



☒ Sheet

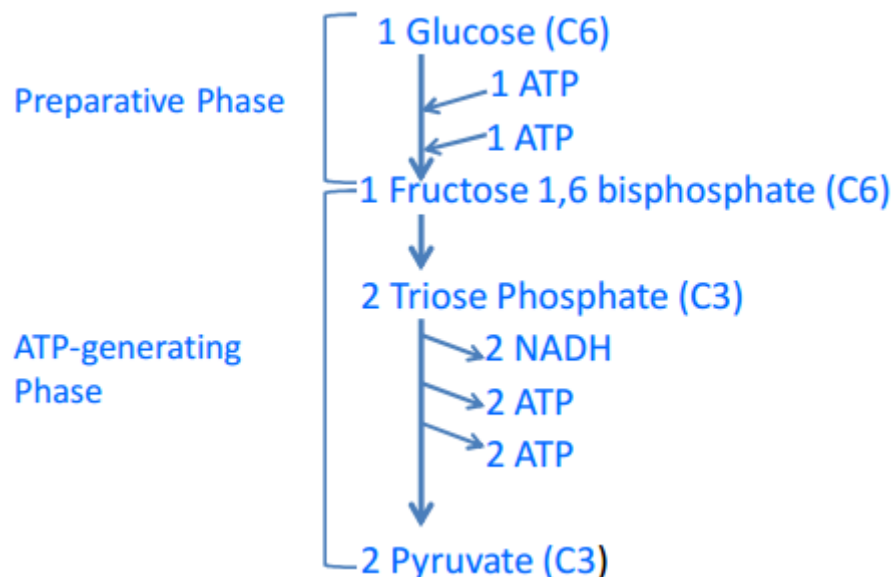
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Subject :	Glycolysis
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Number :	11

Introduction

Glycolysis is a universal pathway in all cell types. It occurs by the same mechanism and with similar enzymes. It is a pathway for generating ATP with or without the presence of oxygen (anaerobic). In addition to that, it produces important biosynthetic precursors for anabolic pathways; for example, some amino acids are produced from its intermediates, in addition to fats.

Phases of the Glycolytic Pathway

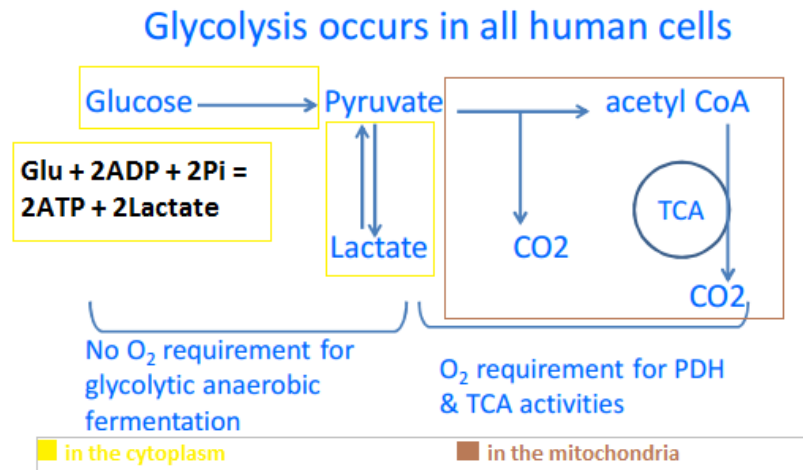


Glycolysis is divided into two phases:

- 1- **Preparative phase:** includes consumption of 2 ATP molecules per one glucose molecule. We "prepare" the molecule by energizing it so it can undergo oxidation. It starts with glucose "6 carbons", and ends with fructose 1,6-bisphosphate "6 carbons". It is also called investment phase, because we invest 2 ATP molecules.
- 2- **ATP generating phase:** includes 2 NADH molecules and 4 ATP molecules production per one glucose molecule "net production = 2 ATP + 2 NADH". It starts with fructose 1,6-bisphosphate "6 carbons", which turns to 2 trioses, and ends with 2 pyruvate "3 carbons" molecules. Pyruvate is not the end; it is still an energy

rich compound. So, to extract its energy, it gets oxidized to acetyl CoA which in return enters the TCA cycle in aerobic cells.

So as we see, glycolysis does not include production or consumption of CO₂. It starts with one molecule of glucose "6 carbons", and ends with 2 molecules of pyruvate "3 carbons". Note that all steps of the pathway happen simultaneously; we do not need to end the first phase to start the second phase.

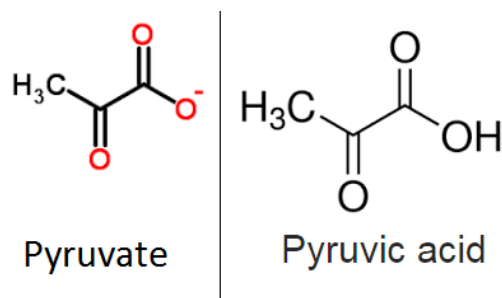


***Remember:** Glycolysis happens in ALL human cells, including anaerobic cells such as: mature RBCs.

Some tissues have an absolute requirement for glucose; because they depend completely (or almost completely) on glycolysis to produce energy. And such tissues include:

1. Brain
2. Red Blood Cells
3. Cornea lens and retina
4. Kidney Medulla
5. Testes
6. Leukocytes
7. White muscle fibers: during exercise, energy is required so we have the anaerobic pathway going in addition to the aerobic one.

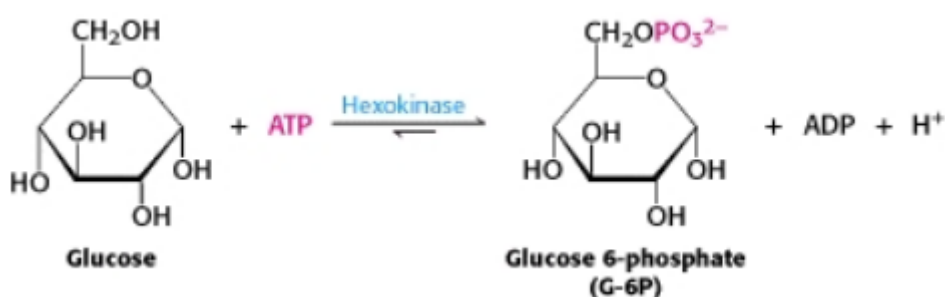
Pyruvate vs. Pyruvic acid: Pyruvate is the salt ion of the acid Pyruvic acid.



0:00 – 10:00

Glycolysis: Step by Step

First step:



This step is addition of phosphate group from ATP to the sixth carbon atom of glucose, so it is catalyzed by a kinase enzyme, which is hexokinase in all cells, except in liver cells where glucokinase "an isoenzyme" does the job. This step is irreversible (one of the three irreversible reactions in this pathway); because it includes breaking of high energy bond in ATP, and formation of a low energy ester bond between the phosphate group and the sixth carbon atom of glucose "usually, when a high energy molecule is transformed into a low energy molecule, the reaction is irreversible".

This step is important in capturing glucose inside the cell, because when it is phosphorylated, then it is unable to exit the cell because of the large charged group on it (phosphate group).

This glucose 6-phosphate stands at a central position, and it can:

- Continue glycolysis
- Enter the pentose phosphate pathway when the cell needs
- Enter glycogen synthesis when there is excessive glucose

- Hexokinase vs. Glucokinase:

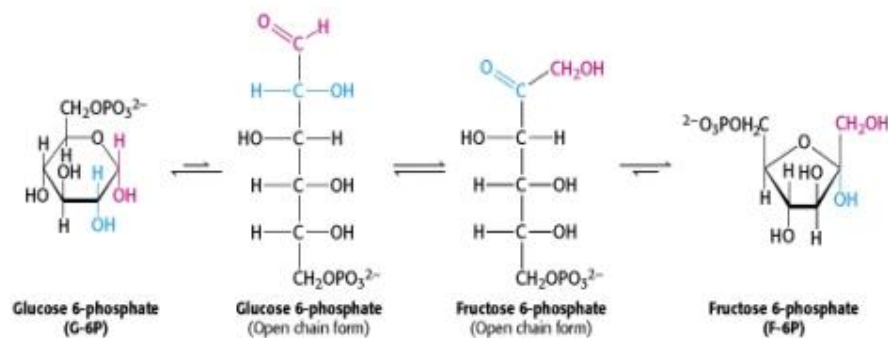
	Hexokinase	Glucokinase
Place	In most tissues	In liver
K _m	<0.02 mM	10 - 20 mM
Substrate(s)	Hexoses: Glu,Fru,Man,Gal	Glucose
Induction	Null	Insulin and Glucagon
Function	even when glucose levels are low	only when glucose levels >100mg/dl "~5mM"

Analysis of the table:

- Km values: HK has a low Km, which means high affinity, which enables tissues, especially absolute glucose requiring tissues, to have their need of glucose met even with low glucose levels in the blood. However, GK has high Km and V_{max} values, which suits its job in working only in high blood glucose levels(hyperglycemia) " i. e. while digesting a meal" to store glucose in the form of glycogen, or convert it into fatty acids for storage purposes to normalize glucose level in the circulation. Remember that $K_m = [S]_{\text{at } 0.5 V_{\text{max}}}$.
- Induction: means the activation of enzyme synthesis. GK is induced by insulin and glucagon levels. High insulin/ glucagon levels promote GK synthesis.
- Note that these enzymes work in the same mechanism.

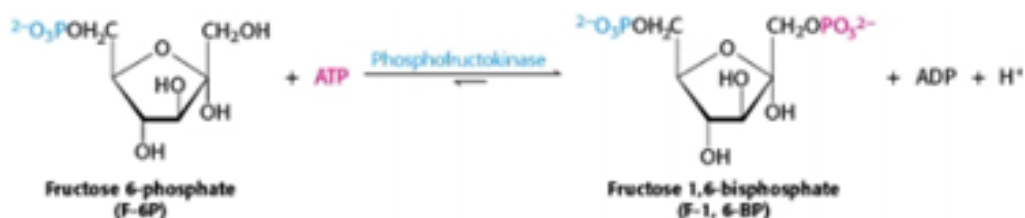
- HK can phosphorylate hexoses other than glucose but with lower affinity. Those sugars have their own kinase enzyme, but when they are in high concentrations HK can help.

Second step:



This step is an isomerization reaction from G-6P to F-6P (from an aldose to a ketose), so it is catalyzed by an isomerase enzyme, which is phosphoglucose isomerase. Notice that fructose 6-phosphate and glucose 6-phosphate are isomers; they only differ in the arrangement of atoms around carbon atoms number 1 and 2. In isomerization reactions, 1 reactant gives 1 product; no addition or production of other molecules. This step is reversible; when G-6P concentration increases, the reaction will produce more F-6P.

Third step:



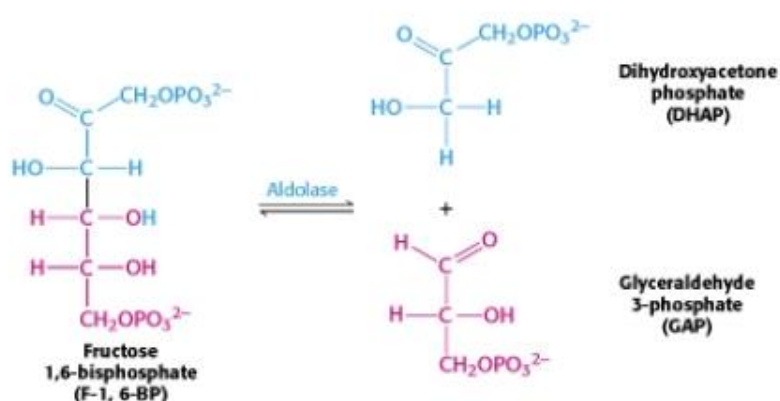
In this step, phosphofructokinase transfers a phosphate group from an ATP molecule to carbon number 1 of fructose 6-phosphate. In addition to being the second irreversible step in the pathway, this step is the committed step of the pathway, which means that its product "fructose 1,6-bisphosphate" is only for glycolysis, whereas F-6P "the reactant" can

be consumed by other pathways. Because of that, this important step is highly regulated. By now, 2 ATP molecules are invested, and the ATP-generating phase starts with the next step.

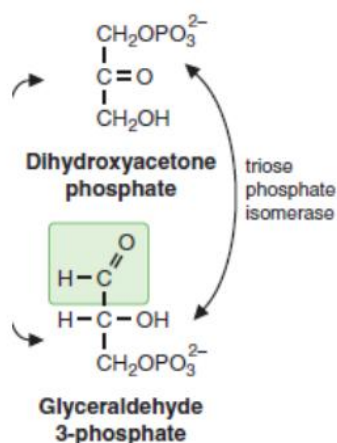
Note that *bis*phosphate is different from *diphosphate*; since diphosphate indicates that both phosphate groups are bound to the same carbon atom.

10:00 – 20:00

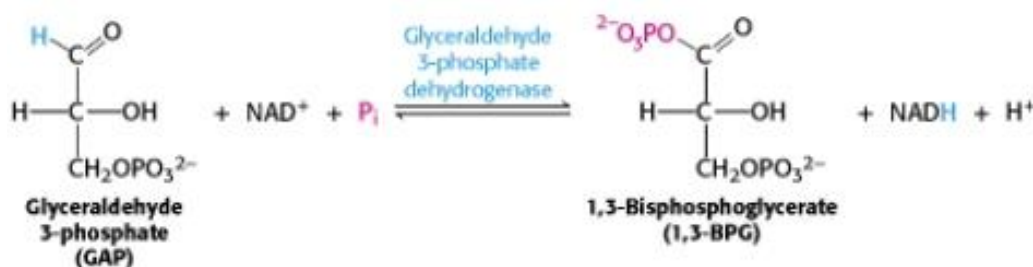
Fourth and fifth steps:



In the fourth step, fructose 1,6-bisphosphate is cleaved from the site of the bond between carbon 3 and carbon 4, to give two isomers, an aldose phosphate "glyceraldehyde 3-phosphate" and a ketose phosphate "dihydroxyacetone phosphate", each with 3 carbon atoms (a triose). It is catalyzed by aldolase (it produces an aldose "glyceraldehyde 3-phosphate"). Note that the reaction is reversible. Glyceraldehyde 3-phosphate is the one which continues in glycolysis, but the 2 triose phosphates are interconverted reversibly by the enzyme triose phosphate isomerase "fifth step", so when glyceraldehyde 3-phosphate gets consumed by glycolysis, the reaction produces more glyceraldehyde 3-phosphate from dihydroxyacetone phosphate.



Sixth step: the first oxidative step

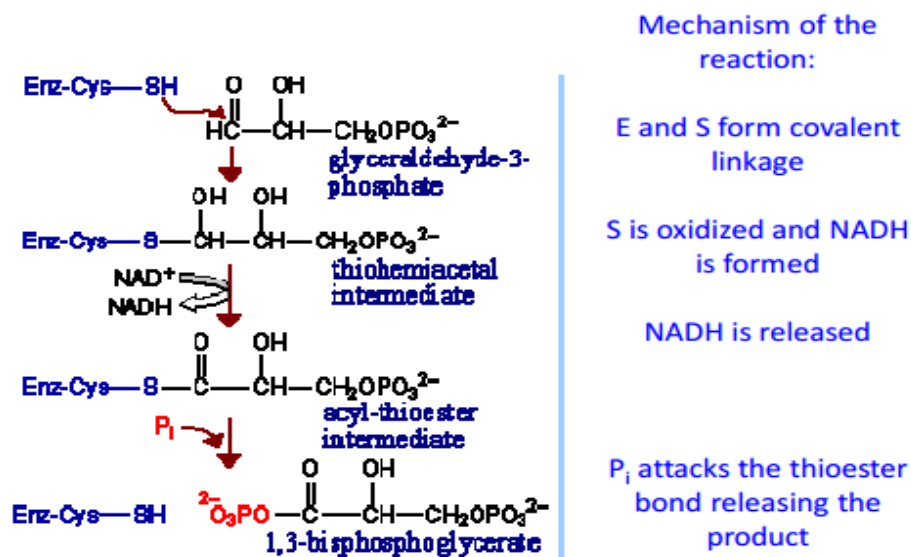


This oxidation-reduction step is catalyzed by glyceraldehyde 3-p dehydrogenase, with the presence of NAD⁺ as an oxidizing agent "gets reduced". This reaction includes several steps "explained in the following paragraph", but the redox step has the priority in naming, so the enzyme is called "dehydrogenase". Remember that dehydrogenases use NAD⁺ as a coenzyme "oxidizing agent". This step is reversible.

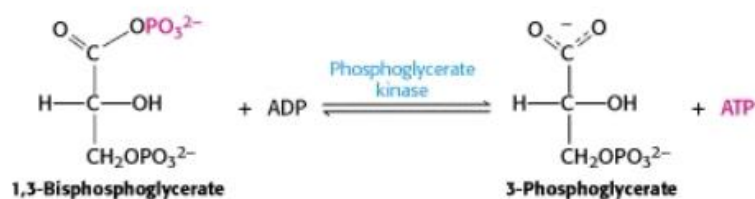
20:00 – 35:00

The mechanism of this reaction is not simple. It starts with binding of the substrate "glyceraldehyde 3-p" to the cysteine –SH, to form a thiohemiacetal. Then, oxidation occurs by removing 2H⁺ which were bound to C atom and O atom to form thioester linkage, which is a high energy bond "similar to acetyl-coA bond". Then, a phosphate group is added "instead of cleaving the bond with H₂O, which will lead to losing all the energy", and energy is captured in the high energy bond of the product 1,3-bisphosphoglycerate "1,3-BPG". The bond is a high energy bond since it binds 2 acid groups "which are –COO and the phosphate" with each other, and it has energy more than that of ATP.

Arsenic "poison" may compete with the inorganic phosphate, which results with direct hydrolysis and production of 3-phosphoglycerate which is not a high energy molecule, and very big amount of energy is lost as heat.

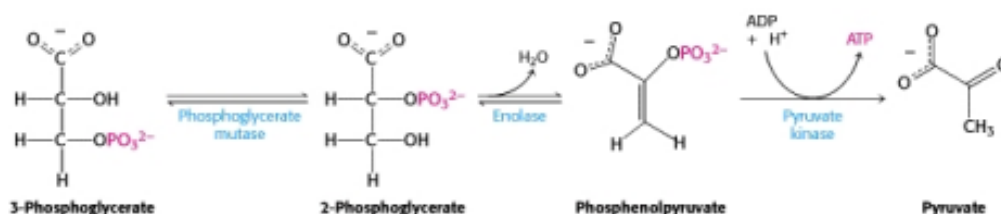


Seventh step:



In this step, the phosphate which was added in the previous step will be transferred to ADP to form ATP "Kinase activity" (substrate level phosphorylation). This step is catalyzed by phosphoglycerate kinase "3-phosphoglycerate is the product". Enzyme's name refers to the backward direction". This step is reversible.

Steps; 8, 9 and 10:



Phosphoglycerate mutase "an isomerase" transfers the phosphate from the third carbon to the second carbon atom "reversible" (This

reaction needs 2,3-BPG which is produced partly from 1,3-BPG by a mutase). Then, enolase catalyzes the dehydration reaction to produce phosphoenolpyruvate. In Phosphoenolpyruvate, -en- stands for the double bond, and -ol- refers to alcohol. This compound is a high energy compound. In the last step, pyruvate kinase "named according to the backward direction" transfers the phosphate group of the high energy phosphoenolpyruvate to an ADP molecule producing ATP (2nd substrate level phosphorylation reaction). This reaction produces large amount of energy as heat, which contributes to the irreversibility of the reaction; since when heat is produced in big amounts from a reaction, then it will be irreversible.

To sum up, we see that 3 of the 10 steps of glycolysis are irreversible and are all under regulation, these are:

- 1- 1st step "by hexokinase or glucokinase".
- 2- 3rd step "by phosphofructokinase".
- 3- 10th step "by pyruvate kinase".

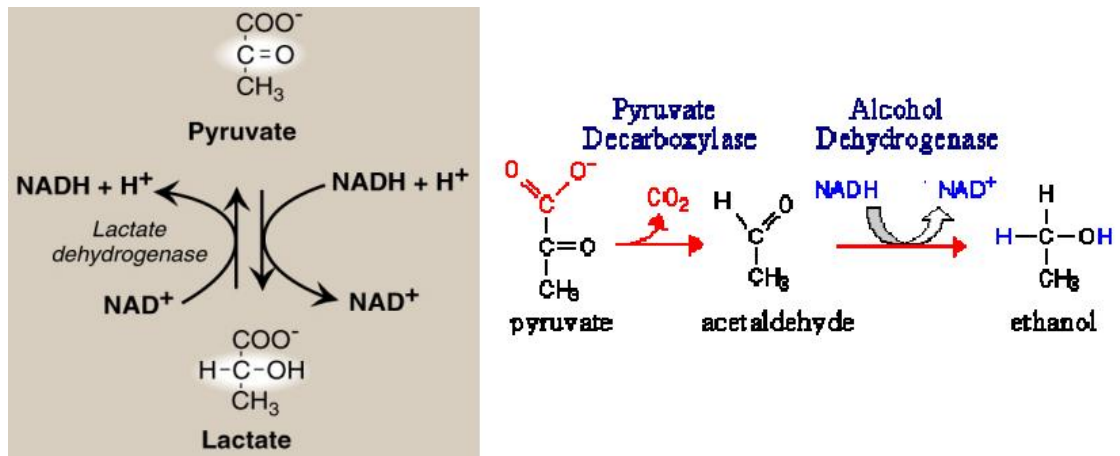
*Remember that 1 glucose molecule is converted to 2 trioses (at step 4), so every product after that step will be multiplied by 2. At the end 1 glucose molecule produces 2 pyruvate molecules which is the final product of glycolysis.

Pyruvate produced from glycolysis occupies a central position. It can be converted to acetyl CoA by pyruvate dehydrogenase to make fat (in the liver) or to produce energy by the citric acid cycle and the oxidative phosphorylation "in muscles and brain". Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase to maintain the intermediates of the citric acid cycle. Also this reaction is the first step in gluconeogenesis (which will be studied later).

Note that glycolysis produces 2 molecules of NADH, which need to get oxidized to keep glycolysis running. And that is done by either one these two ways:

- 1- Oxidative phosphorylation in the mitochondria, with the presence of oxygen.
- 2- Lactate fermentation. Oxygen is not needed, and the net ATP production is 2ATP/1glucose. Pyruvate is reduced to lactate (the end product) by lactate dehydrogenase.

The third way does not occur in humans but in some microorganisms, such as yeast. It is alcoholic fermentation (2-step process), which has ethanol as the final product, and produces 2ATP/1glucose.



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الحشر: ٩