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:

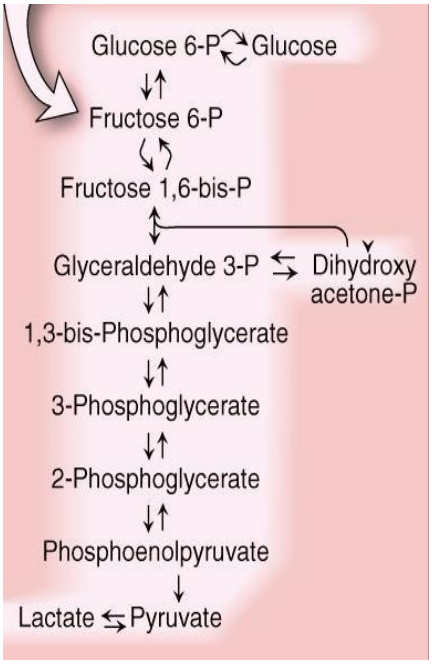
1-we want to modify glucose to make it a molecule which can be divided into two almost identical molecules(rearrangement).

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

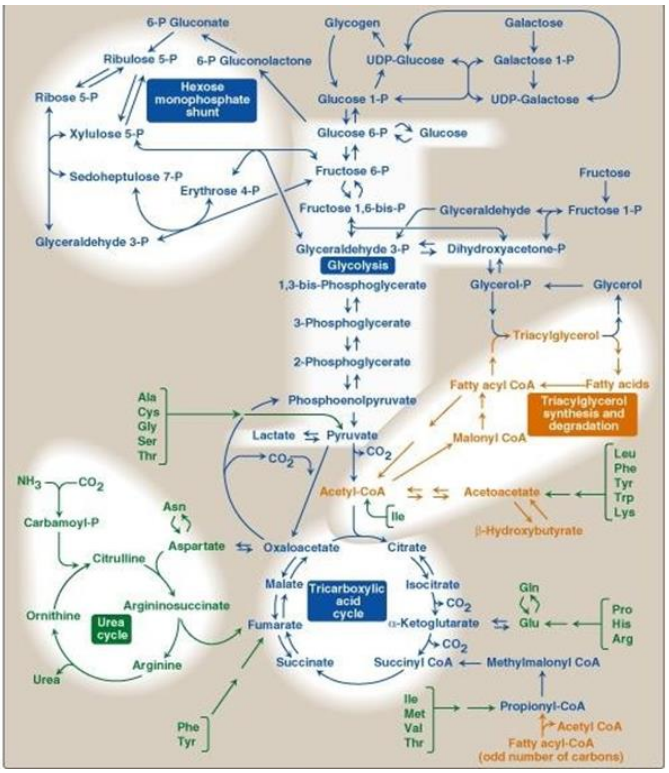
The steps of glycolysis:

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

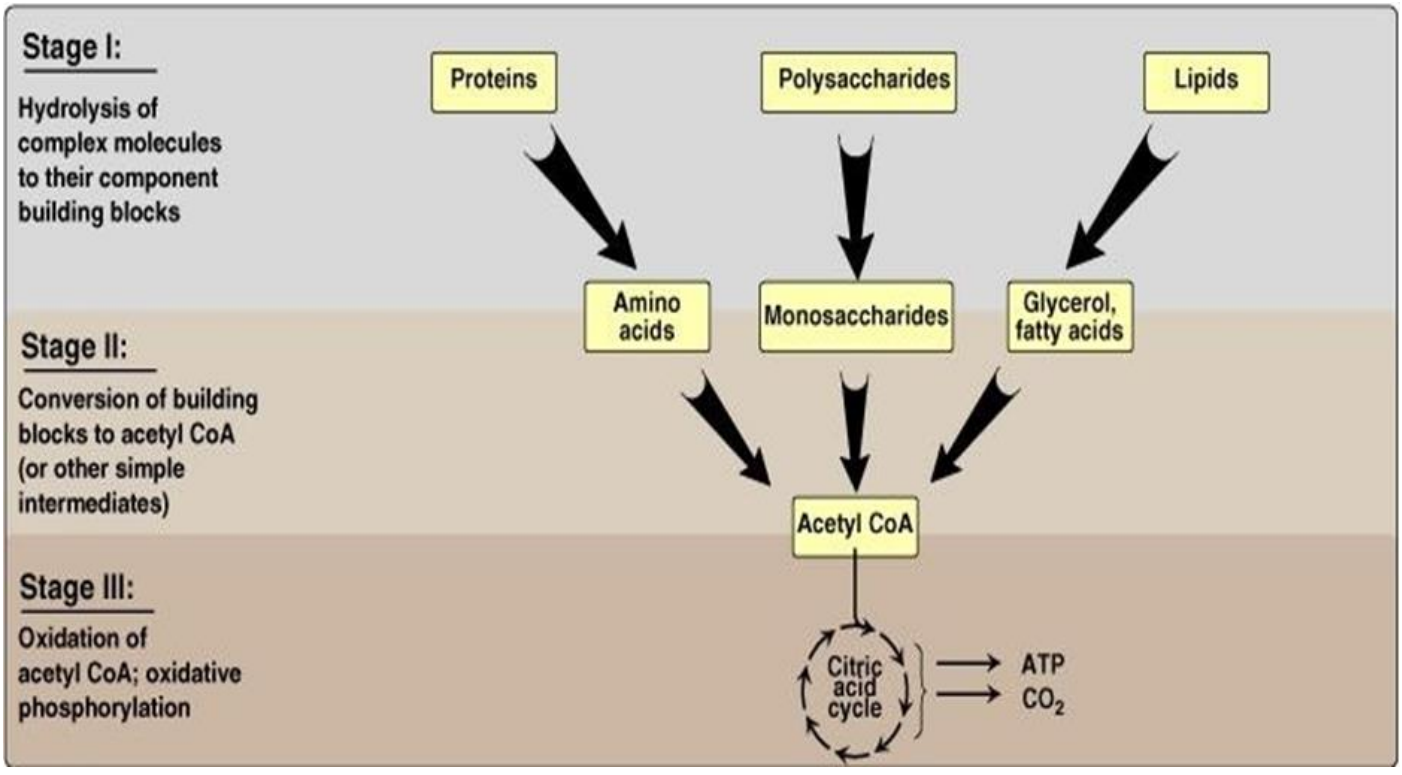
In the upper left it's the opposite pathway of glycolysis (glucogenesis).

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

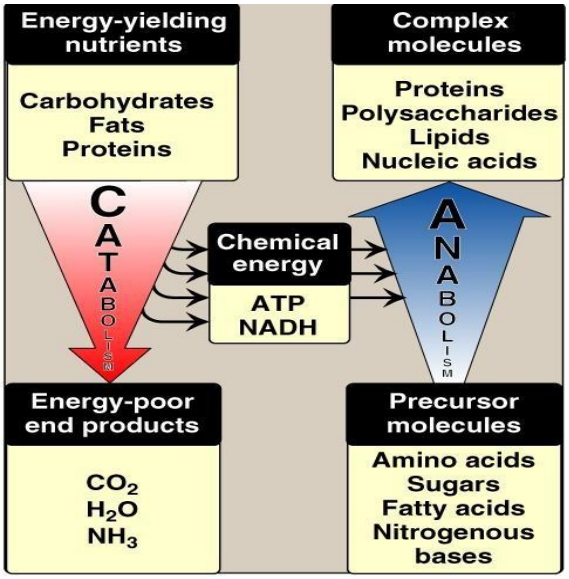
GENERAL STAGES OF METABOLISM



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)

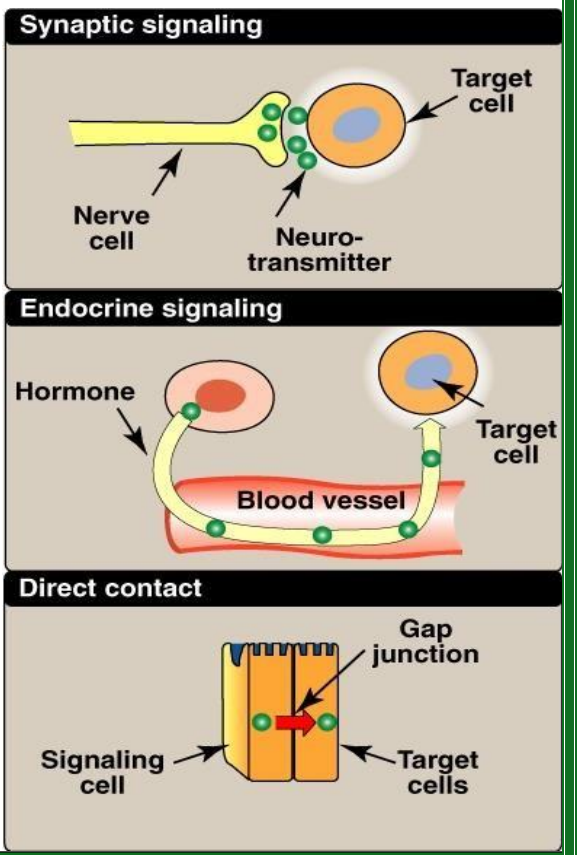
  product inhibition (feedback inhibition)

  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.

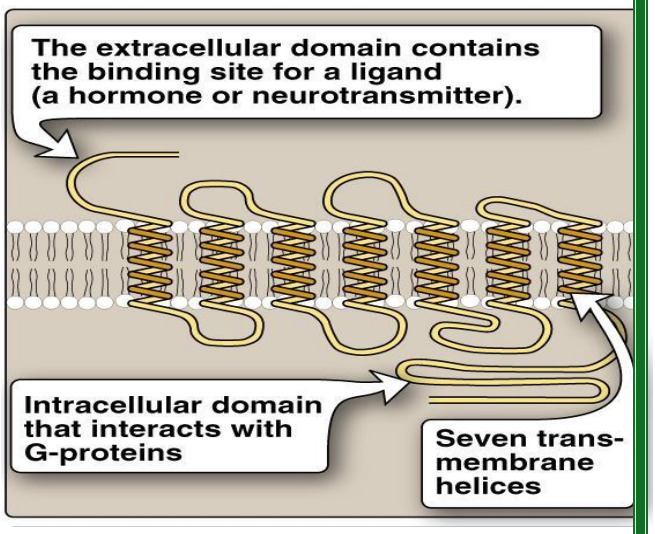
  Examples:

  – **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

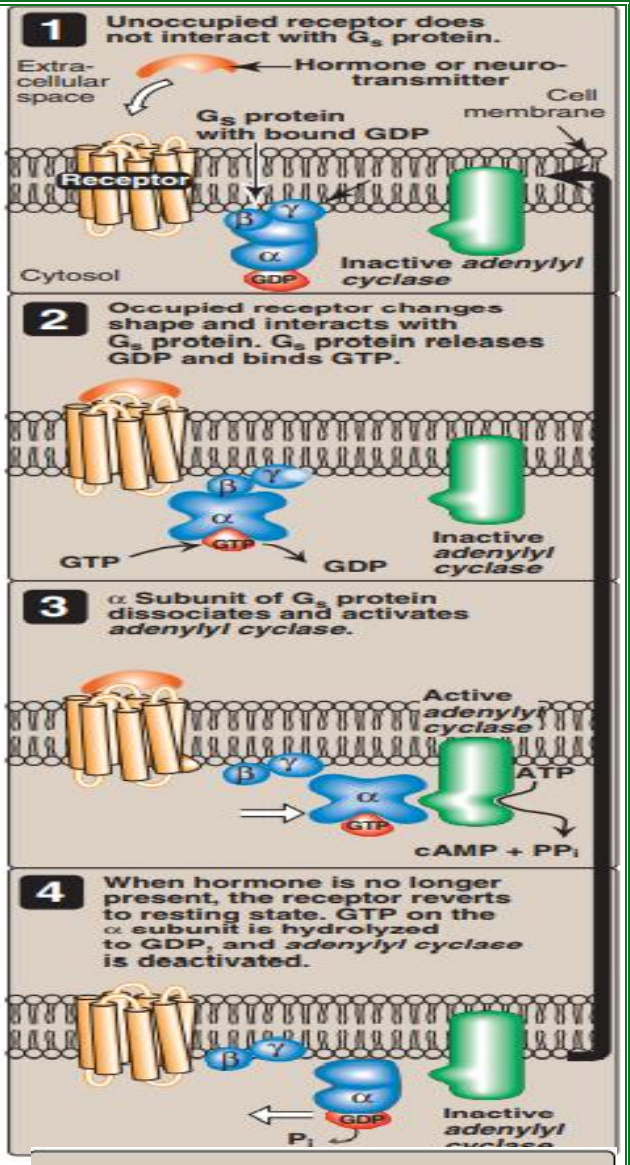
2 regulatory subunits (allosteric regulation)

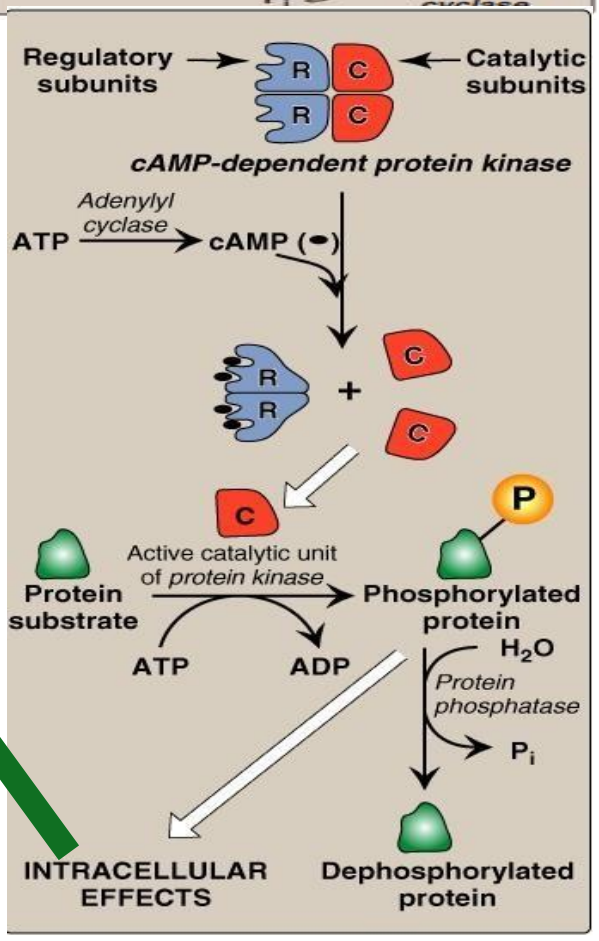
2 catalytic subunits(phosphorylation)

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

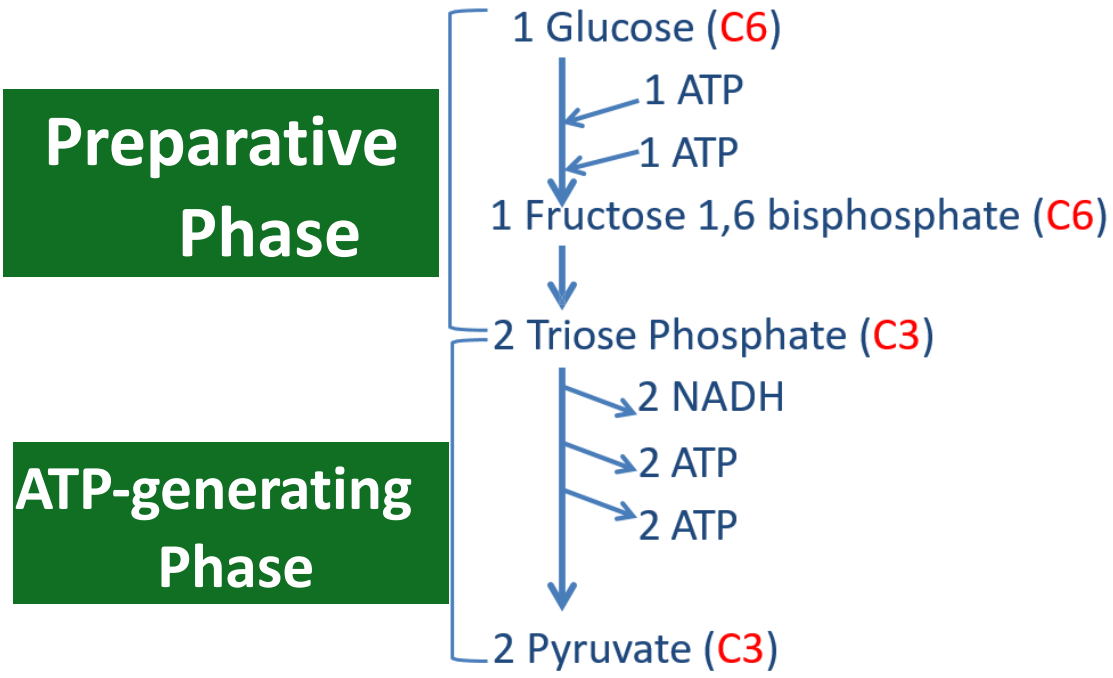
- ✓ **Activated enzymes**
- ✓ **Inhibited Enzymes**
- ✓ **Cell's ion channels**
  (Calcium channels)
- ✓ **Bind to promoter** (activate gene expression)

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



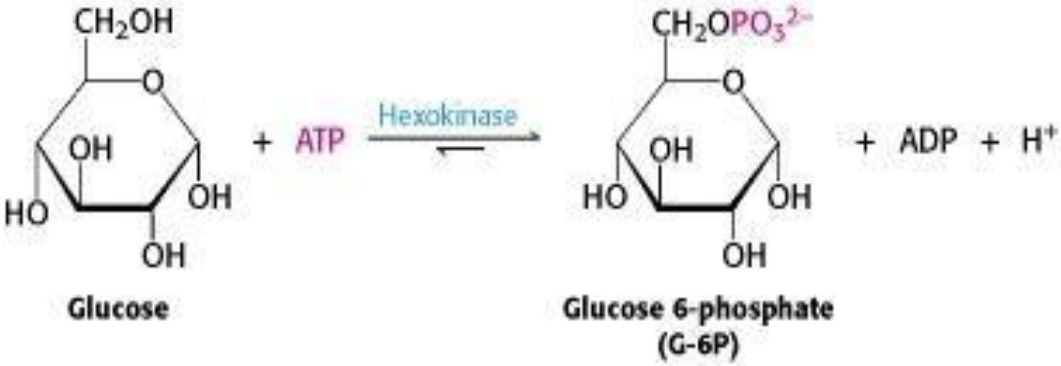
We discussed these phases in the beginning of this sheet go back and read it please

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

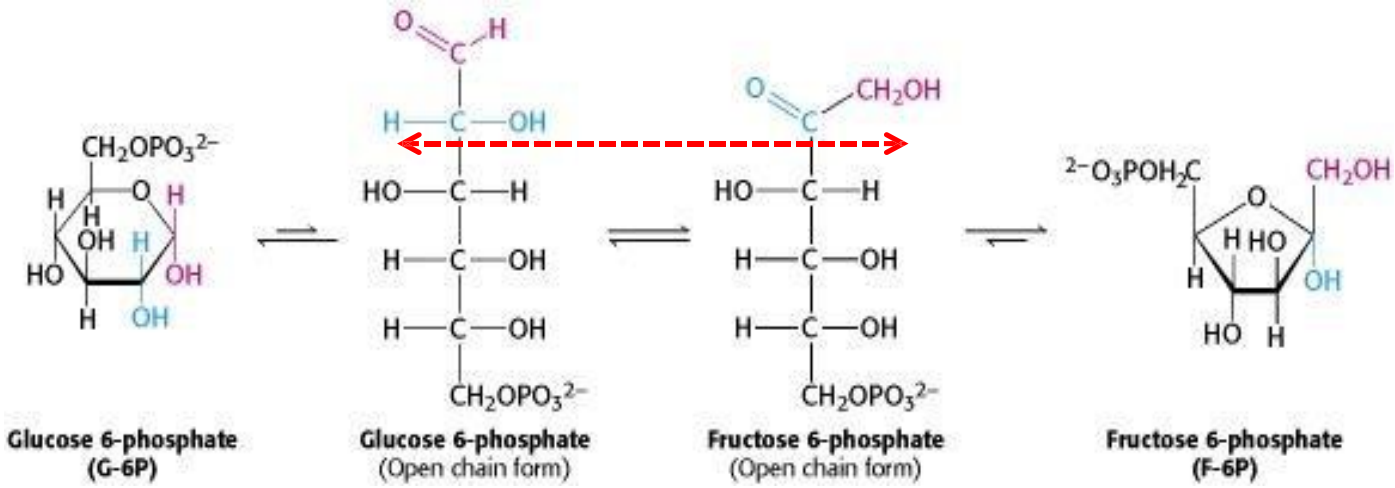
  Why phosphate is added to glu?

  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

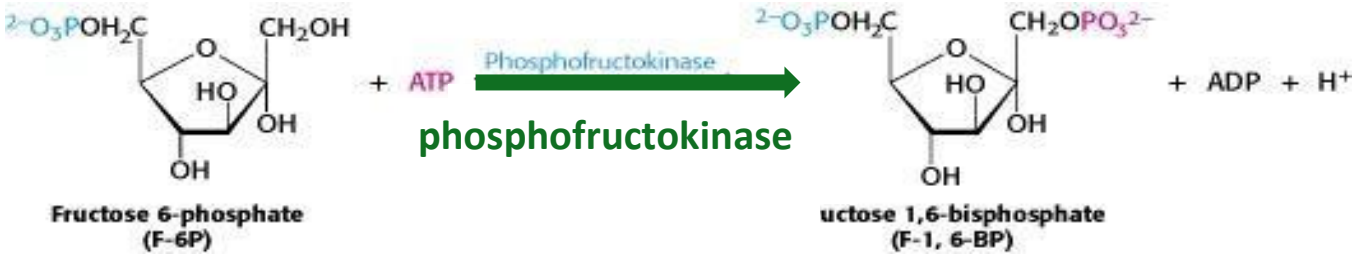
Why does glucose6-p get isomerized to fructose 6-p?

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)

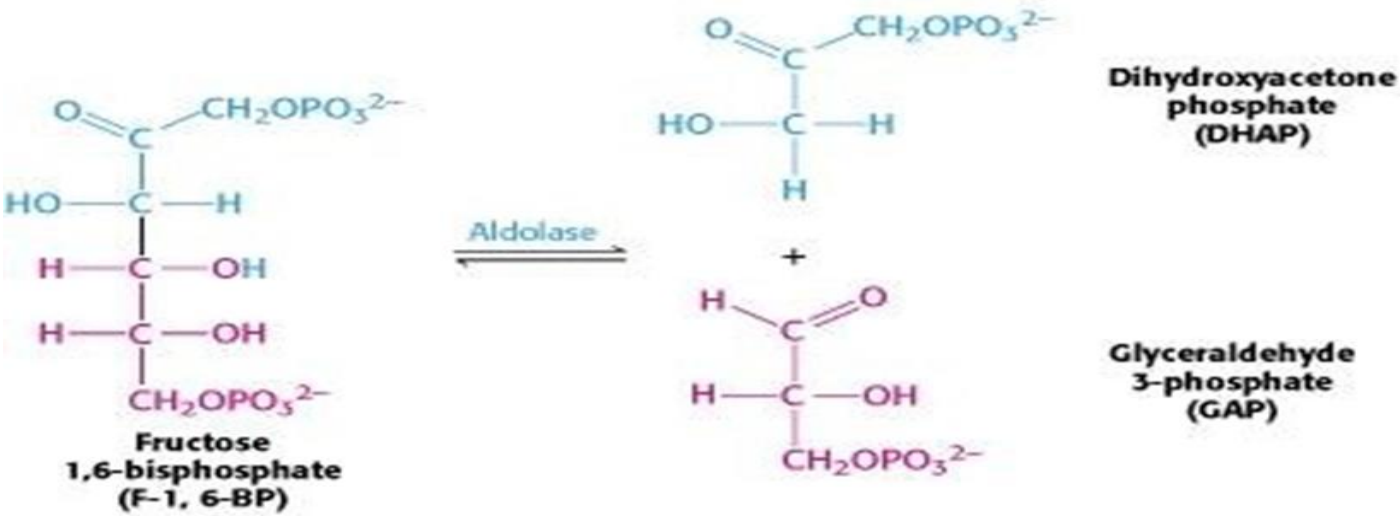
Now we have 1 phosphate on c6, so we add another phosphate on c1 to make it more Suitable for dividing in step no:3

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

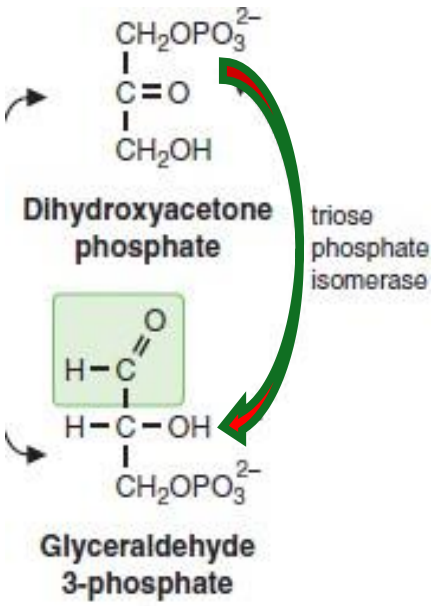
STEP 5:

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

Until now we don't generate energy?

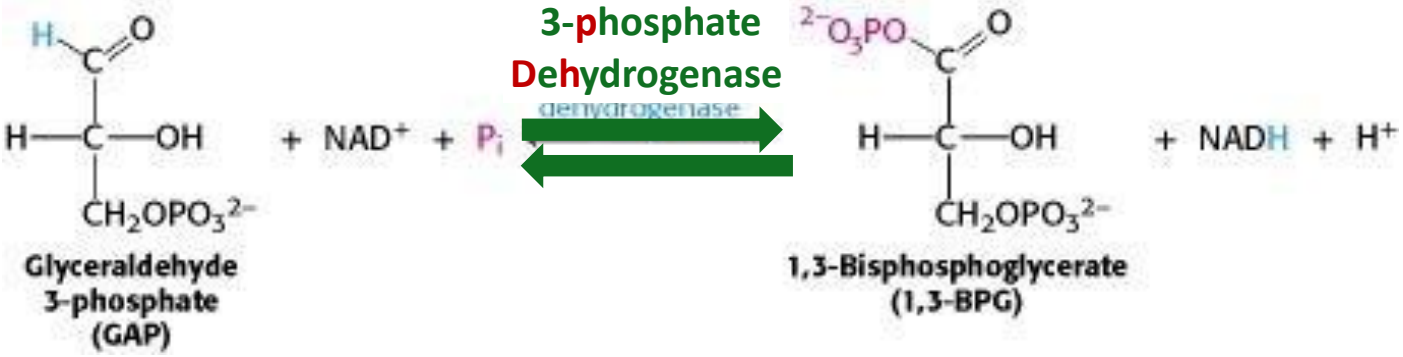
We started from GLU(6c) until we reached two molecules with 3c

Two ATP have been used



STEP 6:

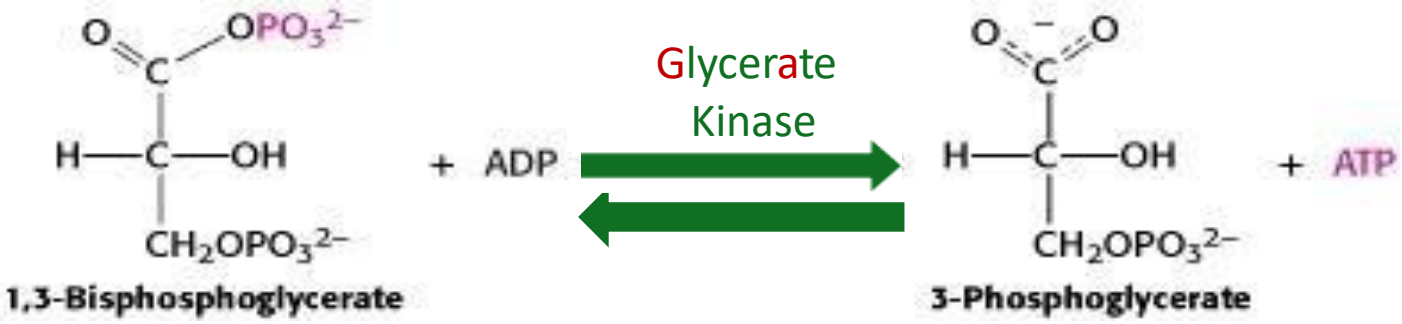
Glyceraldehyde 3-phosphate Dehydrogenase



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

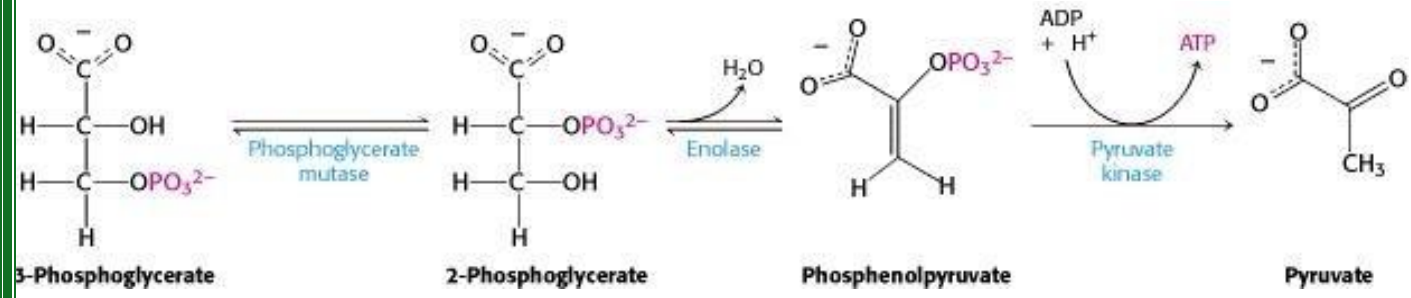
All enzymes must be memorized so Watch out for them

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:

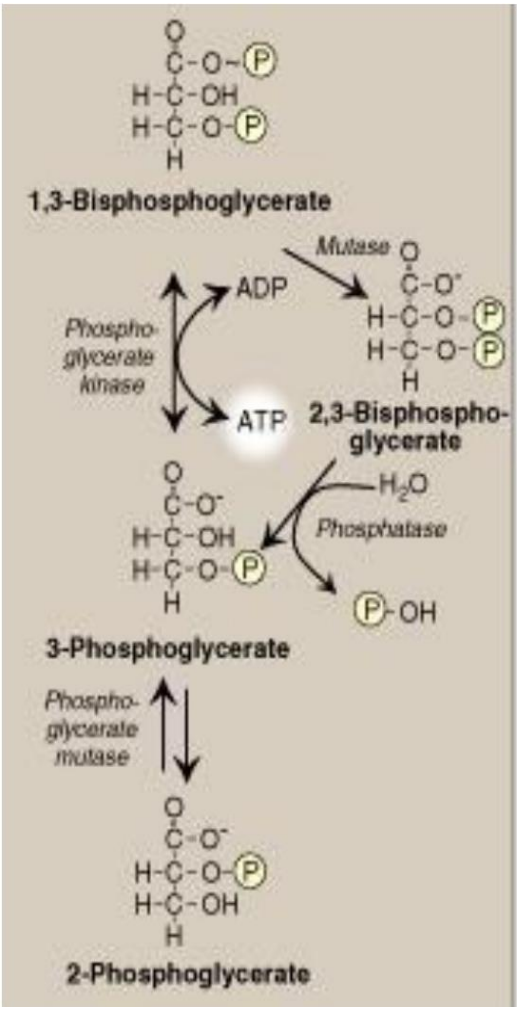
In the first phase two ATP is utilized

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

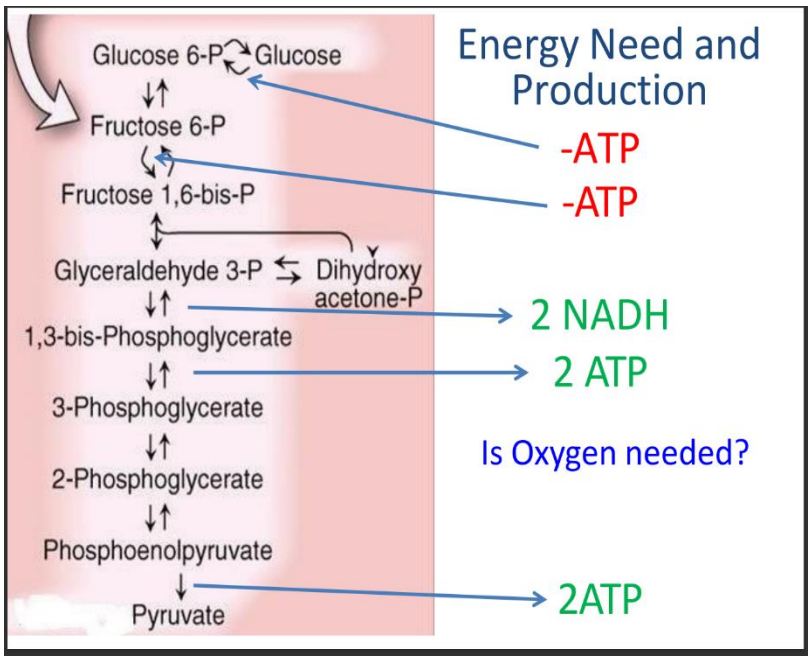
- **increase Oxygen delivery to tissues**
- **By binding to deoxyhemoglobin reducing its affinity to O2 and increasing O2 release to tissues**



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

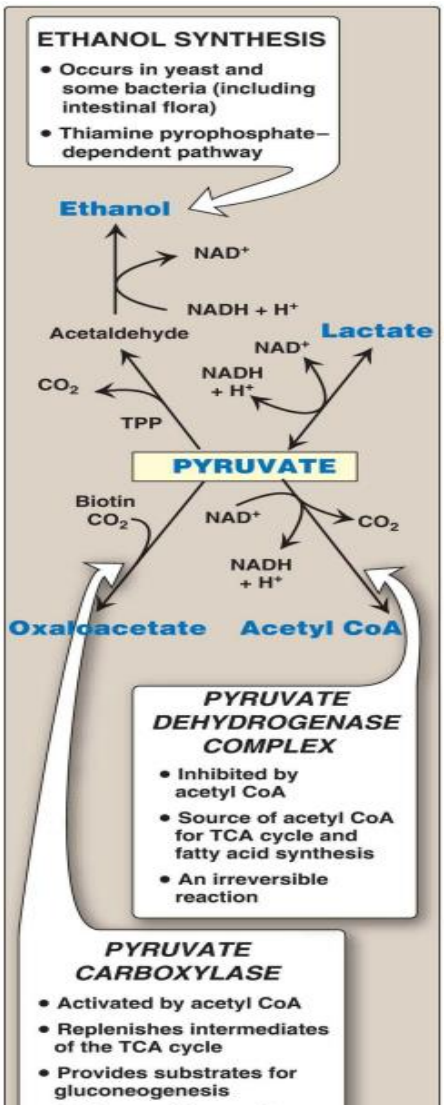
   Oxaloacetate is a 4c molecule thus pyruvate is carboxylated (addition of carbon)

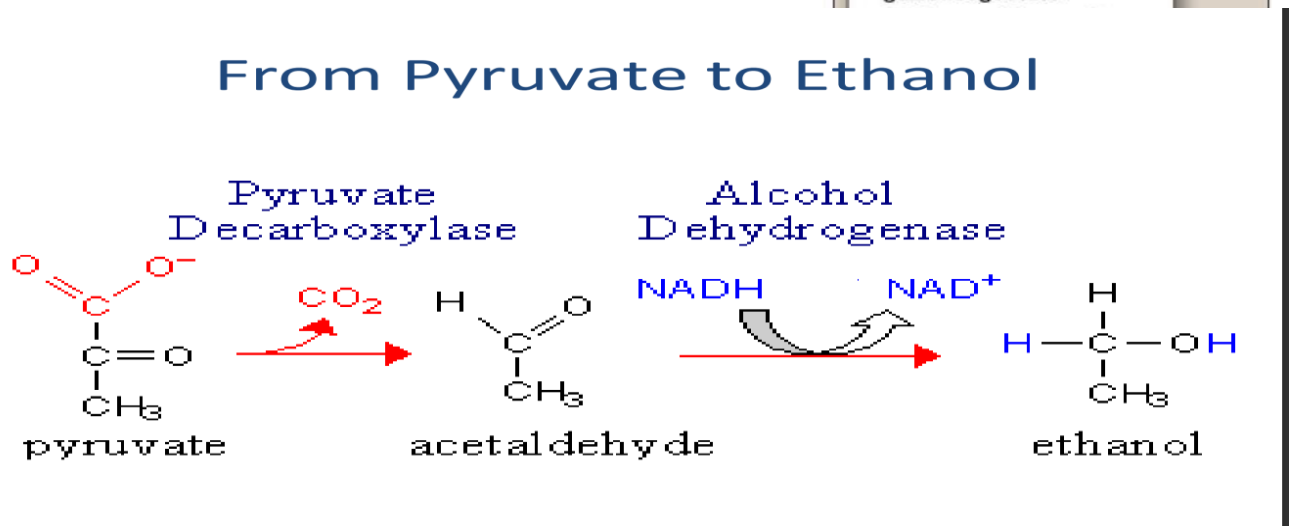
3. Anaerobic respiration

   like in RBCs or in lower energy demand cells

4. Decarboxylation and Reduction to ethanol

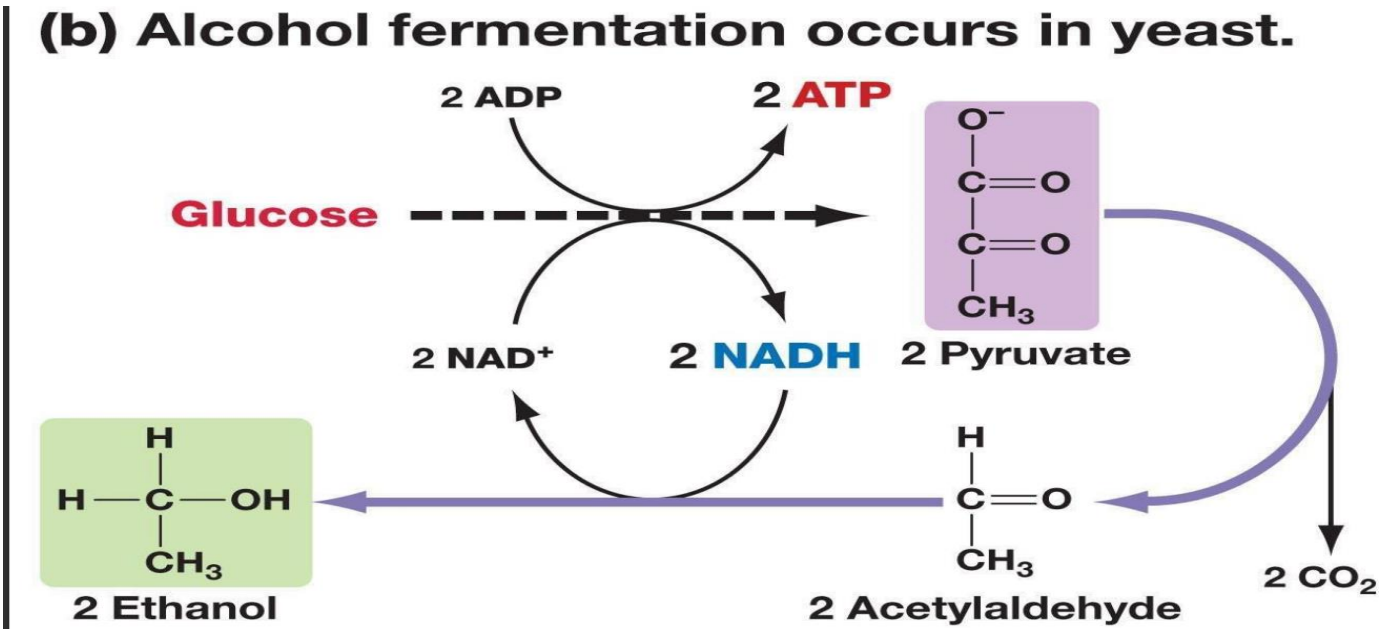
   Occurs in yeast





Why we put sugar on the yeast? عشان تنفخ العجينة

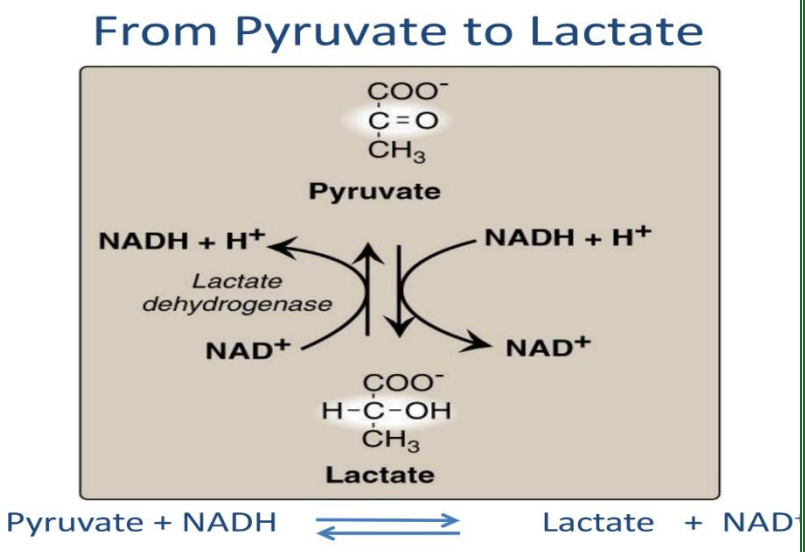
Yeast produces CO_2 after glycolysis by decarboxylation of pyruvate



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.

REGULATION OF GYCOLYSIS:

Regulation happens on the 3 irreversible steps which are:

1- Conversion of glucose to glucose 6 phosphate (glucokinase and hexokinase)
2- Phosphorylation of fructose 6 phosphate to fructose 1-6 bisphosphate (phosphofructokinase)
3- Conversion of phosphoenolpyruvate to pyruvate (pyruvate kinase)

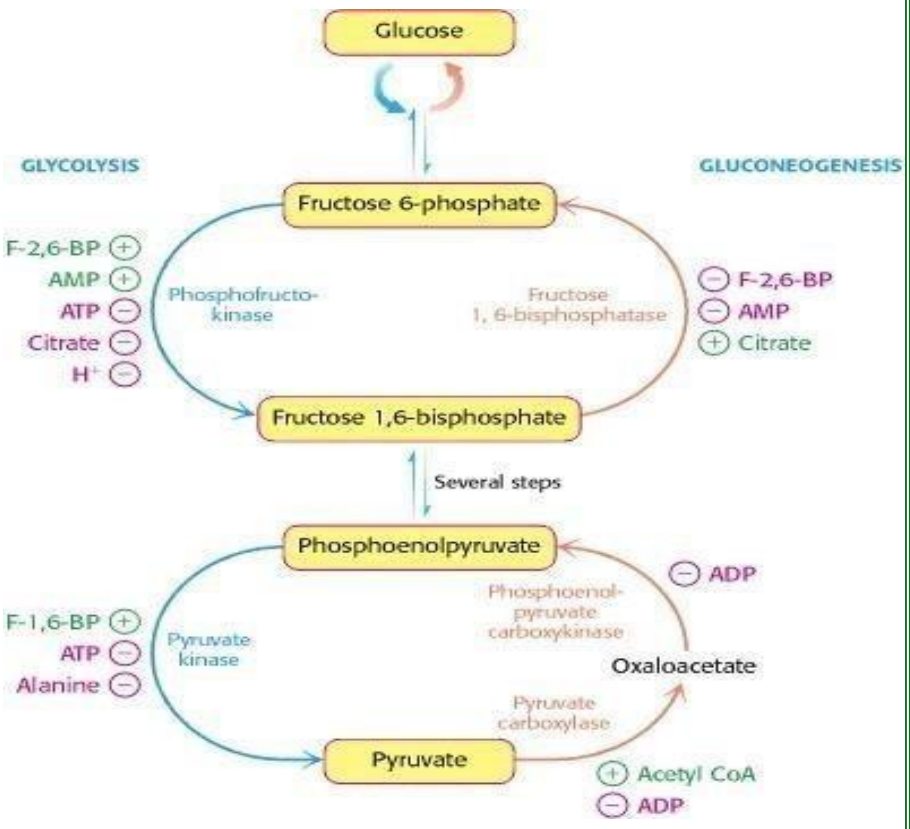
REGULATORS OF PFK AND PK:

We have different ways of regulation.

In the left side of the picture, we have the regulation of Glycolysis while the right side explains the regulation of Gluconeogenesis.

As we see in the picture inhibitors of Glycolysis are activators of Gluconeogenesis and vice versa.

And now darling lets rock this picture….



1- Phosphofructokinase inhibitors and activators:
   A- Fructose 2,6 bisphosphate is an activator if it is a product then it will be an inhibitor.
   B- AMP: it indicates low energy state in the cell so when energy level is low in the cell the cell asks PFK to breakdown glucose in order to generate energy so PFK activates glycolysis.
   C- ATP is an inhibitor because it indicates high energy state and it activates the storage of glucose as glycogen or other shapes.
   D- Citrate (from Krebs cycle) : high amounts of citrate means that TCA cycle is working a lot and there is high production of energy so there is no need to activate more breakdown of glucose. (inhibitor)

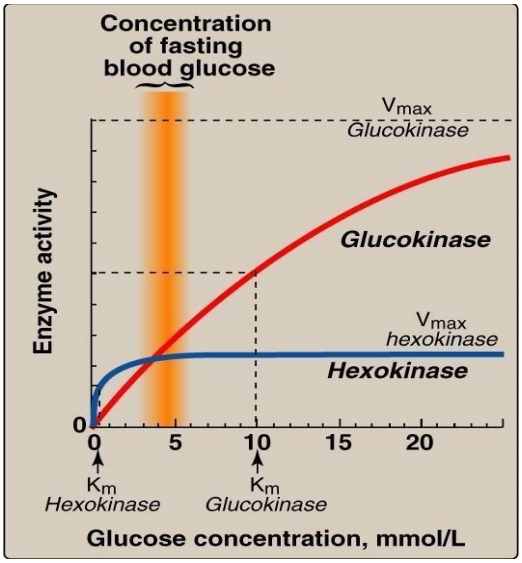
E- Protons (H+): it means that TCA cycle and oxidative phosphorylation are active and produce energy, in a way or another it indicates high energy levels. (Inhibitor)
Fructose-2,6-Bisphosphate has a tale that we will talk about soon …

2- Pyruvate kinase:
A- Fructose-1,6-Bisphosphate which is the product of the previous regulated step is an activator. (When the product of any step increases it will stimulate other steps to happen)
B- ATP is again an inhibitor that indicates a high energy level so there is no need to breakdown more glucose.
C- The last one is Alanine an amino acid which become pyruvate… here is an explanation darling …

When Alanine is metabolized it releases NH3 the amino group and becomes α keto acid this α keto acid of Alanine is our lovely pyruvate… I guess that you reach the information that Alanine is the source of pyruvate... U are awesome!!!

And since we have the end product why to breakdown more glucose? That's why Alanine works as inhibitor.

GLUCOKINASE AND HEXOKINASE ACTIVITY:



And now let's talk about glucokinase and hexokinase focusing on their kinetics.

Hexokinase works in all cells all the time at low concentration of glucose so its Km is very small with high affinity of glucose … but why?...

To catch (يلقط) any glucose presented under these conditions, whereas Glucokinase is activated by high amounts of glucose for example after a meal … so its stimulated not self-activated all the time, it is expressed by hepatocytes in the liver and gets activated under high concentrations of glucose … our gorgeous doctor called glucokinase system (راعي الفزعة او سستم الفزعات)

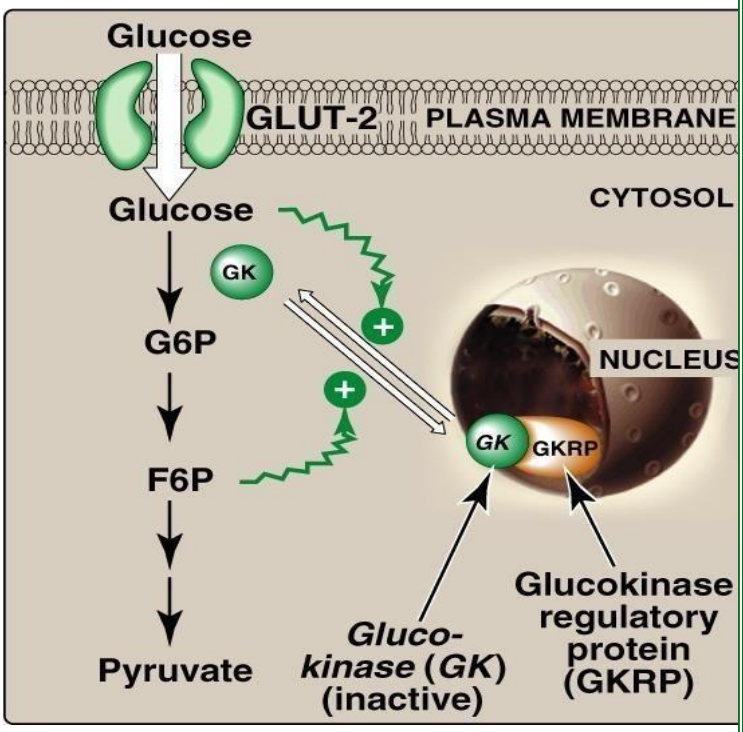
remember that Km is half of V max.

Km value of Glucokinase is much larger than that of Hexokinase and that's why its affinity for glucose is less it wont bind glucose unless its concentration is high.

The orange zone here indicates the level of sugar under fasting conditions (fasting blood sugar), if the level of glucose falls down this level this will cause loss of consciousness. تمام؟؟؟

at the level of fasting hexokinase is working at Vmax but glucokinase V is much lower than Vmax, it doesn't even reach 1/4 Vmax.

REGULATION OF GLUCOKINASE:



To regulate the activity of glucokinase in the cell it is bounded to a regulatory protein (GKRP) Glucokinase Regulatory Protein which works in sequestering glucokinase in the nucleus

(زي كأنه بينفي الجلوكوكاينيز و برميه بالنواة بعيدا عن مكان عمله)

Because glucokinase cannot function in the nucleus it only functions in the cytosol so as soon as it is in the nucleus it is inactive, so when it becomes activated?

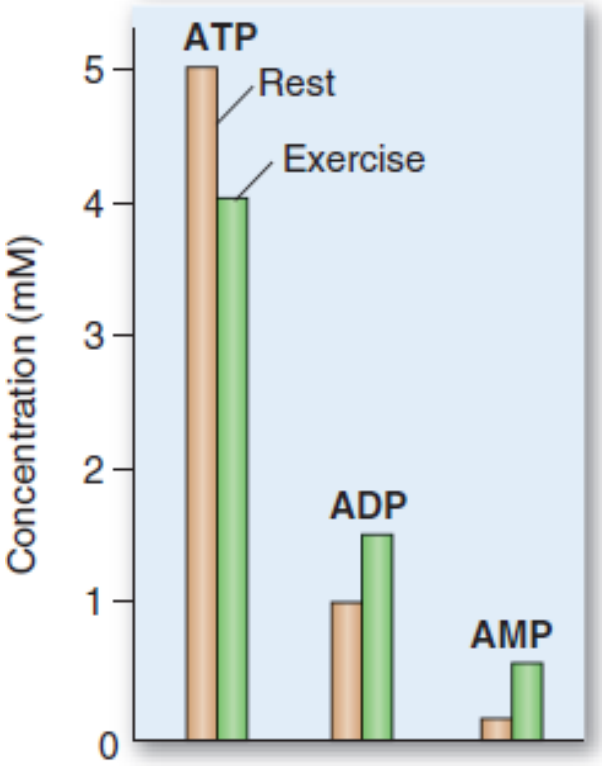
When Glucose concentration is high after glucose enter the cell through GLUTs.

The presence of glucose will activate the untie of this binding so the glucokinase can be released into the cytosol and it can act on glucose to phosphorylate it to Glucose-6-phosphate and then continue in glycolysis.

When Fructose-6-phosphate is generated due to the degradation of glucose this would activate the sequestration of glucokinase back to the nucleus as a result GK will return back to nucleus binds to GKRP and become inactive.

وكأنه بيقول للإنزيم ما فش داعي تضل تكسر جلوكوز كتير مدام صار عندك كمية كبيرة من الفركتوز 6 فوسفات

REGULATION BY ATP AD AMP:



In this slide the doctor is shoeing us the ATP, ADP and AMP under rest and exercise conditions, which explains the regulation of glycolysis by ATP and AMP.

We already said that ATP and AMP appear in more than step affecting more than enzyme either as activators or as inhibitors.

ATP level increases under rest because we are not consuming it and decreases under exercise because we are consuming it.

In the other hand, ADP level decreases under rest when I am not consuming ATP and increases under exercise because we are hydrolyzing ATP to ADP to get energy.

I guess that u have realized with your luscious eyes our dear that AMP follows ADP so they are the same.

And that's how they indicate the energy state inside the cell and how this would affect the activity of our ugly lovely GLYCOLYSIS.

Look over this equation sweety….

ADP + ADP ⟶ ATP + AMP

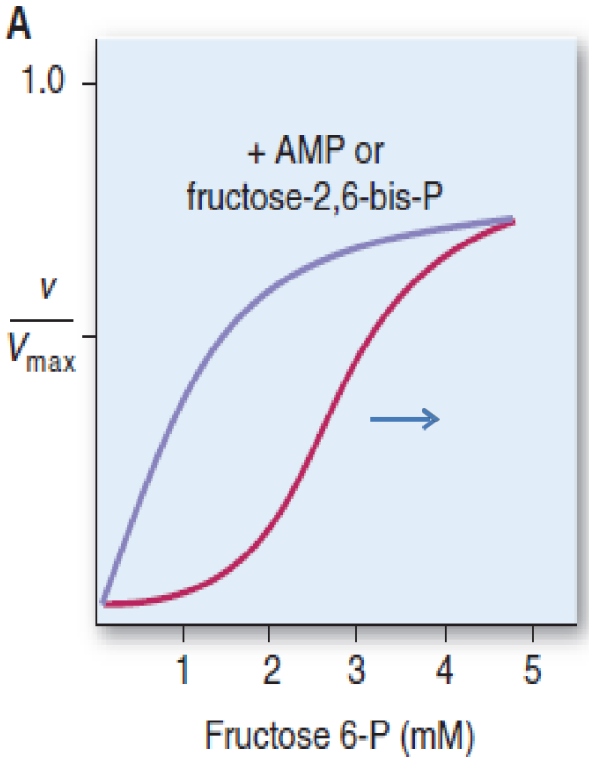
REGULATION OF PFK BY FRUCTOSE- 2,6-BISPHOSPHATE :

And now lets talk about the second enzyme which is phosphofructokinase isn't its name glum!!

We said that AMP is an activator.

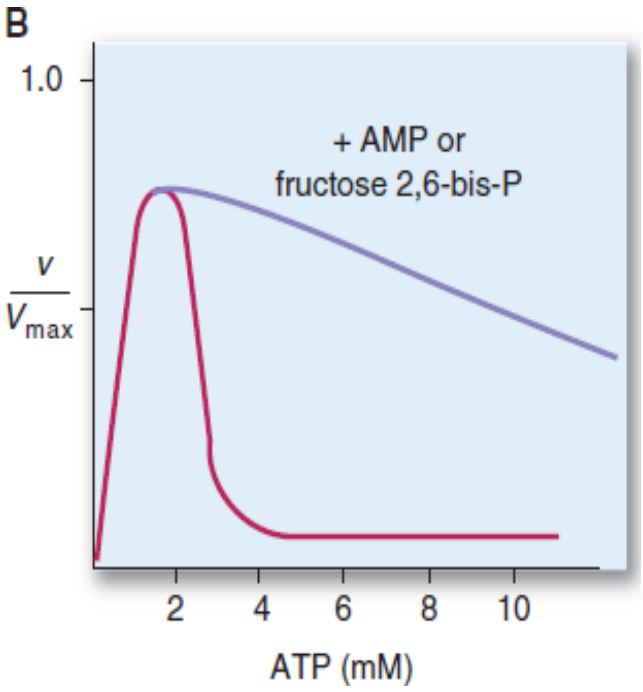
The pinkish red curve is the regular curve without any effectors neither activators nor inhibitors the conversion of F-6-P to F-2,6-bis-P.

When we add AMP or F-2,6-bis-P (activators) V is increased notice that we didn't increase Vmax what happened is that we shift the curve to the left which means that we can reach Vmax earlier at a lower concentration of the substrate which is F-6-P.



HOW ABOUT THE OTHER SUBSTRATE OF PFK ?

PFK brings phosphate from ATP which is a substrate during this reaction, look what happens in response to changes in ATP concentration alone without any other effectors.



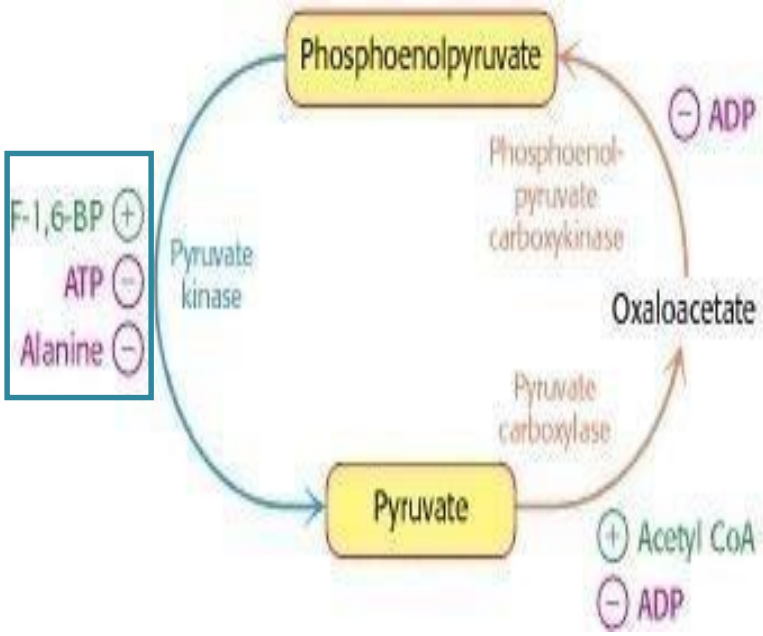
When ATP concentration increases firstly the velocity increases then it decreases so it is not the indicator because it is affected by the other substrate which is F-6-P, so if we don't have F-6-P even if we have a lot of ATP but we don't have anything to phosphorylate and that's why the curve goes down again.

When AMP or F-2,6-bis-P are presented the curve is going to go doen again but slower which give the enzyme better chance to work and to use a

higher concentration of the substrate… so here we have 2 curves for the same reaction but in relation or regard to different substrates.

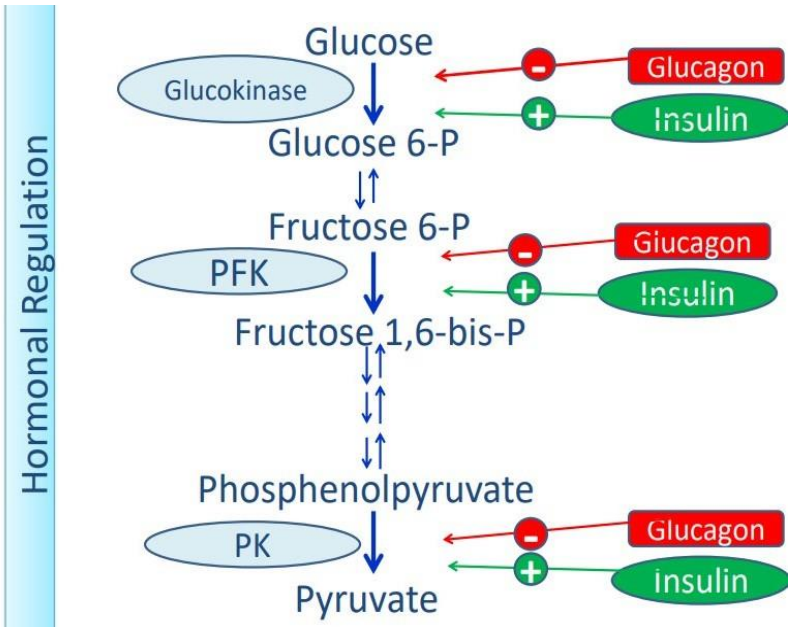
REGULATION OF PYRUVATE KINASE:

we already said that F-1,6-BP activates it while ATP and Alanine inhibit it.



HORMONAL REGULATION

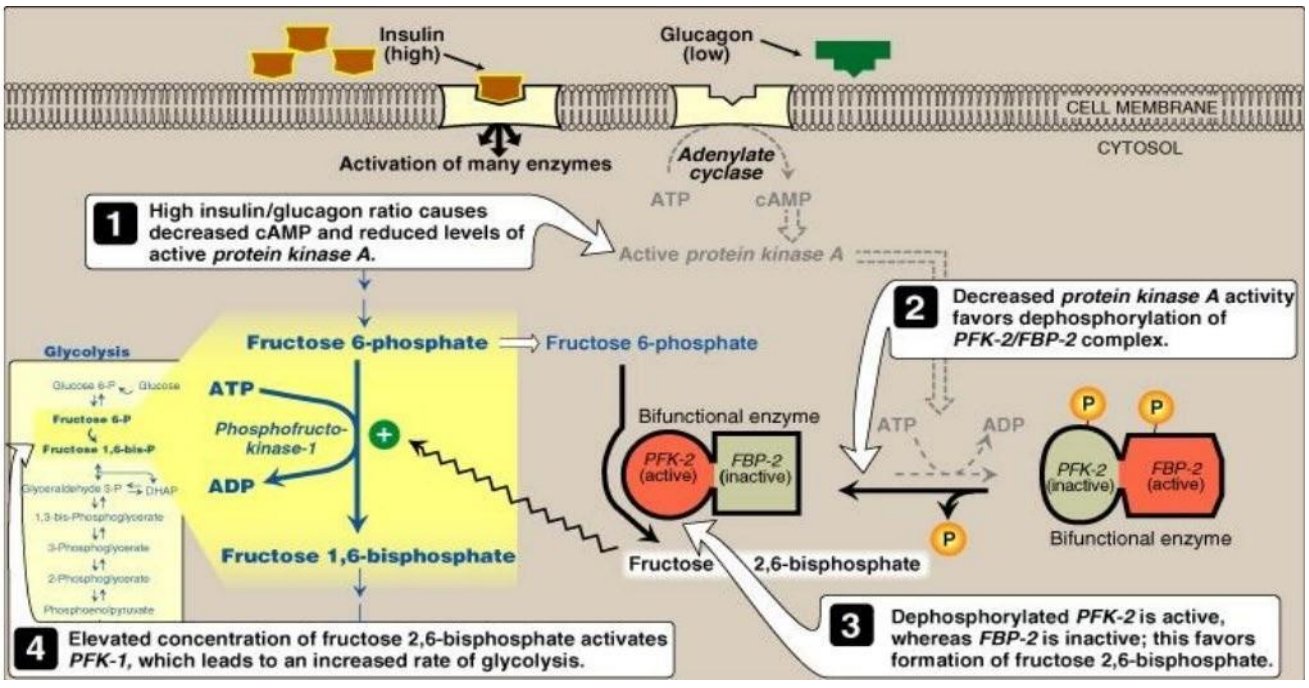
Discussing hormones now, we should re-emphasize that glycolysis is active at high glucose conc. **where Insulin is predominantly active, note how Insulin activates all the three irreversible steps. On the other hand, glucagon inhibits all of them.** THEY MUST OPPOSE EACH OTHER IN THEIR MECHANISM OF ACTION.



- The insulin is secreted when there is a highconc of glucose at **well- fed state**, while theglucagon is released at **fasting condition**. Note that both hormones are secreted separately at different time.

- They actually don't directly bind to the enzymes regulating the process, rather they work as a part of a long signaling pathway that activates different downstream target molecules, one of them being a protein kinase that phosphorylates an enzyme switching it 'on or off.

HORMONAL REGULATION OF PHOSOHOFRUCTOKINASE



NOTE: Insulin receptors are enzyme-linked receptors (RTKs or receptor tyrosine kinases) while glucagon performs its action through G-protein coupled receptor (GPCR).

- The occurring situation in the figure is the high presence of Insulin compared with lower glucagon. Provided that glucagon conc. is low, activation of GPCR &Adenylate cyclase won't be initiated, thus cAMP won't get activated in order to stimulate downstream target proteins, including protein kinase (e.x: PKA&PKC). Note that faint pathway drawn out of glucagon.

- One of the prominent targets is the enzyme complex (bifunctional enzyme) consisting of PFK-2 (phosphofructokinase-2) & FBP-2(Fructose-bisphosphatase2), which are completely opposite in terms of their function, with one phosphorylates and the other dephosphorylates. Thus, they mustn't be active at the same time.

- If the glucagon had been present, and the pathway proceeded, this complex would have been phosphorylated (by upstream proteins in the cascade, e.g: PKA), inactivating the 'kinase' part while turning on the 'phosphatase' one, which is fine and logical. Here glucagon pathway is locked, so the enzyme will be dephosphorylated, with kinase being active and phosphatase inactive.

- The substrate of these 2 enzymes (PFK-2 & FBP-2) is Fructose-2,6-bisphosphate, one of the allosteric activators of PFK-1 that changes its conformation preventing other inhibitors from binding (e.x: H, citrate).

  - High insulin⟶ PFK-2 active (**dephosphorylated**)⟶Fructose-2,6-bisphosphate increase ⟶ glycolysis activation.

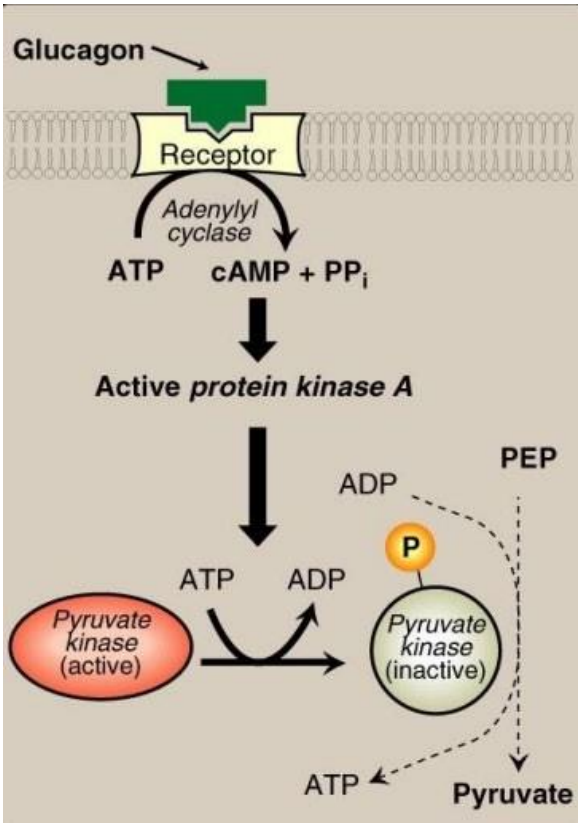
  - High glucagon ⟶ FBP-2 part is active (**phosphorylated**) ⟶ less Fructose-2,6- bisphosphate ⟶ deactivating glycolysis.

- Don't forget that the bifunctional enzyme responsible for the aforementioned situation (activating PFK-1 as well as glycolysis) is the dephosphorylated form, which results from a low conc. of Glucagon, and high conc of Insulin (increasing glucose levels).

- To sum up, when Insulin is present in low conc. (e.g: low sugar), glucagon is the manipulator now (the faint pathway previously discussed will take place). GPCR is activated followed by cAMP and the subsequent protein kinases (PKA&PKC), the latter will phosphorylate the bifunctional enzyme (the 'kinase' part is inactive, the 'phosphatase' is active-opposing the first situation). Now, the active phosphatase is going to remove the additional phosphate of Fructose-2,6-bisphosphate, returning it into Fructose-6- phosphate. As a result, the activator of PFK-1 is absent, which will inhibit the enzyme and inevitably the glycolytic pathway.

HORMONAL REGULATION OF PYRUVATE KINASE

- Glucagon regulatory effect doesn't manifest only in modulating PFK-1 function by the bifunctional enzyme complex, yet there are many other target proteins, activated by GPCR, cAMP and the downstream protein kinases (such as PKA).



- The target of interest now is Pyruvate kinase, the enzyme responsible for pyruvate production from phosphoenolpyruvate (the 10th step).

- When Pyruvate kinase gets phosphorylated by PKA, it switches to the INACTIVE STATE. This does perfectly make sense because glucagon naturally inhibits glycolysis so working on the enzyme responsible for such a significant step that outlines glycolytic progression will definitely inhibit it.

CLINICAL HINT: PYRUVATE KINASE DEFICIENCY

The most common among glycolytic enzyme deficiencies. (due to genetic mutations)

RBCs are affected (because it is mainly dependent on glycolysis unlike other cells that also undergo Krebs cycle)

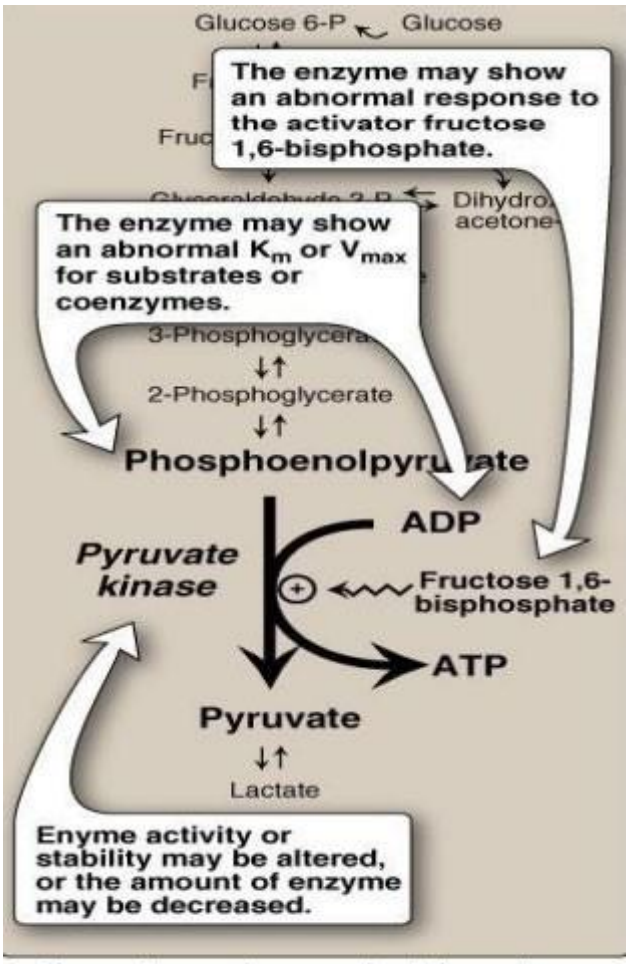
RBC lacks mitochondria so there is no Krebs cycle in RBC.

RBC losses its flexibility due to malfunctioning of Na+ - K+ Pumps due to the reduced amount of ATP.

Accordingly, RBCs energy will be very low, therefore, Na+ - K+ Pumps will be deficient so the shape of RBCs will not be maintained (losing of shape leads to losing of function) so RBCs will die (Hemolysis).

Side note: RBC has biconcave shape.

To sum up,without pyruvate kinase deficiency RBCs have a zero net energy yield from glycolysis. HAVING PYRUVATE KINASE DEFICIENCY, THIS ZERO BECOMES '-2'.



Alterations observed with various mutant forms of pyruvate kinase

- **Mild to severe chronic hemolytic anemia** (depends on the kind and severity of the mutation)
- **ATP is needed for Na+/K+ pump ⟶ maintain the flexible shape of the cell.**
- **Low ATP ⟶ premature death of RBC**
- **Abnormal enzyme; mostly altered kinetic properties**

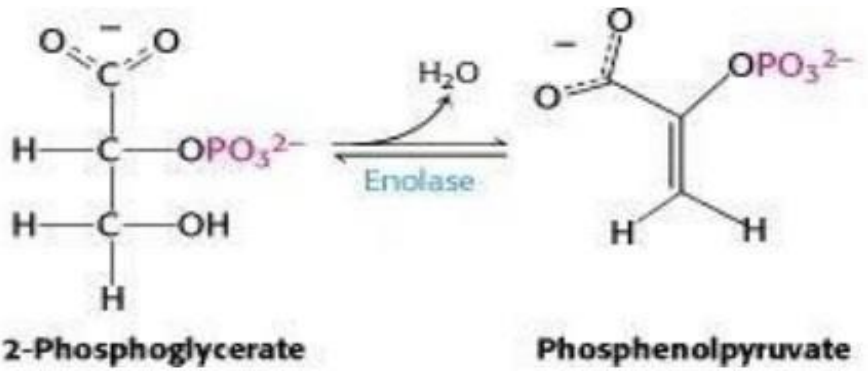
INORGANIC INHIBITORS OF GLYCOLYSIS

FLUORIDE

It is a regulatory mechanism from outside the body rather than inside such as Fluoride .

- **Fluoride inhibits Enolase**

- **Fluoridated water ⟶ bacterial enolase ⟶ Prevention of Dental Carries.**



We can find Fluoride in toothbast and in water .

بعد دراسات عديدة في الطب الوقائي وجد أن إضافة الفلورايد على معجون الأسنان أو الماء بكميات ضئيلة جدا (جزء من مليون) تخفف نسبة التسوس على مستوى العالم
الكالسيوم يساعد في نمو الأسنان ولكنه غير فعال بإزالة التسوس من الأسنان كالفلورايد
معجون الأسنان للأطفال لا يحتوي على فلورايد لأنه في حالتهم بلعه سيصلهم تركيز عال من الفلورايد فيصابوا بالتفلور

Fluorosis التفلور

A relatively high dose of fluoride has an opposite effect (it weakens the structure of teeth)

ARSENIC POISONING

Another external inhibitor is Arsenic

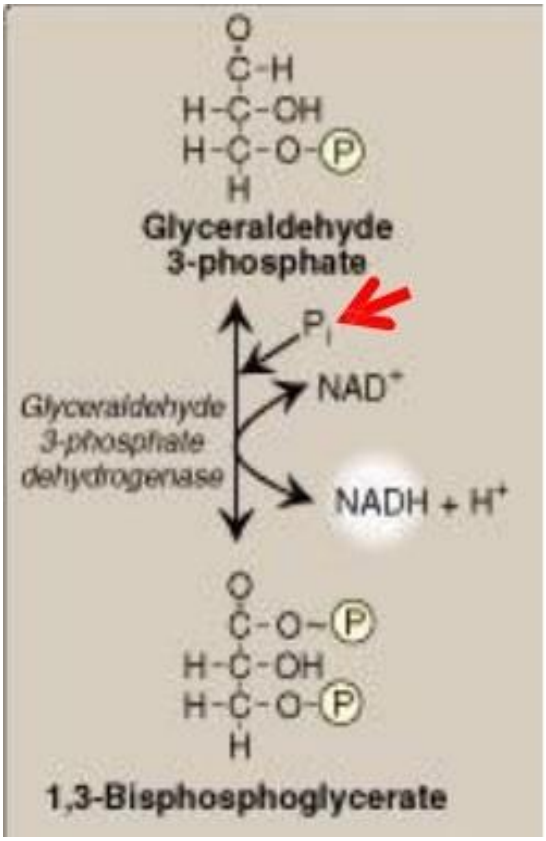
Arsenic is a transition metal so it has two ionizational states (Pentavalent Arsenic and Trivalent Arsenic).

- **Pentavalent Arsenic (Arsenate) competes with phosphate as as a substrate for GA3PDH**

  ↓ **ATP synthesis.**

Arsenate works on the beginning of second phase of glycolysis especially on the step which converts Glyceraldehyde-3-Phosphate to 1-3-Bisphosphoglycerate

Arsenate is going to compete with inorganic phosphate (which is added to carbon number 1 of Glyceraldehyde-3-Phosphate), after this competition there will be no phosphate that can be used to generate ATP in the next step, so energy will be reduced.



- **Trivalent Arsenic (Arsenite) Forms stable complex with -SH of lipoic acid.**

  ↓ **Pyruvate Dehydrogenase**

  ↓ **α ketoglutarate Dehydrogenase**

  → **Neurological disturbances…….DEATH**

- **Arsenite** acts on another enzyme which is Pyruvate Dehydrogenase (which converts Pyruvate to Acetyl CoA).
- **Arsenite** forms a complex with lipoic acid (as we remember Lipoic acid is one of the coenzymes that is used for E2).
- **Arsenite** is much more dangerous than Arsenate.

- **Arsenate** reduces ATP although it can undergo Glycolysis WHILE Arsenite reduces the activity of Pyruvate Dehydrogenase so Acetyl CoA content will be reduced then Krebs Cycle will be affected, more and more leading to severly reduced energy (it may causes death)

- To sum up, **Arsenite** affects Lipoic acid so Krebs will be affected. Lipoic acid is present in both alpha-Ketogluterate and Pyruvate dehydrogenase, so they both get affected by Arsenite poisoning.