DOCTOR 2020 | JU

METABOLISM

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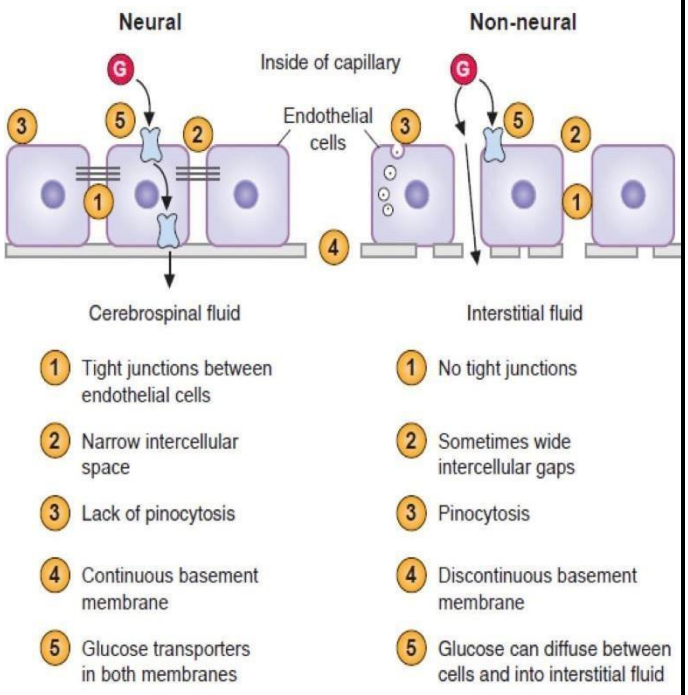
We talked before about different types of transporters (GLUTs), some of them specifically found in Barriers such as the blood-brain barrier.



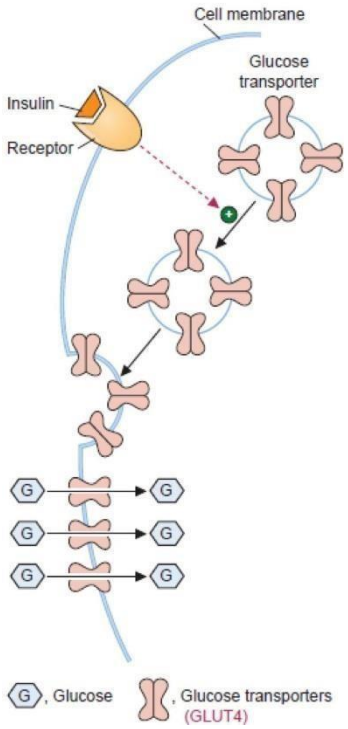
Glucose transport in Neural cells

These barriers are found in the form of tight junctions between endothelial cells, the intercellular space is close so molecules have to pass through the cells via Transporters, so we can see that these cells have transporters for glucose in one surface and on the other side too (must be in 2 sides). and the basement membrane underneath these cells is continuous.

Glucose transport in non-Neural cells

in this type of cell, the basement membrane is discontinuous and there are spaces between cells so substances and compounds can pass intercellular, also no need for transporter in the basal surface(the other side) because glucose can diffuse between cells.

effect of insulin : **Insulin stimulates transport of glucose into muscle and adipose tissue**



GLUT4 is sensitive to insulin.

When we eat a meal that contains sugar, insulin is secreted and bound to the **tyrosine kinase receptor** on the target cell leads to activation of this receptor then activating a cascade of events (large groups of proteins and molecules) that end up with activation Transcription factors, these TFs activate gene expression of the target genes, one of them for GLUT4 then synthesized as protein after this we put it in vesicles and these vesicles get diffuse in the plasma membrane. so, you will have a higher concentration of these transporters on the cell membrane and **more glucose** will get into the cells.

❖ An over view of glucose metabolism

In the next coming lectures, we will take several metabolic pathways that deal with sugars especially glucose for example :

Glycolysis : breaks down glucose into (3 carbon compound) pyruvic acid or lactate and generatesenergy.

Gluconeogenesis : process that transforms non-carbohydrate substrates into glucose. Ex : **Lactate**

Glycogenolysis : glycogen breaks down into glucose. (release)

Glycogenesis : convert excess glucose to glycogen.(storing)

Convert glucose to pentos : for production of ribose sugar (nucleotide) and becoming part ofDNA and also for the production of cofactor (NADPH).

Oxidation of glucose to glucuronic acid : used in drug metabolism to convert hydrophobic molecules to hydrophilic .

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before we start with Glycolysis, let's talk about the regulation of metabolic pathways and the relations between them.

The relations between metabolic pathways :

- Metabolic pathways intersect to form network of chemical reactions. Metabolic pathways do not occur in isolation. Instead, they are organized into multistep sequences called pathways, such as that of glycolysis.

- Glycolysis found in the middle of the others pathways and it's universal

- Conversion pyruvate into Acetyl-CoA is not part of glycolysis

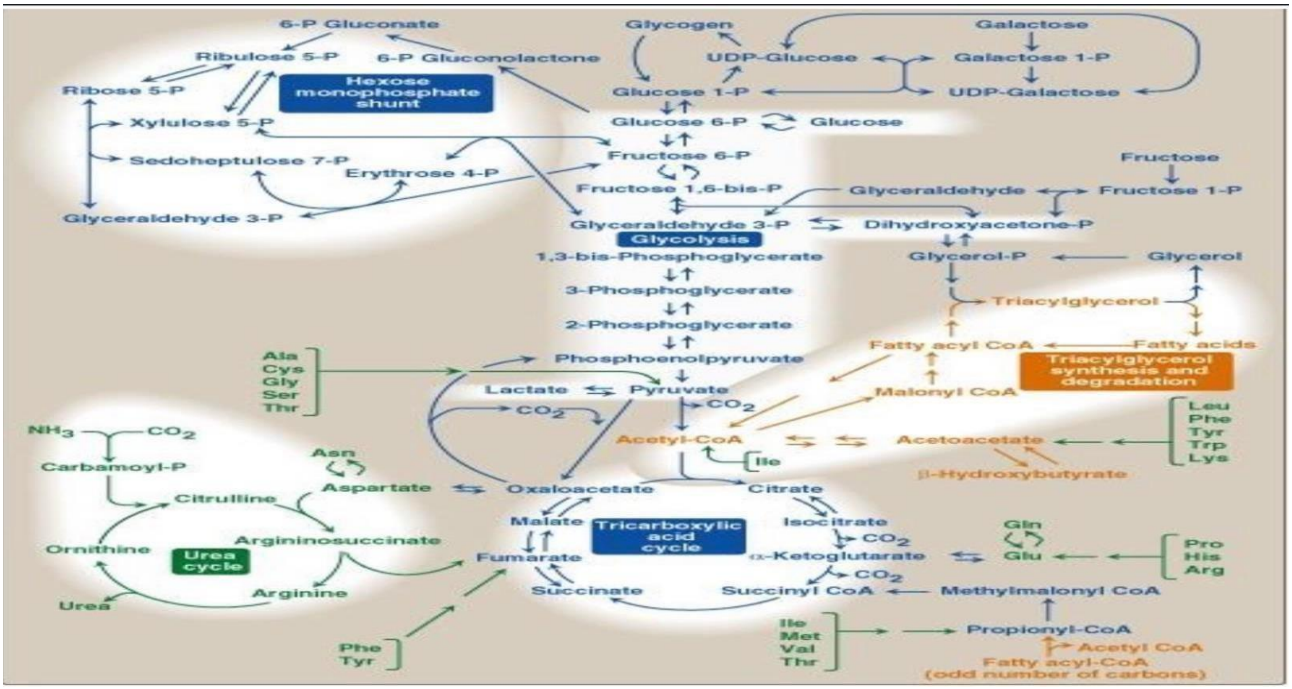
Some notes from the picture below :

-urea cycle : Resulting from the metabolism of amino acids, notice that arrows get out from it toward Krebs cycle and other pathways (crosstalk)

-Triacyglycerol synthesis and drgradation: producing Acetyl-CoA and goes to krebs

- Krebs cycle happens after degradation of the molecules (proteins, lipids) and not only for carbs.

The main idea here is complex pathways interacts with each other



General stages of metabolism :

➢ Stage 1

Hydrolysis of complex molecules to their components building blocks.

-**Sources** of molecules that end up in the metabolic pathways

1- from diet : contain mostly polymers , protein , polysaccharides , ……

- they get simplification by **digestion** to their monomers and these monomers get into metabolism pathways.

Note: digestion is not a metabolism pathway, it is for simplification.

2- proteins from our bodies at some point we need to **degrade** them because of :

a) I need to stop their function as a sort of regulation

b) unfunctional proteins

c) it was made incorrectly

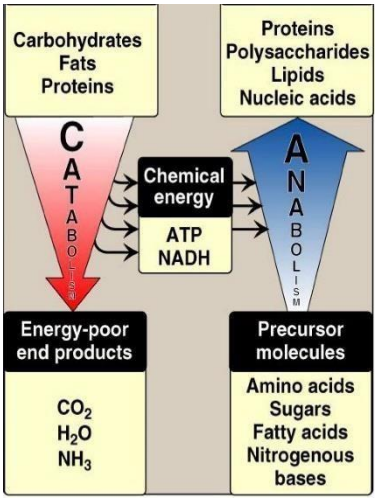
➢ Stage 2

Conversion of building blocks to Acetyl-CoA (or other simple intermediates)

➢ Stage 3

Oxidation of Acetyl-CoA ; oxidative phosphorylation

Types of Metabolic pathways :



Anabolic pathway: synthesizing large molecules (not always polymers) out of small molecules(precursor)

-Need energy

catabolic pathway: degradation of large molecules into smaller ones.

-we started from polymers or monomers

-I simplified them into first small molecules (commons and very simple)

resulting in producing energy in form of ATP.

general regulation of metabolism :

1- **signals from within the cell**: the cell itself that does the metabolic pathway will regulate the process and its rapid response , how?

a) **substrate availability**: if the substrate is available the process will be activated and vice versa.

b) **enzyme concentration**: more concentration => more active sites => faster reaction. if I don't have the enzyme synthesized that's mean the reaction all stopped.

Note: some proteins always exist in the cells because of its genes, we called these genes: **constitutively active genes**(always active and synthesizing proteins)

and the other gene called **inducible genes**: must be induced by a certain effector to synthesize proteins.

c) **Feedback inhibition**: if the concentration of the product is high, the product will bind to the enzyme and inhibit the reaction for saving energy.

E) **Allosteric regulators**: they bind to a site other than the active site

two types:

positive allosteric regulators: activate the enzyme

negative allosteric regulators: inhibits the enzyme

-binding of regulators will induce conformational changes (active or inactive)

-Many enzymes have positions for both regulators.

2- communication between cells (intercellular):

-slower response, longer range

a) **paracrine**: between closed cells or neighboring cells.

-one cell will secrete ligand and the other cell will bind with this ligand through receptors and get activated => activate a cascade of events within the cytosol.

b) endocrine: the cell that secret the hormones are located far away from the target cell, the hormones will reach the target cell through the **bloodstream.**

3- **second messenger**: the first molecule that can disassociate from the pathway happening in the membrane.

-not required to disassociate after the receptor gets activated directly, maybe it will disassociate after a few steps but these steps must be happening in the membrane, once a molecule dissociates from the membrane we called it the second messenger.

Ex: Ca, cAMP, IP3 , adenylcyclase system

communication between cells through receptors -GPCR

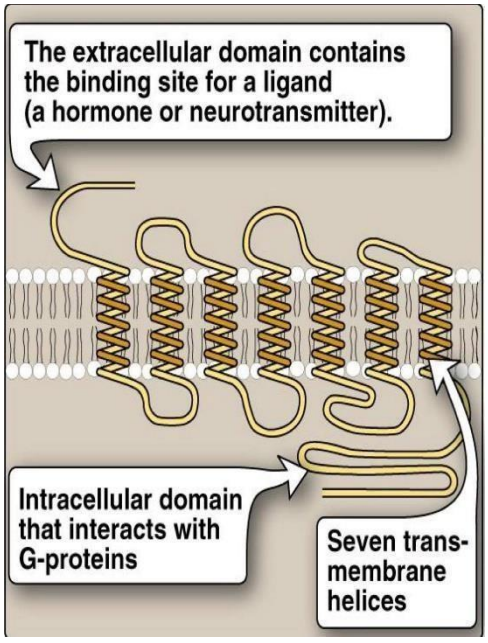
G protein-coupled receptor (GPCR) :

-the most common type of receptors

-majority, not the only ones (Ex; insulin binds to receptor tyrosine kinases)

- Examples for its ligand (glucagon, parathyroid, epinephrin)

-composed of 7 transmembrane helices, and this is shared with all GPCR but eventually, there are differences between subtypes that can recognize specific ligand for example glucagon will only bind to its receptors.



mechanism of GPCR :

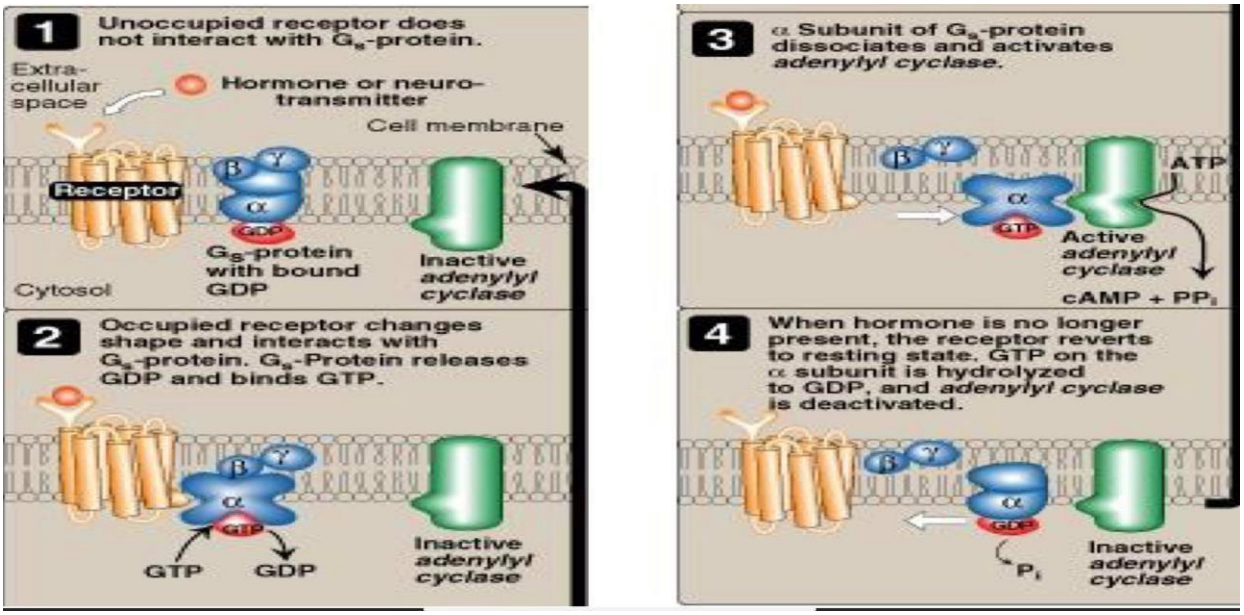
1- When we don't have any ligand, the receptor does not interact with G-protein, G-protein remains 3 subunits (α bound to GDP)

2- when the ligand bind to the receptor, the binding makes a small conformational change in helices so G-protein will bind with it, which activates the exchange of GDP with GTP at the alpha subunit.

Note: we know that proteins move in the aspect of the fluid mosaic model.

3- Once GDP is exchanged with GTP, conformational change will happen because of the phosphate group with a negative charge. α subunit dissociates from βϒ complex and activates adenylyl cyclase => activate synthesize of cAMP (second messenger).

4- when hormone (ligand) is no longer present, the receptor reverts to resting state, GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.



Then, cAMP is produced which binds to the regulatory subunits of protein kinase C

Protein kinase C: in the inactivation state composed of 4 subunits: 2 regulatory and 2 catalytic for phosphorylation.

- 2 cAMP can bind on each regulatory subunit so, 4 molecules bind to one kinase, this will induce conformational change on the regulatory subunits (dissociation from catalytic) and this step is ATP dependent.

- Now we have free catalytic subunits, The active sites were covered and now it is open and can bind to a substrate.

intracellular effects:

1) activated enzymes

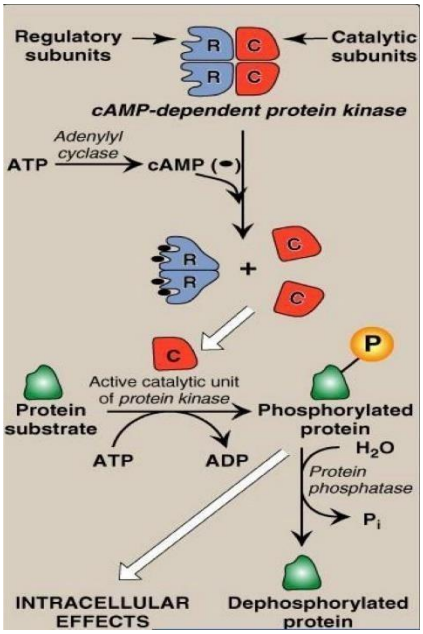
2)inhibited enzymes

-some proteins once get phosphorylated they become active, and others get inactivated, this is a very active mechanism for high organization.

3- cell's ion channels: on or off

4- bind to promoter: Activate or inhibit certain TFs.

-At some point, I need to phosphatases enzymes to remove the phosphate group from phosphorylated proteins (regulation)



Glycolysis

Glycolysis means sugar degradation

-breakdown of glucose to 2 pyruvates.

pathway characteristics:

-its linear pathway: the product of the first reaction is the reactant of the second reaction, differing from the cyclic pathway, in all cyclic pathways there is a compound that comes from out of the cycle such as Acetyl-CoA and must interact with the last intermediate of the cycle then the cyclic begins.

-the majority of the reactions are reversible, have some irreversible

- 10 steps, divided into 2 phases

-universal pathway: in all cells : Bacteria, RBC …

-generation of ATP: not that much compared to TCA

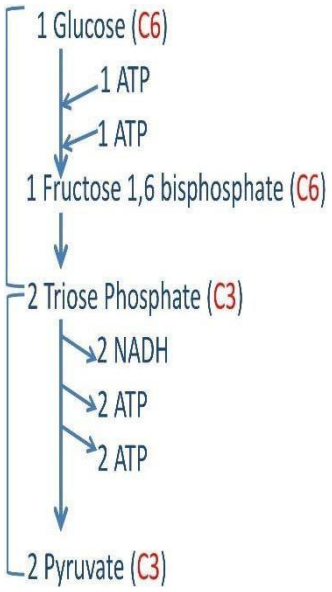
-with or without O2: aerobic or anaerobic

-in the cytosol: no need for specialized organelles

-Anabolic pathway => biosynthetic precursor

its a catabolic pathway for glucose but it also can be anabolic for synthesizing other molecules that serve as precursor for other pathways.

the two phases of Glycolysis :



- **Preparative phase**

-where we can change the shape of glucose to be cleaved in an identical way, once we cleaved it into 2 molecules (3 carbon in each) the second phase will be for ATP.

- **ATP-generating phase**

-moving of phosphate group to release of the chemical energy stored in the bonds in form of ATP

❖ Types of glycolytic reactions

1. Phosphoryl transfer
2. Isomerization
3. Cleavage
4. Oxidation reduction
5. Phosphoryl shift
6. Dehydration

Steps of glycolysis

- **step 1**

Glucose **Glucose 6-phosphate (G-6P)**

-phosphorylation of glucose on carbon no.6 and become glucose 6-phosphate

- can be achieved by 2 enzymes: hexokinase and glucokinase, not in a random way.
- the rection Whether it is hexokinase or glucokinase is irreversible
- the reaction can be reversible but I need different enzymes instead of these

note: completely reversible reactions: the same enzyme can catalytic forward and backward.

let's talk about both enzymes :

1- hexokinase: Hexo means it can phosphorylate all hexoses not only for glucose, so it's **not specific** (galactose, fructose, ..)

-baseline enzyme: all the time activated in all tissues, it activates in any level of glucose

-it is not induced by any hormone, because it is always activated in any concentration of glucose so no need for certain conditions.

-Km value : <0.02 mM (low Km value) high affinity.

quick revision: Km = substrate concentration needed to reach half of the maximum velocity, it indicates the affinity(strength of binding), lower km means I need lower concentration to reach Vmax so higher affinity and vice versa.

so the reason why glucose can be activated in any concentration is the high affinity

2-glucokinase :

-special, only found in liver

-specific for glucose

-induced by insulin, when it gets higher the enzyme will activate

-: it's only active when the concentration of glucose is high.

only >100 mg/dl

-km value = 10-20 mM: low affinity, it doesn't matter because it will activate only in high concentration.

	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

- **Step 2 :**-isomerization of glucose 6-phosphate to fructose 6-phosphate by transferring the carbonyl group from carbon no.1 to carbon no.2

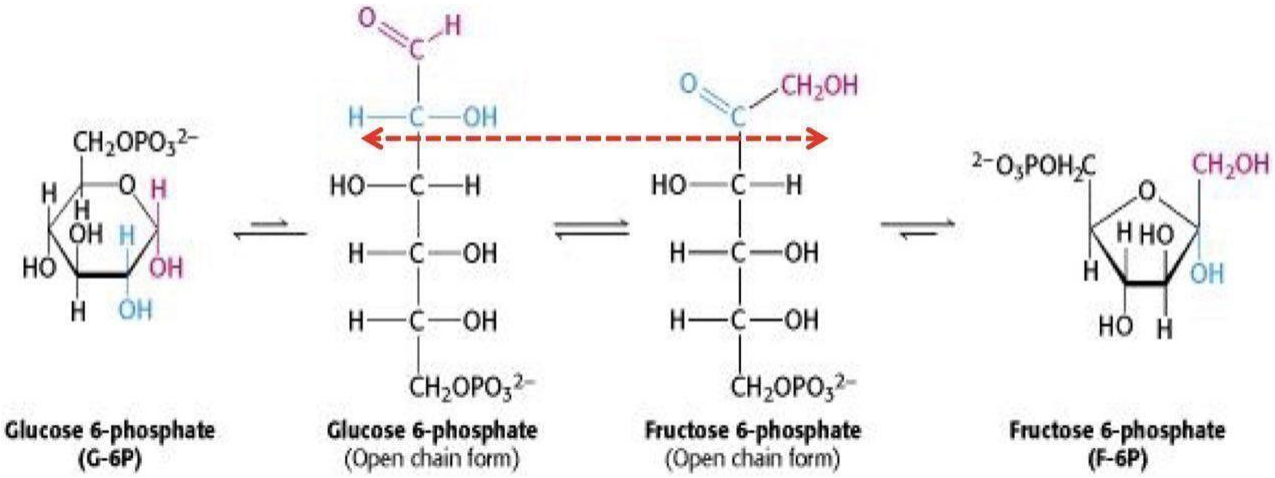
-I had to first convert the reactant to a linear structure

-why we are doing this step? (step 2)

we prepare the molecule for symmetrical shape, look at the reactant and product in form of the ring structure, you will see that both have external carbon atom

(carbon no.6), we make fructose 6-phosphate have 2 external carbon to help me reach symmetric shape.

-we use phosphoglucose isomerase (reversible)

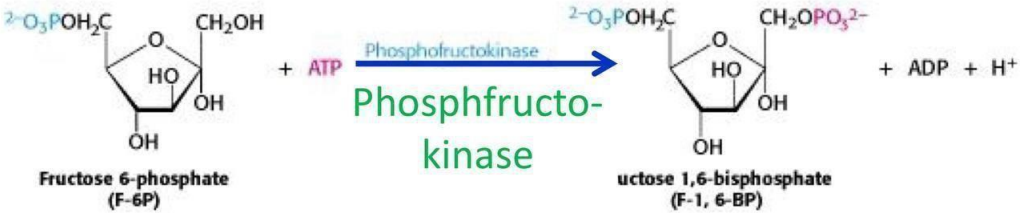


➢ Step 3

in the previus step , we add external carbon , in this step, we will add a phosphate group to this carbon (no.1) to make the molecule symmetric

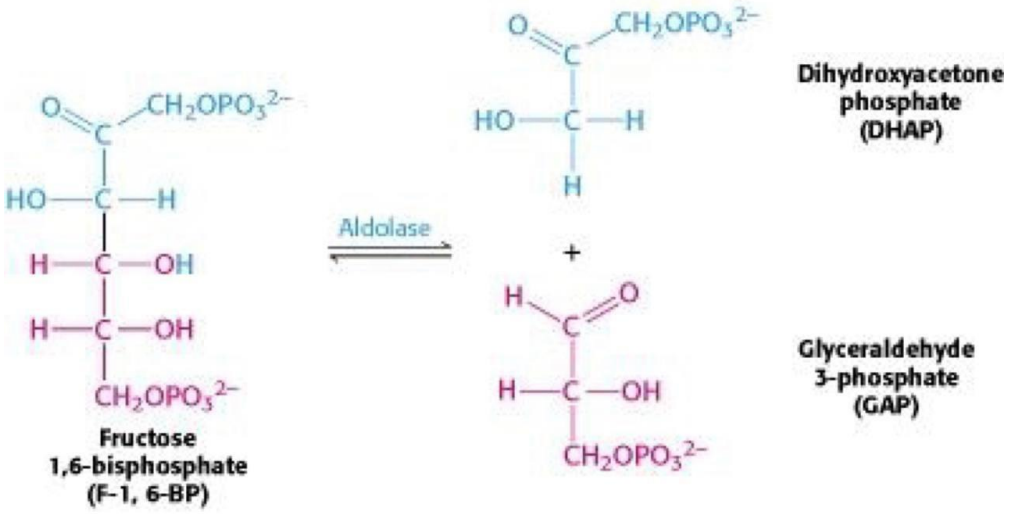
- the name of the new molecule is fructose 1,6-bisphosphate
- we used phosphfructo-kinase (**irreversible**)
- ATP dependent

note: in glycolysis, we have 3 irreversible reactions :
Step 1, step3 and the reaction that produce the pyruvate.
-why our body use irreversible reactions?
1- for regulation
2- to distinguish the forward from reverse reactions when I make the process in reverse way Ex: use pyruvate to produce Glucose.



➢ Step 4

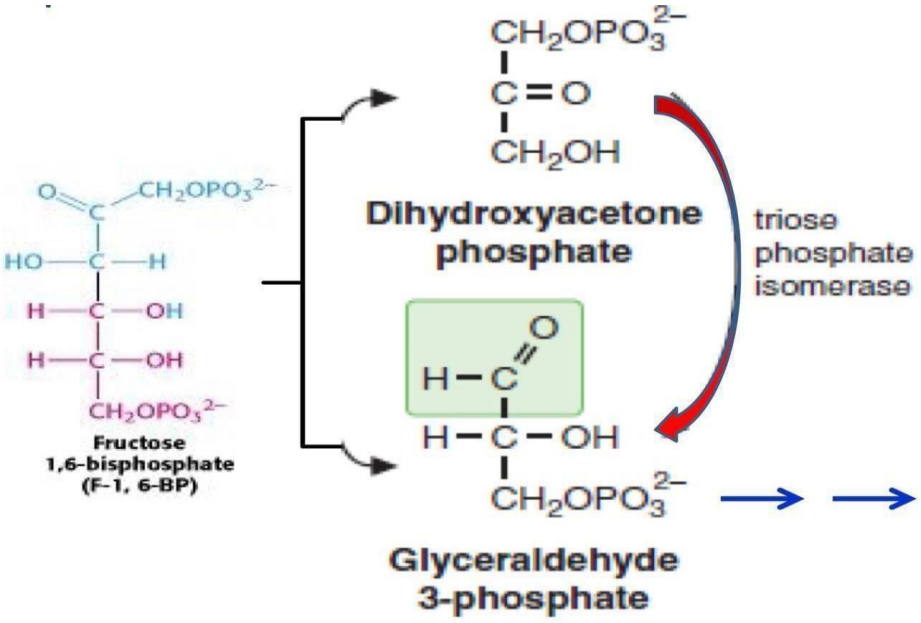
the molecule becomes symmetric because of previous steps, so now I can cleave it into 2 molecules by using a cleavage enzyme called **aldolase**.
-fructose 1,6-bisphosphate cleaved into Dihydroxyacetone phosphate (DHAP) have ketone group and glyceraldehyde 3-phosphate (GAP) have an aldehyde group
- each one of them got one phosphate group

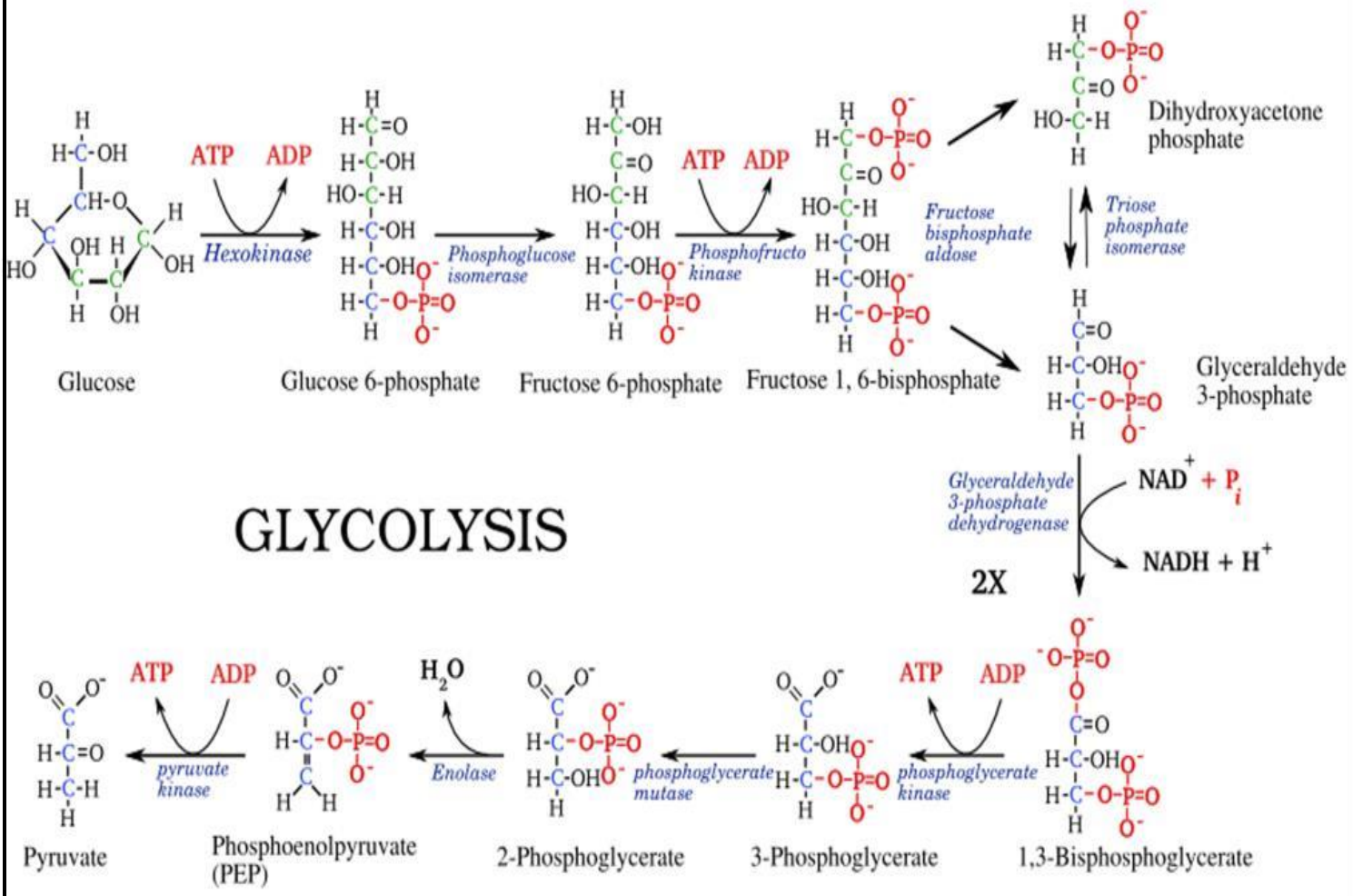


➢ Step 5

isomerization of DHAP to GAP Or vice versa.

- we used triose phosphate isomerase (reversible)
- if we want the pathway continues we must convert DHAP to GAP
- for example, if consumed all GAP the equilibrium will shift towards the production of more GAP





Recommended video:
https://youtu.be/8qij1m7XUhk

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