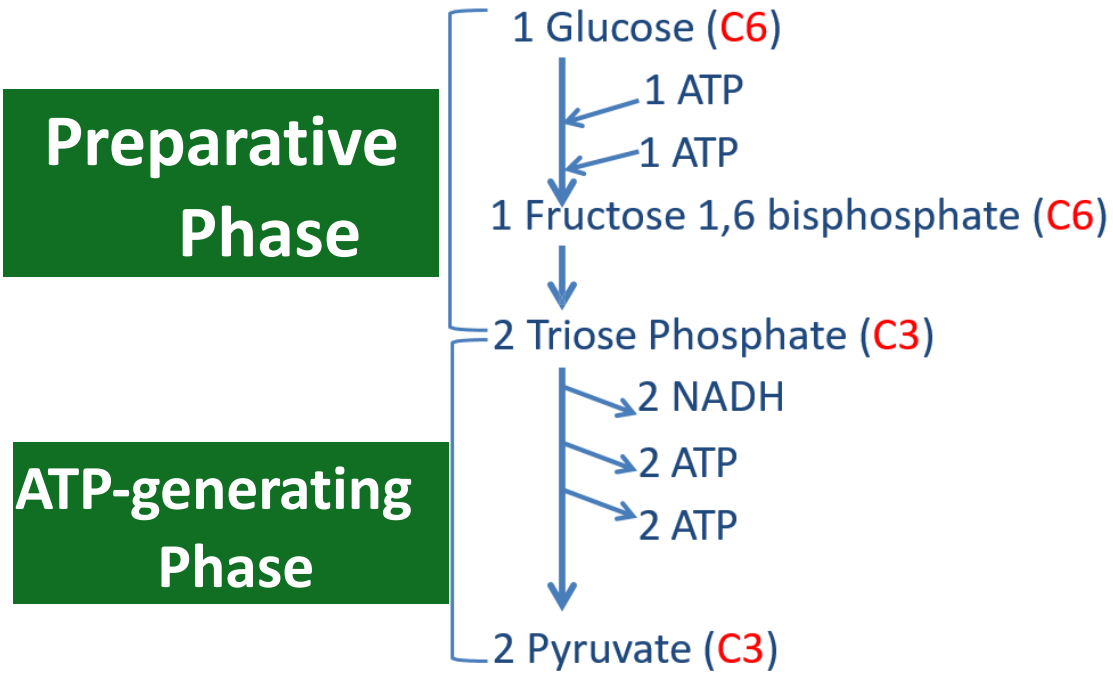
- ✓ **Activated enzymes**
- ✓ **Inhibited Enzymes**
- ✓ **Cell's ion channels**
  (Calcium channels)
- ✓ **Bind to promoter** (activate gene expression)

GLYCOLYSIS

- ✓ **Breakdown of glucose to pyruvate**
  Pathway characteristics:
- ➢ **Universal Pathway: In all cell types, even RBCs**
- ➢ **Generation of ATP**
- ➢ **With or without O_2**
- ➢ **Anabolic Pathway: à biosynthetic precursors (use the intermediates in other reactions)**

This pathway occurs in the cytosol and doesn't require O2 and it generates ATP

THE TWO PHASES OF THE GLYCOLYTIC PATHWAY



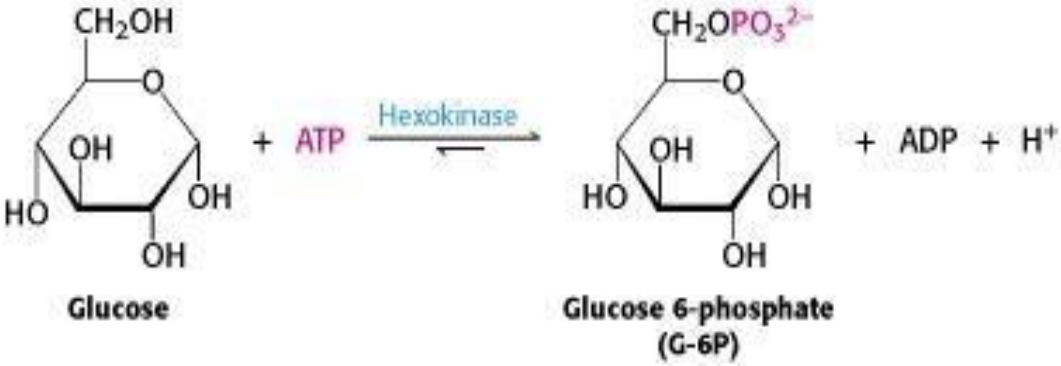
We discussed these phases in the beginning of this sheet go back and read it please

TYPES OF GLYCOLYTIC REACTIONS

- **Phosphoryl transfer**
- **Isomerization**
- **Cleavage**
- **Oxidation reduction**
- **Phosphoryl shift**
- **Dehydration**

STEPS OF GLYCOLYSIS

STEP 1:



Glucose

Glucose 6-phosphate (G-6P)

	Hexokinase	Glucokinase
Occurrence	In all tissues	In liver
Km	< 0.02 mM	10-20 mM
Specificity	Glc., Fruc, Man, Gal	Glc.
induction	Not induced	↑ insulin, Glc
Function	At any glucose level	Only > 100 mg/dl

- **Phosphorylation of glucose to glucose 6- p**

- Irreversible step it needs an enzyme and ATP
- Glucokinase is specific just for glucose

  Glucokinase works under high concentration of glucose that's why km for it so high

  It has low affinity for glucose
- Not all glu that become phosphorylated complete glycolysis

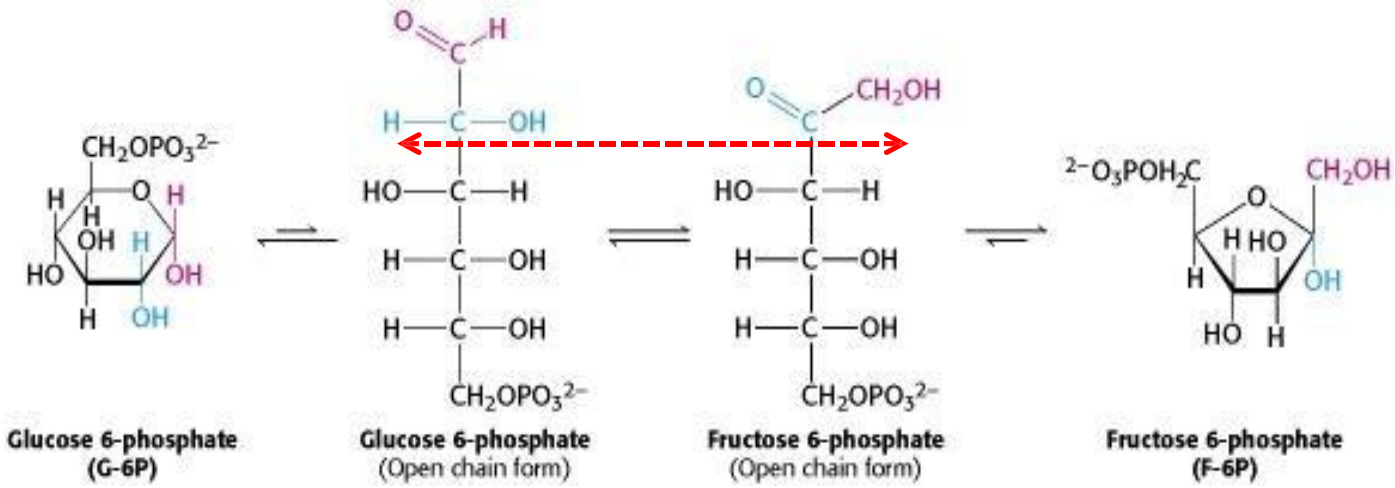
  Why phosphate is added to glu?

  To trap it within the cell

  It has a high effect on the structure because it is a large and charged molecule

  The GLUTs cannot recognize glucose 6-p

STEP 2: ISOMERIZATION



Phosphoglucose Isomerase

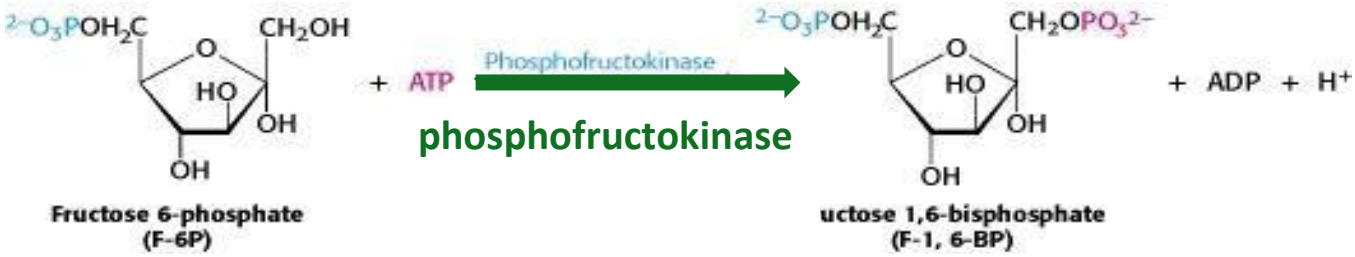
Why does glucose6-p get isomerized to fructose 6-p?

Because fructose has two carbons outside the ring and, that make sense because it must be divided into two almost identical molecules

The double bond was in the first carbon(aldehyde) when glu get isomerized it shifts to the second carbon(ketone)

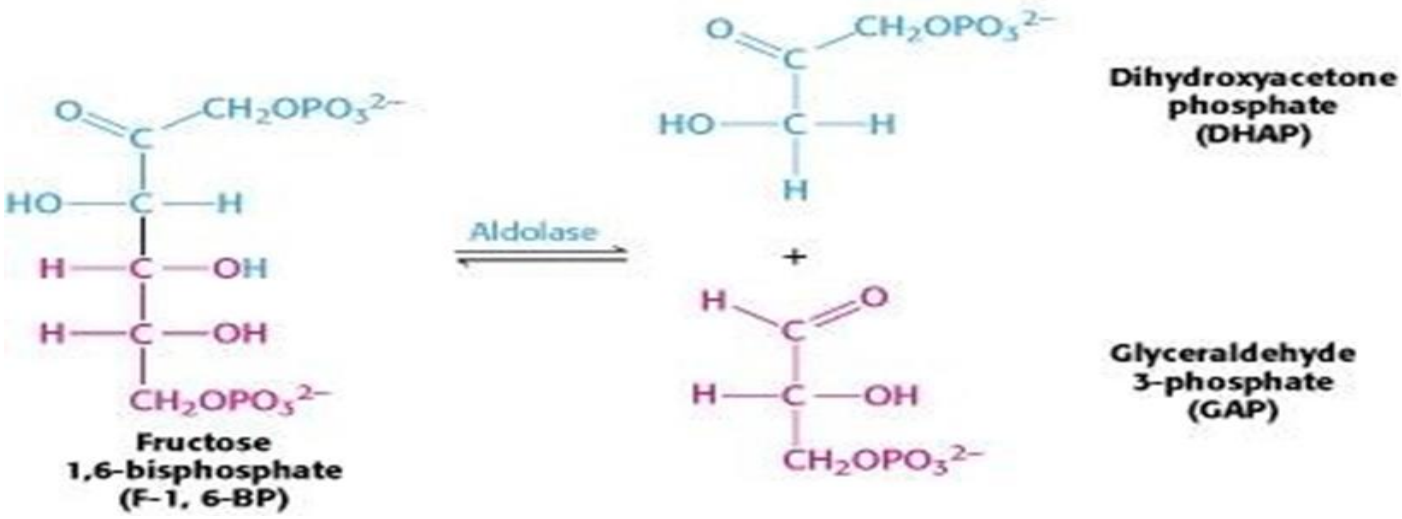
Now we have 1 phosphate on c6, so we add another phosphate on c1 to make it more Suitable for dividing in step no:3

STEP 3: PHOSOHORYLATION OF FRUCTOSE 6-P



- The rate limiting step in the pathway
- Irreversible (we need another enzyme to go backward)
- Need ATP
- Now it is ready for cleavage

STEP 4: CLEAVAGE OF FRUCTOSE 1,6-BISPHOSPHATE



- Aldolase is a lyase enzyme
- Two products DHAP and GAP

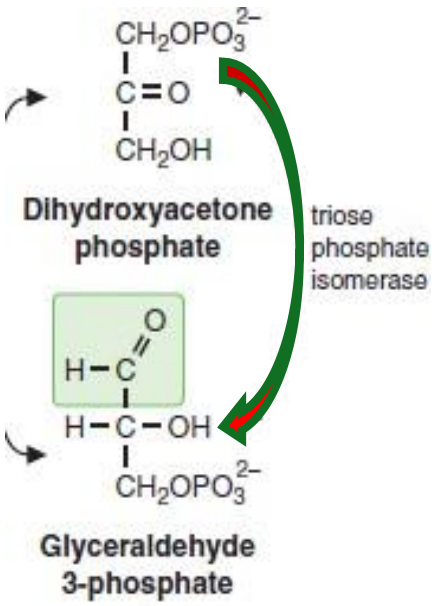
STEP 5:

- DHAP has to be isomerized to GAP to be able to continue

Until now we don't generate energy?

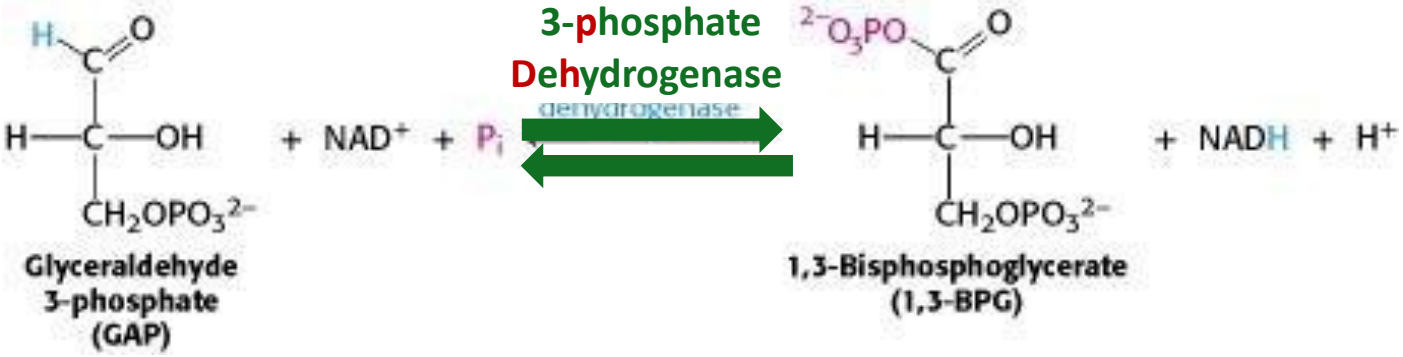
We started from GLU(6c) until we reached two molecules with 3c

Two ATP have been used



STEP 6:

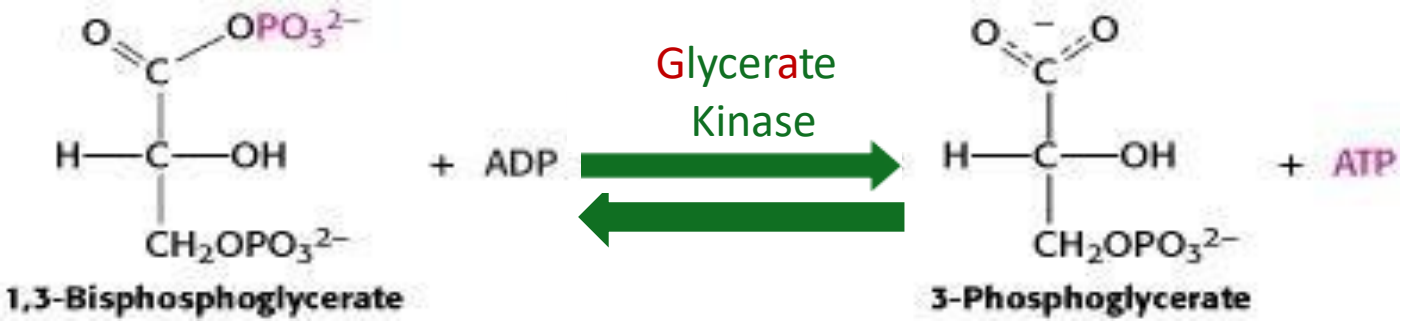
Glyceraldehyde 3-phosphate Dehydrogenase



- Oxidation reduction reaction
- There is addition of inorganic phosphate (not from ATP)
- NAD+

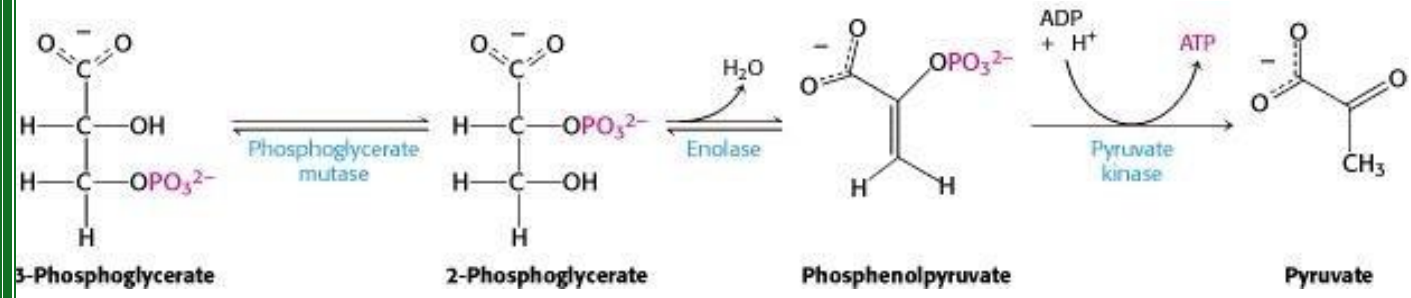
All enzymes must be memorized so Watch out for them

STEP 7:



- Phosphorylation of ADP
- ATP is generated “finally”

STEP 8-10:



step8:

isomerization of 3-phosphoglycerate to 2-phosphoglycerate

phosphoglycerate mutase is an isomerase

step9:

dehydration of 2-phosphoglycerate by removing water molecule to introduce double bond

step10:

irreversible step

another ATP molecule get phosphorylated by pyruvate kinase

IMPORTANT NOTES:

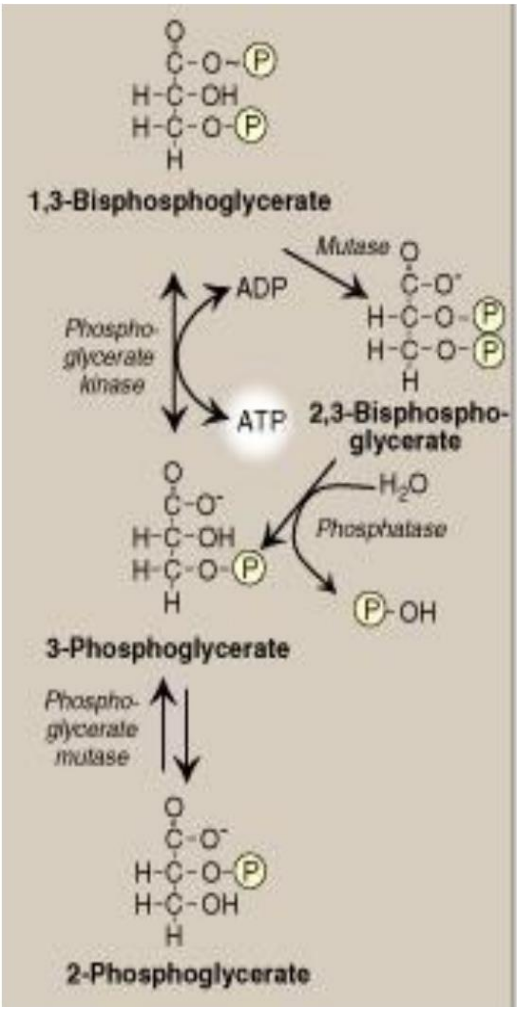
In the first phase two ATP is utilized

For one molecule of GAP two ATP and one NADPH are generated pay attention that every glucose molecule generates two GAP

Calculate the net product 😊

SYNTHESIS OF 2,3 BISPHOSPHOGLYCERATE IN RBC

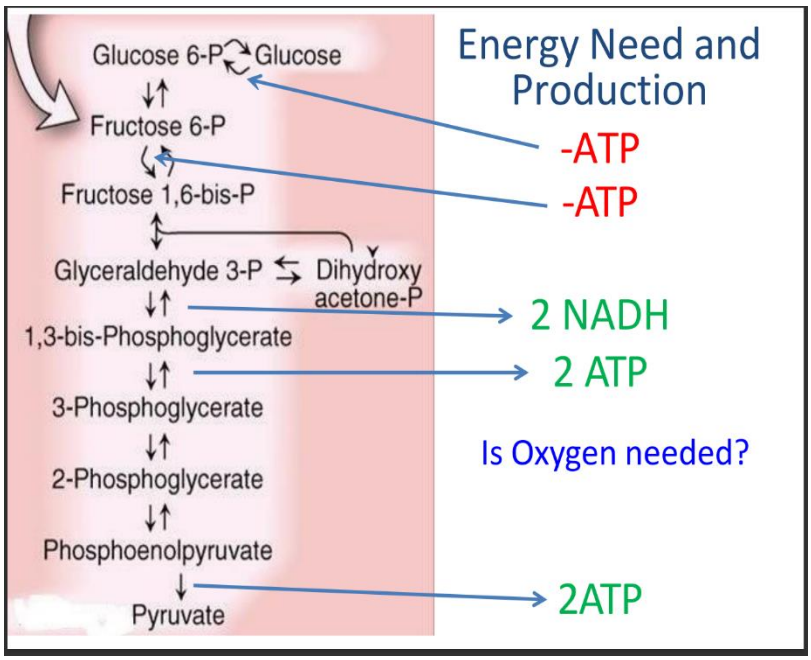
- **increase Oxygen delivery to tissues**
- **By binding to deoxyhemoglobin reducing its affinity to O2 and increasing O2 release to tissues**



There is a "تحويلة"in RBCs in the step which converts 1,3bisphosphoglycerate to 3-phosphoglycerate we said that there is a generation of ATP but if it goes to the "تحويلة" there is no generation of ATP
1,3bisphosphoglycerate is isomerized by MUTASE" ISOMERASE"
To 2,3bisphosphoglycerate
After that hydration and removal of phosphate group by phosphatase
(Hydrolysis of phosphate)
We lost an ATP generating step!!!!!! WHY????
The 2,3bisphosphoglycerate binds to deoxyhemoglobin and decreases the affinity of it toward the oxygen which inhibits rebinding of oxygen to deoxyhemoglobin

- Oxygen isn't needed

This picture shows you where ATP is generated and consumed.
Please ensure that you know these details



Now what will happen to the pyruvate?

- There is an energy production, but it is too little compared to TCA cycle

ALTERNATIVE FATES OF PYRUVATE

1. Oxidative decarboxylation of pyruvate by the PDHC

   PDHC irreversibly converts pyruvate, the end product of glycolysis, into acetyl CoA, a TCA cycle substrate

2. Carboxylation to oxaloacetate

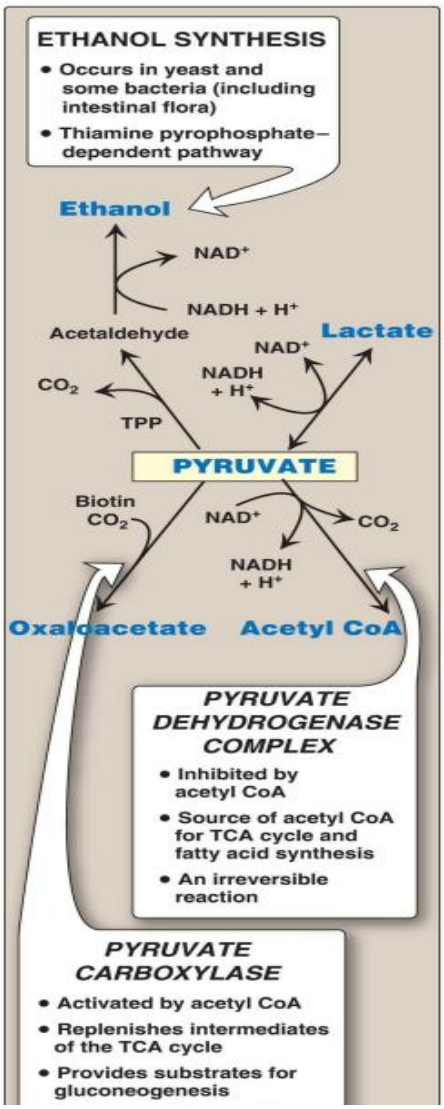
   Oxaloacetate is a 4c molecule thus pyruvate is carboxylated (addition of carbon)

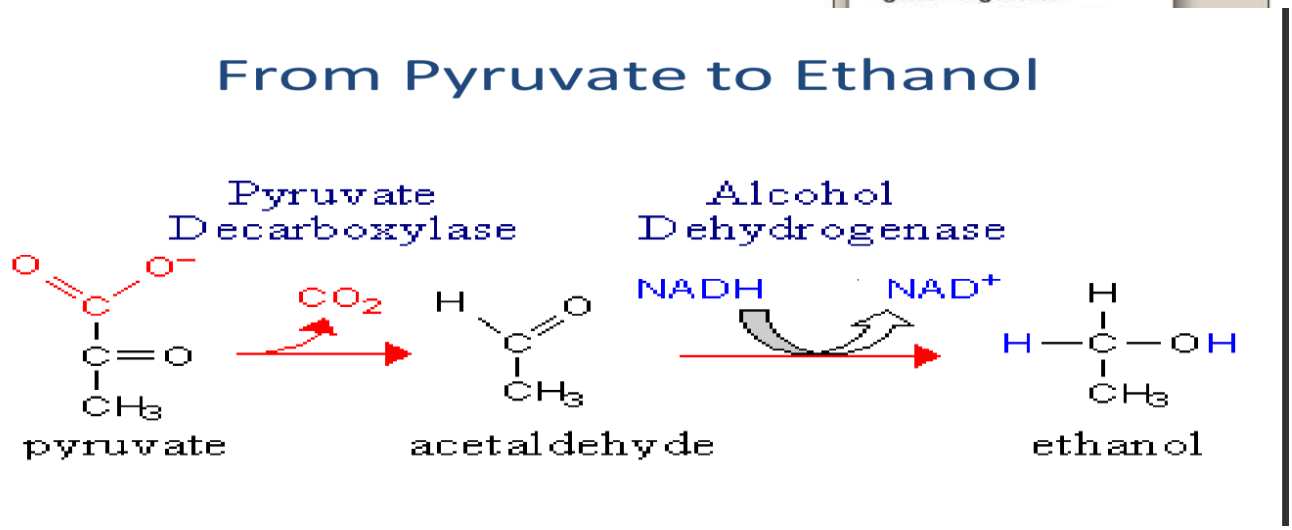
3. Anaerobic respiration

   like in RBCs or in lower energy demand cells

4. Decarboxylation and Reduction to ethanol

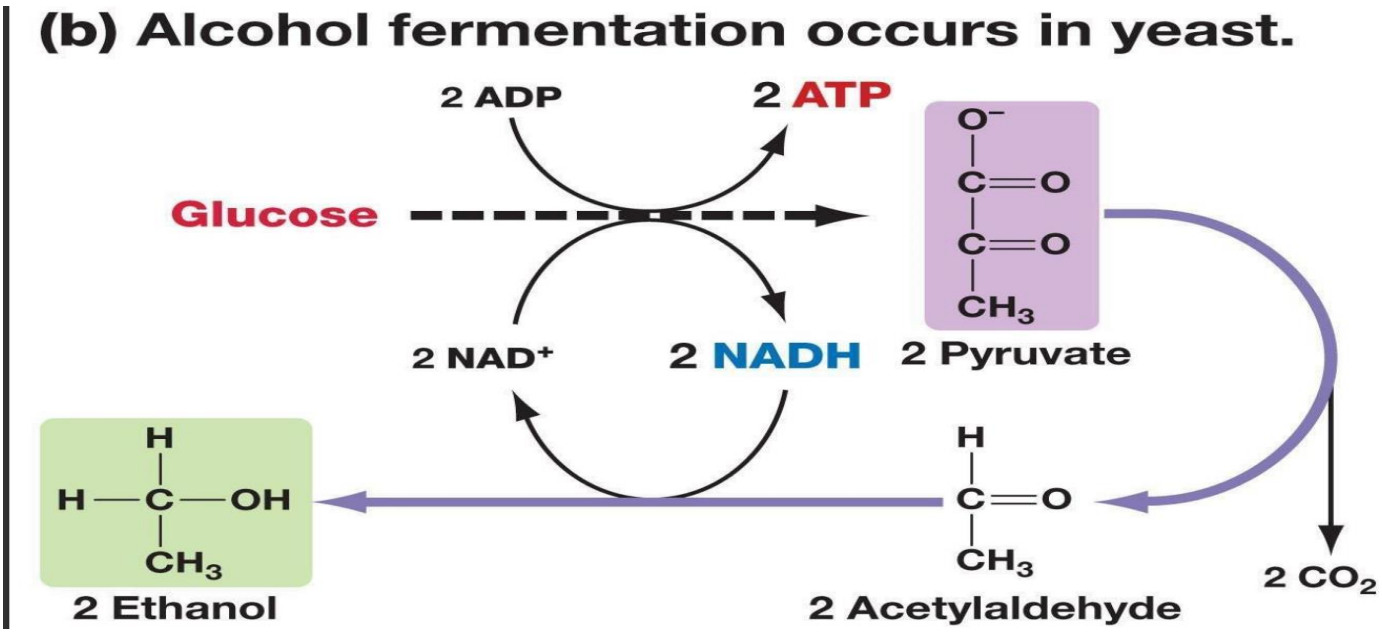
   Occurs in yeast





Why we put sugar on the yeast? عشان تنفخ العجينة

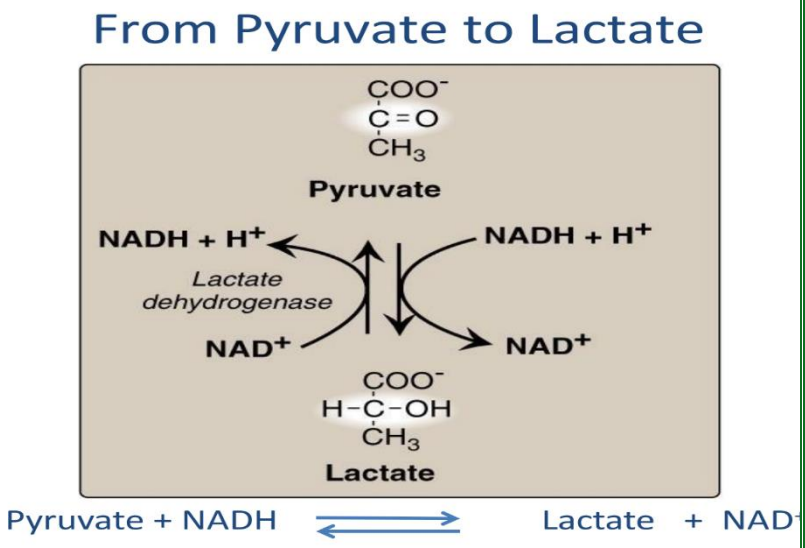
Yeast produces CO_2 after glycolysis by decarboxylation of pyruvate



FROM PYRUVATE TO LACTATE

- By lactate dehydrogenase
- Two ways reaction
- It takes place When O_2 level is low

  You need to know the difference between the two structures (carbonyl become alcohol so it's a reduction reaction)



When is Lactate Produced?

- **Cells with low energy demand**
- **To cope with increased energy demand in rigorously exercising muscle, lactate level is increased 5 to 10 folds**
- **Hypoxia**

  to survive brief episodes of hypoxia (low O2 levels).

CLINICAL HINT: LACTIC ACIDOSIS

- **The most common cause of metabolic acidosis**

– ↑ Production of lactic acid

– ↓ utilization of lactic acid

you are producing too much lactic acid, but you are not using it, and this leads to acidosis, now is it metabolic or respiratory ? It is metabolic.

Pyruvate + NADH ⇌ Lactate + NAD+ "by lactate dehydrogenase"

- **Most common cause: Impairment of oxidative metabolism due to collapse of circulatory system.**

– Impaired O2 transport

– Respiratory failure

– Uncontrolled hemorrhage (blood loss)

you decrease the volume of the blood thus the concentration of lactic acid increases, causing acidosis.

WHEN IT HAPPENS?

- **Direct inhibition of oxidative phosphorylation**
- **Hypoxia in any tissue low O_2 level**
- **Alcohol intoxication (high NADH/ NAD+)**

(Alcohol is oxidized in the cytosol of hepatocytes by alcohol dehydrogenase (ADH), which generates NADH and increases cytosolic $NADH/NAD^+$ ratio) this leads to

- **↓ Gluconeogenesis**
- **↓ Pyruvate Dehydrogenase there is no production of acetyl coA**
- **↓ TCA cycle activity acetyl coA isn't used**
- **↓ Pyruvate carboxylase there is no production of oxaloacetate**

ويَفرغُ المكانُ فيدلُ على قدرِ من كان فيه.