GLYCOLYSIS

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Metabolism

- **Metabolism**, the sum of all the chemical transformations taking place in a cell or organism, occurs through a series of enzyme-catalyzed reactions that constitute **metabolic pathways**.
- Each of the consecutive steps in a metabolic pathway brings about a specific, small chemical change, usually the removal, transfer, or addition of a particular atom or functional group.
- The precursor is converted into a product through a series of metabolic intermediates called metabolites.
- There are **2 categories of metabolism-**
  1. **Catabolism**
  2. **Anabolism**

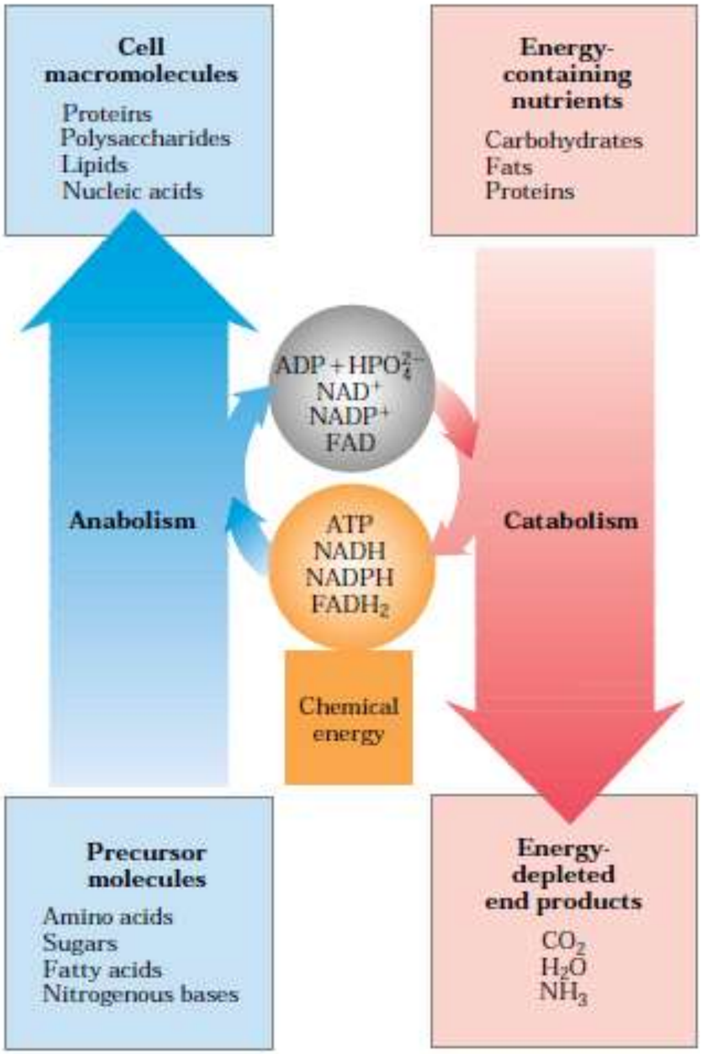
Catabolism

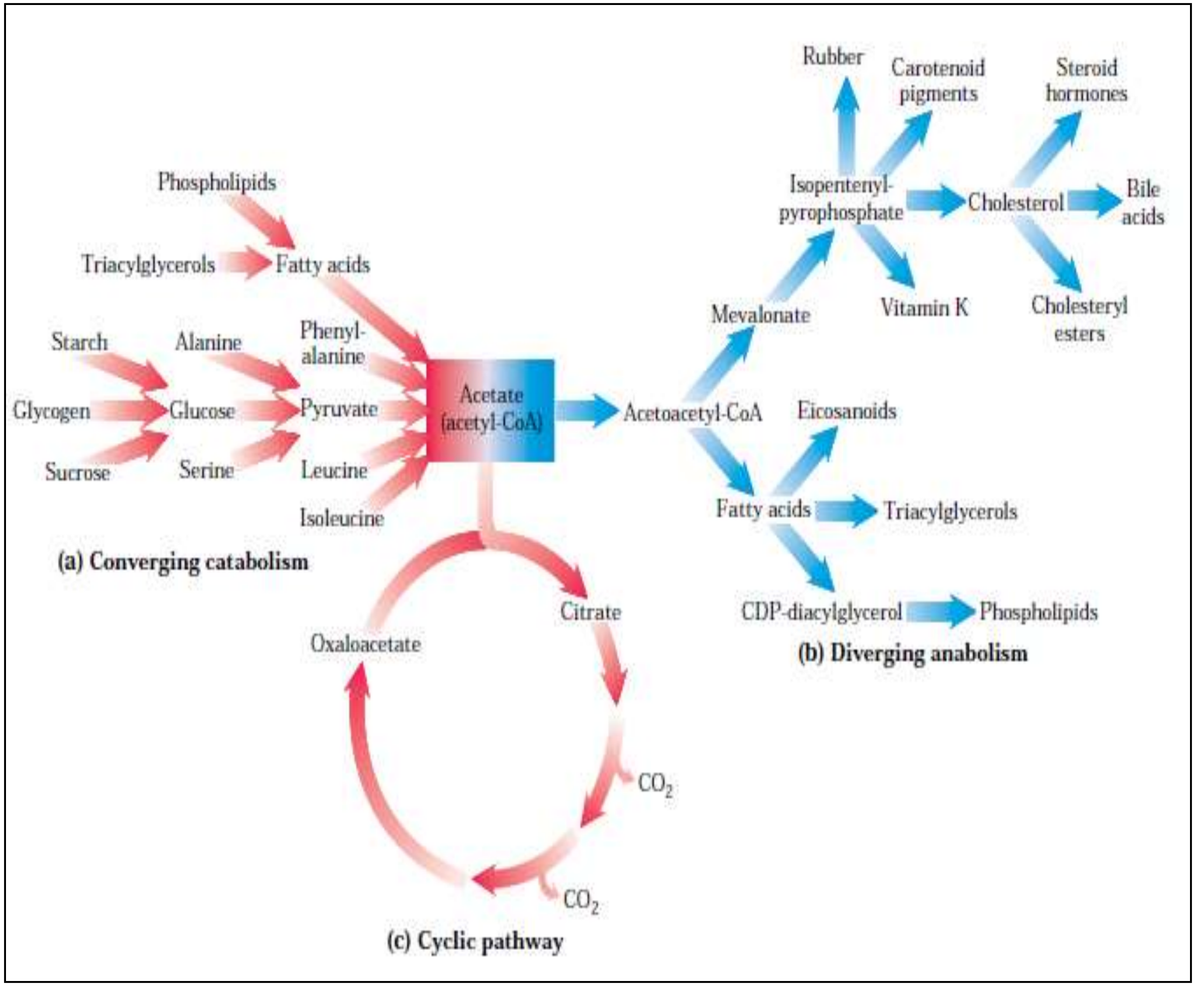
- **Catabolism** is the degradative phase of metabolism in which organic nutrient molecules (carbohydrates, fats, and proteins) are converted into smaller, simpler end products (such as lactic acid, CO_2, NH_3).
- Pathway followed by such molecules are known as **Catabolic pathways**
- Catabolic pathways release energy, some of which is conserved in the formation of ATP and reduced electron carriers (NADH, NADPH, and $FADH_2$); the rest is lost as heat.
- Catabolic pathways are convergent in nature.

Anabolism

- **Anabolism is also called biosynthesis**
- In **anabolism** small, simple precursors are built up into larger and more complex molecules, including lipids, polysaccharides, proteins, and nucleic acids.
- Pathway followed by such molecules are known as **Anabolic pathways**
- Anabolic pathways require an input of energy, generally in the form of the phosphoryl group transfer potential of ATP and the reducing power of .NADH, NADPH, and FADH2.
- Anabolic pathways divergent in nature

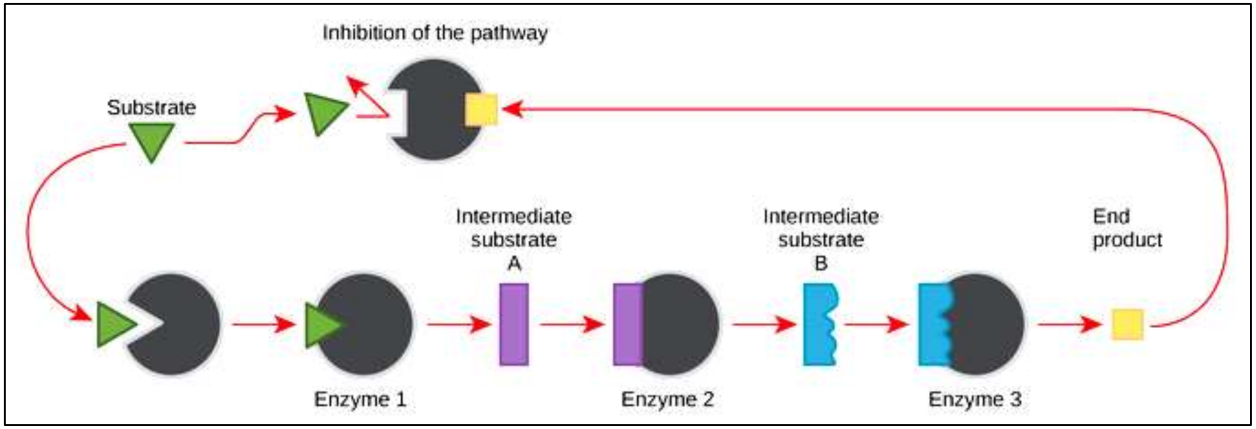
Catabolism & Anabolism



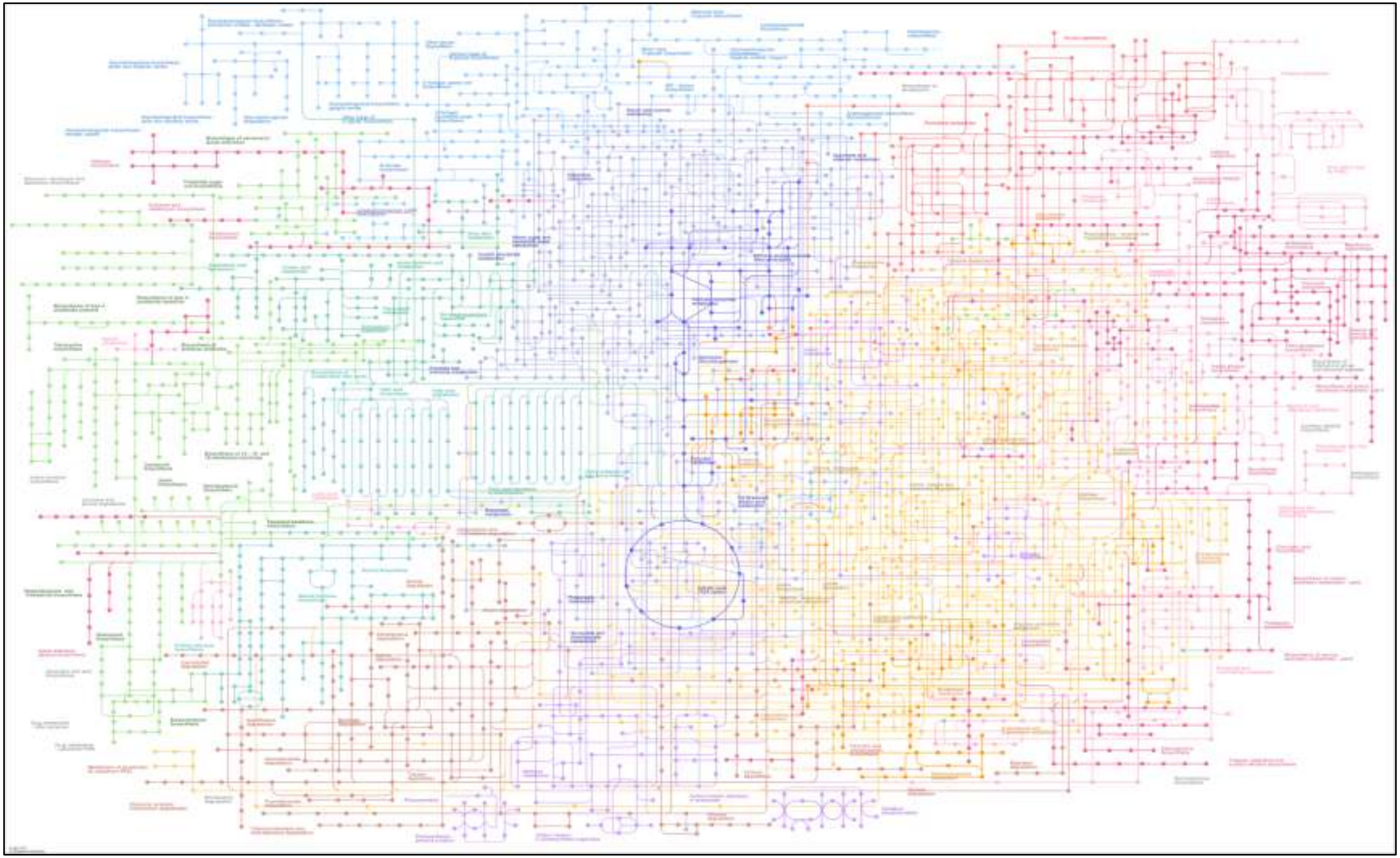


Regulation

- Metabolic regulation **enables the balance between substrate and product of enzyme-catalyzed reactions to be maintained** so that ordered metabolic flow can occur in response to developmental requirements and environment.
- In order to maintain chemical equilibrium and meet the needs of the cell, some metabolic products inhibit the enzymes in the chemical pathway while some reactants activate them.



Metabolic Pathways



Glycolysis

- Glycolysis comes from a merger of two Greek words:

  Glykys (Greek word) = sweet

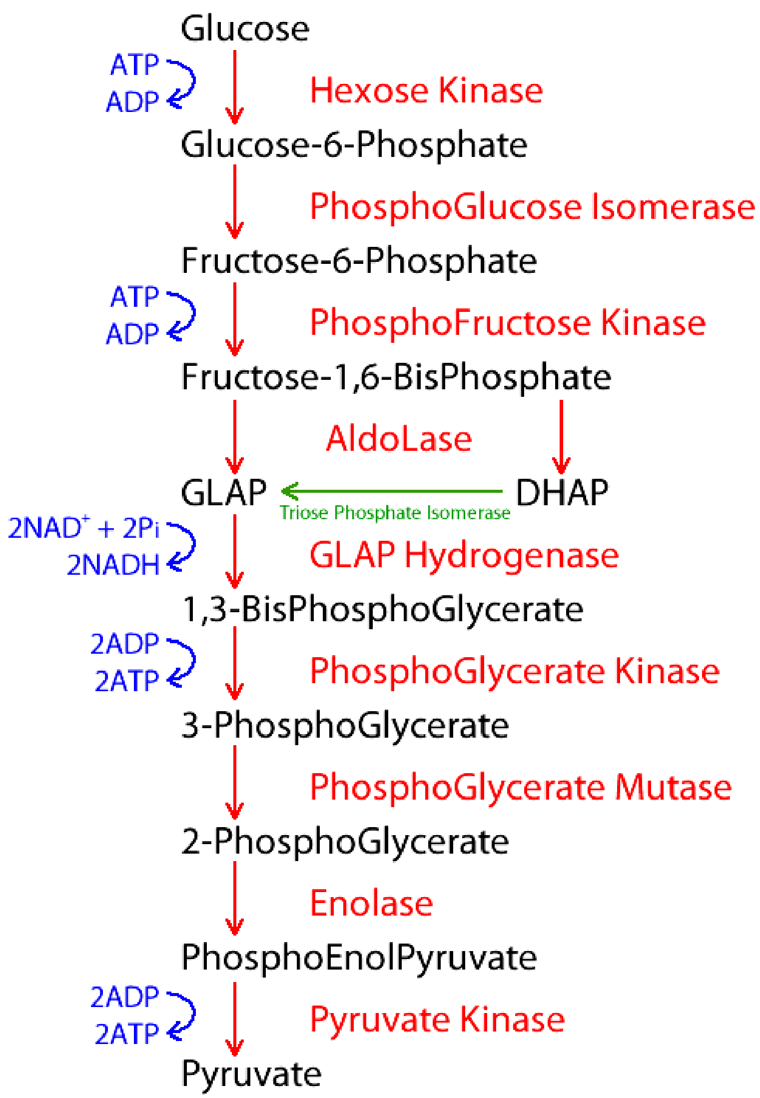
  Lysis = breakdown/ splitting

- It is also known as Embden-Meyerhof-Parnas pathway or EMP pathway.
- Glycolysis is the sequence of 10 enzyme-catalyzed reactions that converts glucose into pyruvate with simultaneous production on of ATP.
- In this oxidative process, 1mol of glucose is partially oxidised to 2 moles of pyruvate.

Glycolysis

- This major pathway of glucose metabolism occurs in the cytosol of all cell.
- This unique pathway occurs **aerobically as well as anaerobically** & doesn’t involve molecular oxygen**.**
- In aerobic organisms, glycolysis is the prelude to Citric acid cycle and ETC.
- Glycolysis is the central pathway for Glucose catabolism.

Glycolysis Pathway



Two Phases Of Glycolysis

- Glycolysis leads to breakdown of 6-C glucose into two molecules of 3-C pyruvate with the enzyme catalyzed reactions being bifurcated or categorized into 2 phases:
  - **Phase 1:** Preparatory phase
  - **Phase 2:** Payoff phase.

Preparatory Phase

- It consists of the first 5 steps of glycolysis

Step 1: Glucose is first phosphorylated at the hydroxyl group on C-6.

Step 2: Glucose 6-phosphate formed is converted to fructose-6-phosphate .

Step 3: Fructose-6-phosphate which is again phosphorylated, this time at C-1, to yield fructose-1,6- bisphosphate.

- For both phosphorylations, ATP is the phosphoryl group donor.

Step 4: Fructose-1,6-bisphosphate is split to yield two three-carbon molecules, dihydroxyacetone phosphate and glyceraldehyde 3-phosphate [this is the “lysis” step that gives the pathway its name].

Step 5: The dihydroxyacetone phosphate is isomerized to a second molecule of glyceraldehyde 3-phosphate, ending the first phase of glycolysis.

- This cleavage requires 2 ATP molecules to activate the glucose mole and prepare it for its cleavage into 3-carbon compound.

Payoff Phase

- This phase constitutes the last 5 steps of Glycolysis.

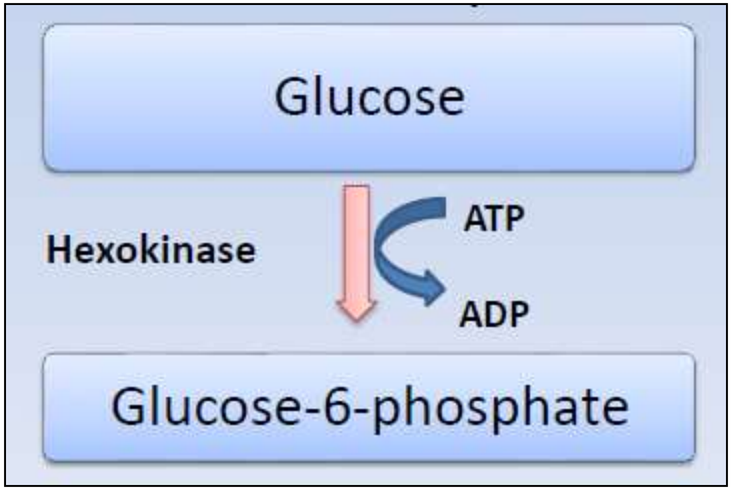
Step 6: Each molecule of glyceraldehyde 3-phosphate is oxidized and phosphorylated by inorganic phosphate (not by ATP) to form 1,3-bisphosphoglycerate .

Step 7-10 : Energy is then released as the two molecules of 1,3 bisphosphoglycerate are converted to two molecules of pyruvate.

- This phase marks the release of ATP molecules during conversion of Glyceraldehyde-3-phosphtae to 2 moles of Pyruvate.
- Here 4 moles of ADP are phosphorylated to ATP.
- Although 4 moles of ATP are formed, the net result is only 2 moles of ATP per mole of Glucose oxidized, since 2 moles of ATP are utilized in Phase 1.

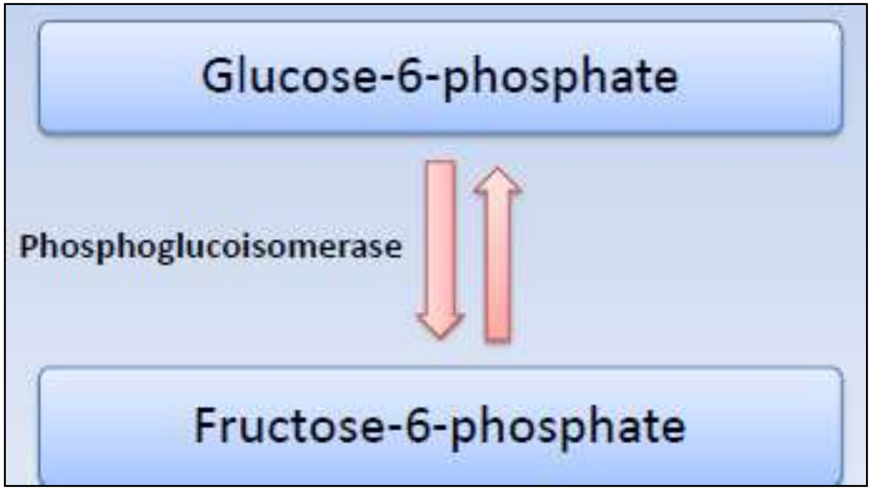
Step 1: Phosphorylation

- Glucose is phosphorylated by ATP to form sugar phosphate.
- This is an irreversible reaction & is catalyzed by ***hexokinase.***



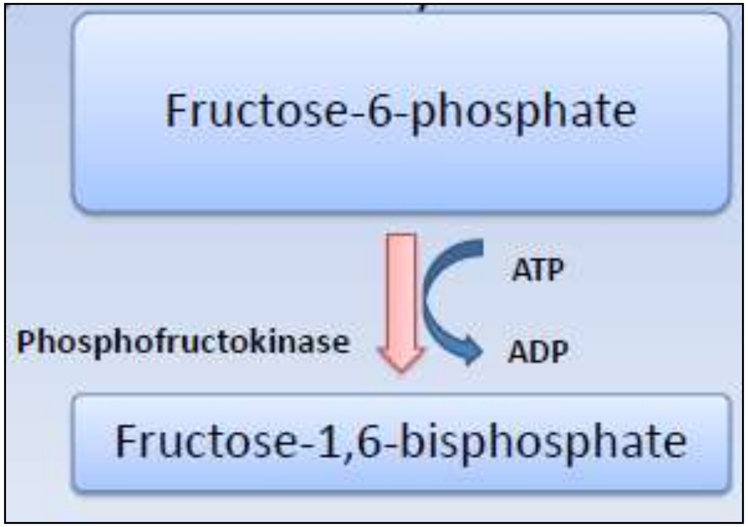
Step 2: Isomerization

- It is a reversible rearrangement of chemical structure of carbonyl oxygen from C1 to C2, forming a Ketose from the Aldose.
- Thus, isomerization of the aldose Glucose6-phosphate gives the ketose, Fructose-6-phoshphate.



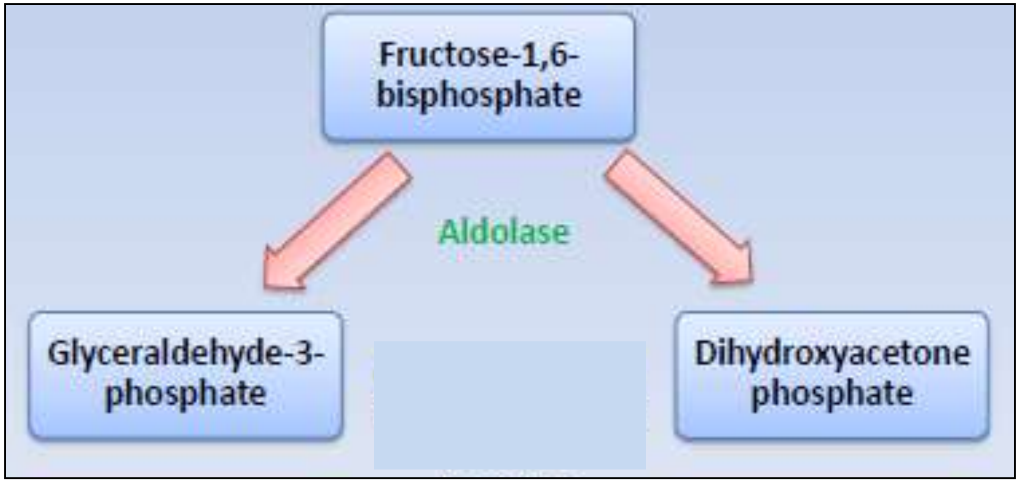
Step 3: Phophorylation

- Here the Fructose-6-phosphate is phosphorylated by ATP to fructose-1,6-bisphosphate.
- This is an irreversible reaction and is catalyzed by phosphofructokinase enzyme.



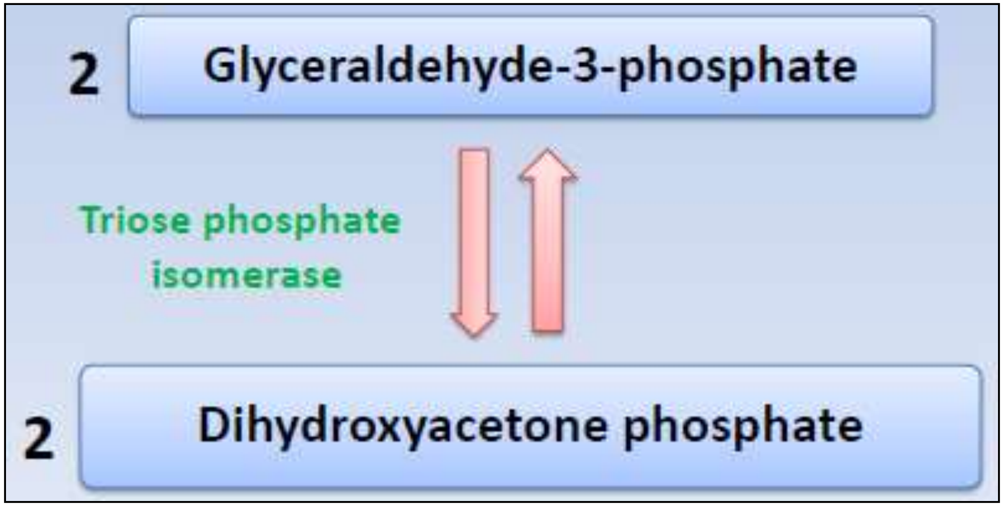
Step 4: Breakdown

- This six carbon sugar is cleaved to produce two 3-C molecules: glyceradldehyde-3-phosphate (GAP) & dihydroxyacetone phosphate(DHAP).
- This reaction is catalyzed by Aldolase.



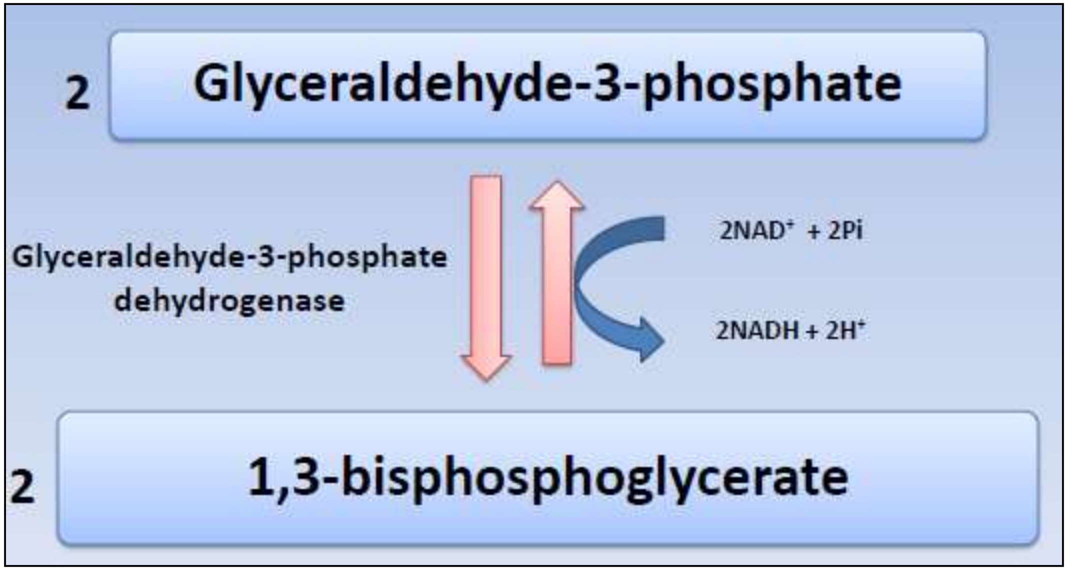
Step 5: Isomerization

- Dihydroxyacetone phosphate is oxidized to form Glyceraldehyde-3-phosphate.
- This reaction is catalyzed by triose phosphate isomerase enzyme.



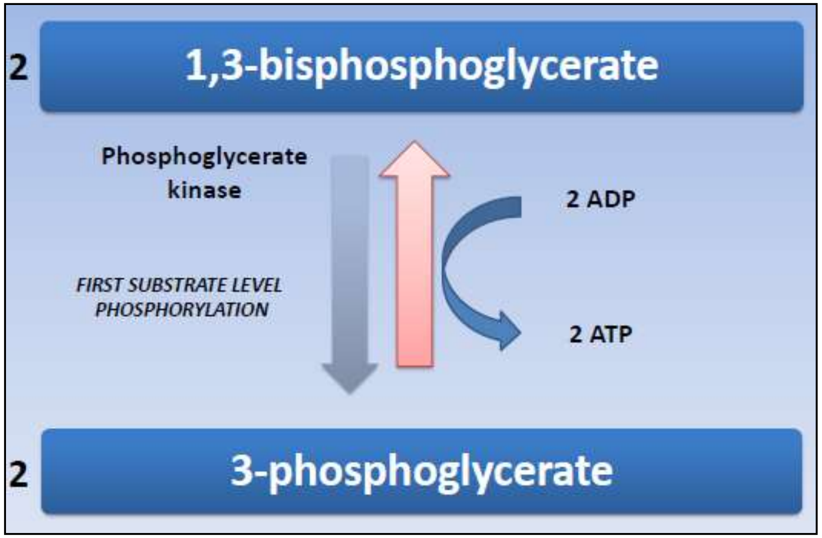
Step 6: Oxidization

- 2 molecules of Glyceraldehyde-3-phosphate are oxidized.
- Glyceraldehyde-3-phosphate dehydrogenase catalyzes the conversion of Glyceraldehyde3-phosphate into 1,3-bisphosphoglycerate.



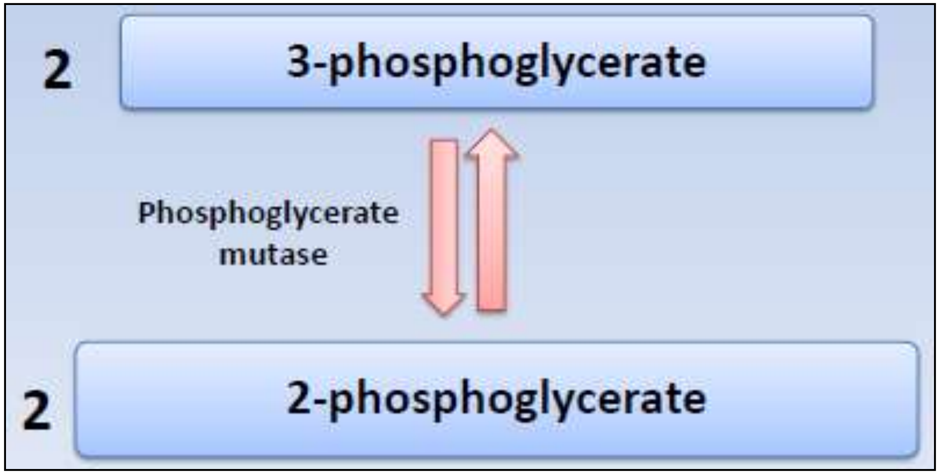
Step 7: 1st Substrate Phosphorylation

- The transfer of high-energy phosphate group that was generated earlier to ADP, form ATP.
- This phosphorylation i.e. addition of phosphate to ADP to give ATP is termed as substrate level phosphorylation as the phosphate donor is the substrate 1,3-bisphosphoglycerate.
- The product of this reaction is 2 molecules of 3-phosphoglycerate.



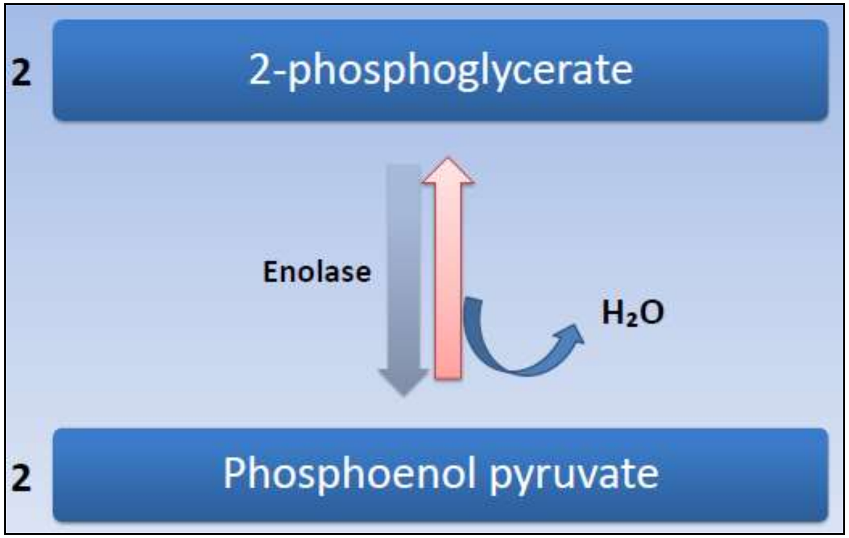
Step 8: Mutation

- The remaining phosphate-ester linkage in 3-phosphoglycerate, is moved from carbon 3 to carbon 2 ,because of relatively low free energy of hydrolysis, to form 2-phosphoglycerate(2-PG).



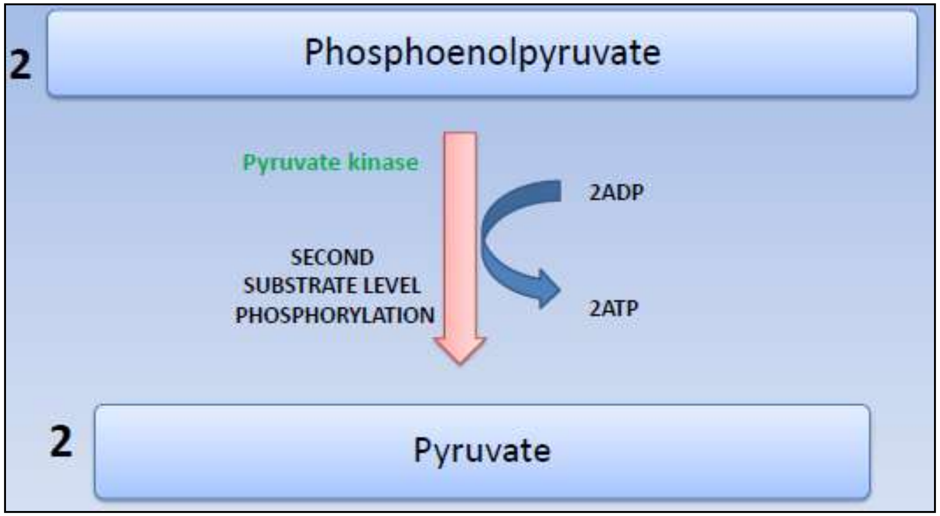
Step 9: Dehydration

- This is the second reaction in glycolysis where a high-energy phosphate compound is formed.
- The 2-phosphoglycerate is dehydrated by the action of enolase to phosphoenolpyruvate(PEP). This compound is the phosphate ester of the enol tautomer of pyruvate.
- This is a reversible reaction.

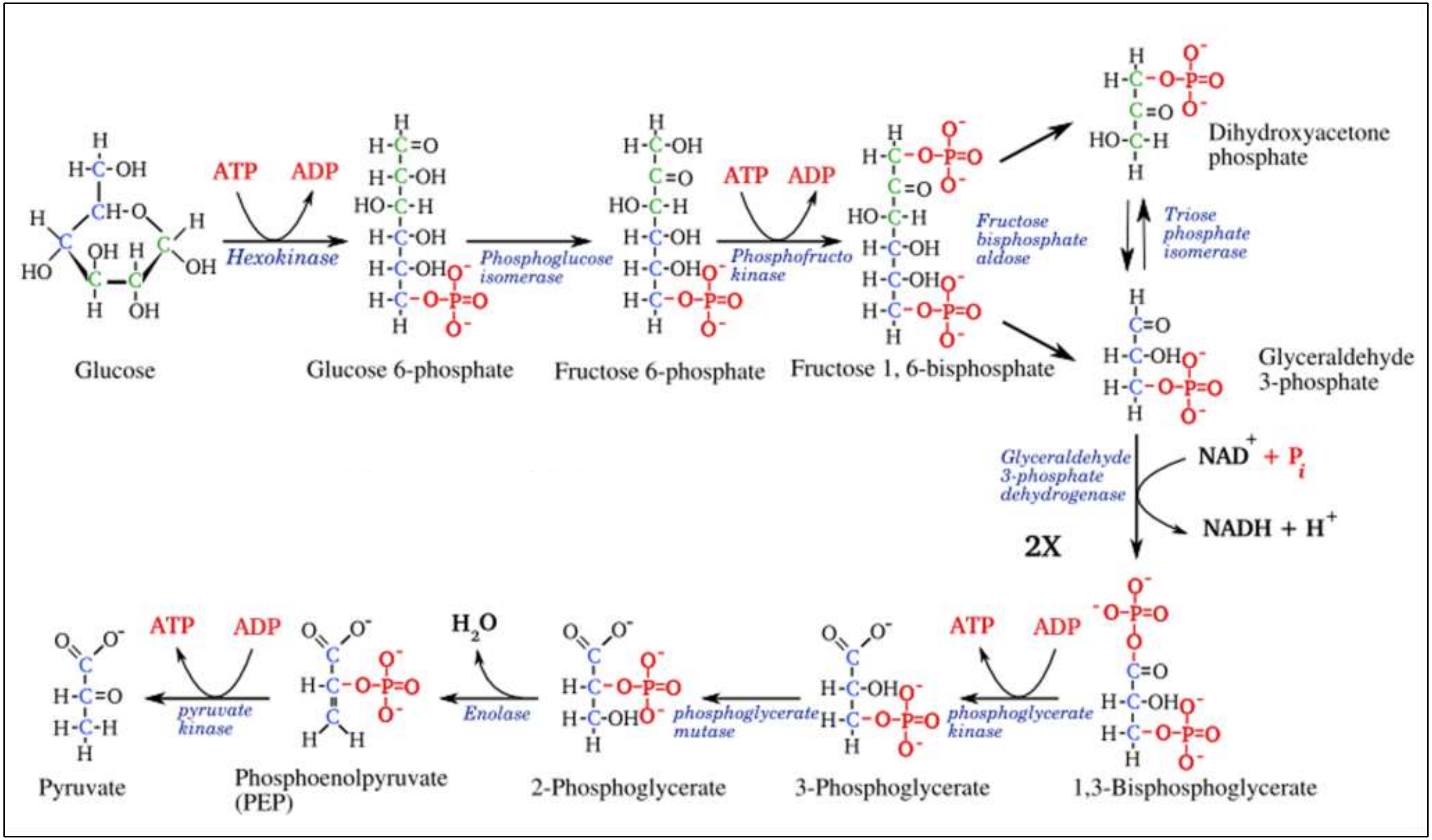


Step 10: 2nd Substrate Phosphorylation

- This last step is the irreversible transfer of high energy phosphoryl group from phosphoenolpuruvate to ADP.
- This reaction is catalyzed by pyruvate kinase.
- This is the 2nd substrate level phosphorylation reaction in glycolysis which yields ATP.
- This is a non-oxidative phosphorylation reaction.



Glycolysis Pathway



Overall Balance Sheet Of Glycolysis

- Each molecule of glucose gives 2 molecules of Glyceraldehyde-3-phosphate.
- Therefore , the total input of all 10 reactions can be summarized as:

$$\text{Glucose} + 2ATP + 2Pi + 2NAD^+ + 2H^+ + 4ADP$$

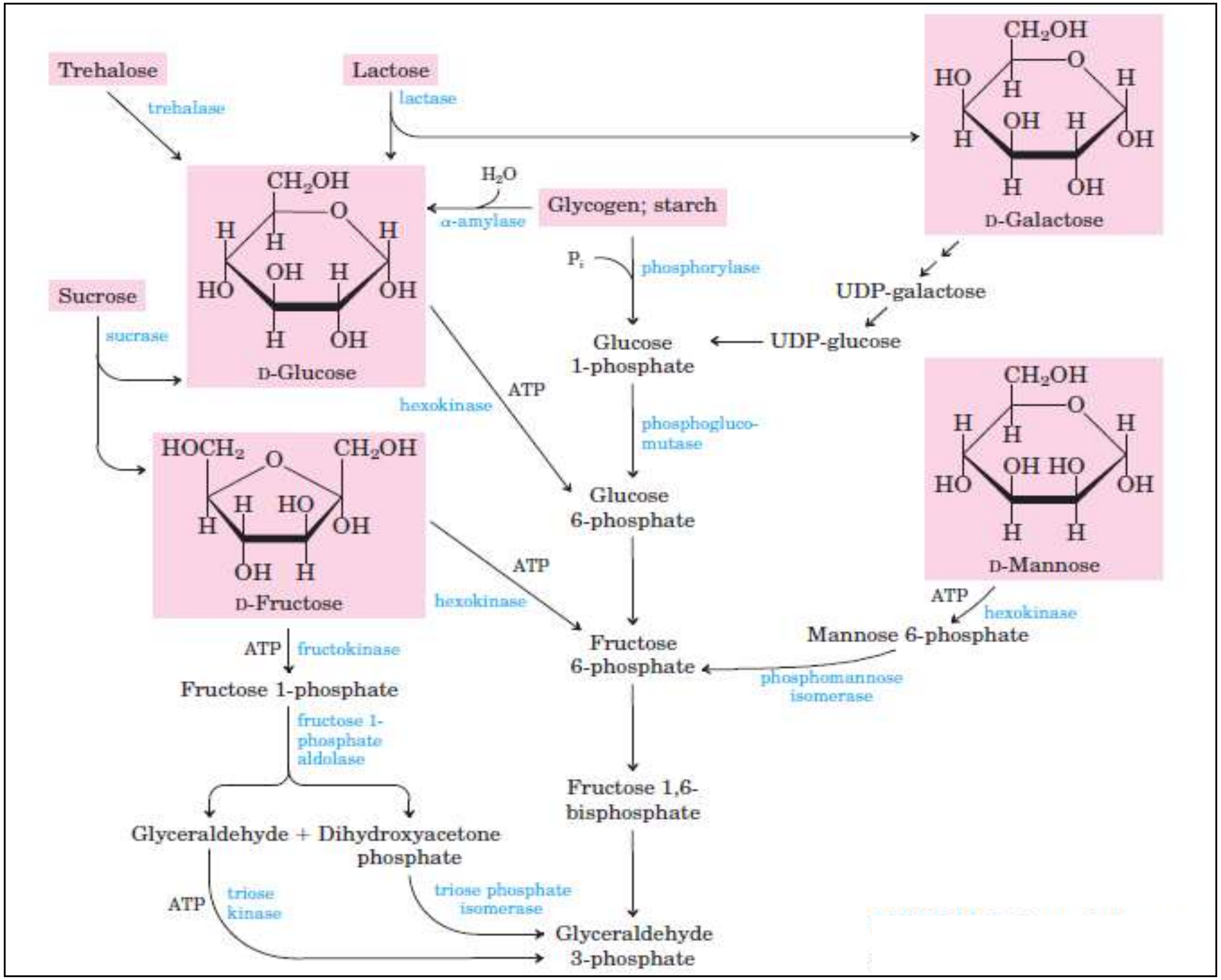
$$\downarrow$$

$$2\text{Pyruvate} + 2H^+ + 4ATP + 2H_2O + 2NADH + 2ADP$$

Feeder Pathways for Glycolysis

- Many carbohydrates besides glucose meet their catabolic fate in glycolysis, after being transformed into one of the glycolytic intermediates.
- The most significant are the storage polysaccharides glycogen and starch; the disaccharides maltose, lactose, trehalose, and sucrose; and the monosaccharides fructose, mannose, and galactose.

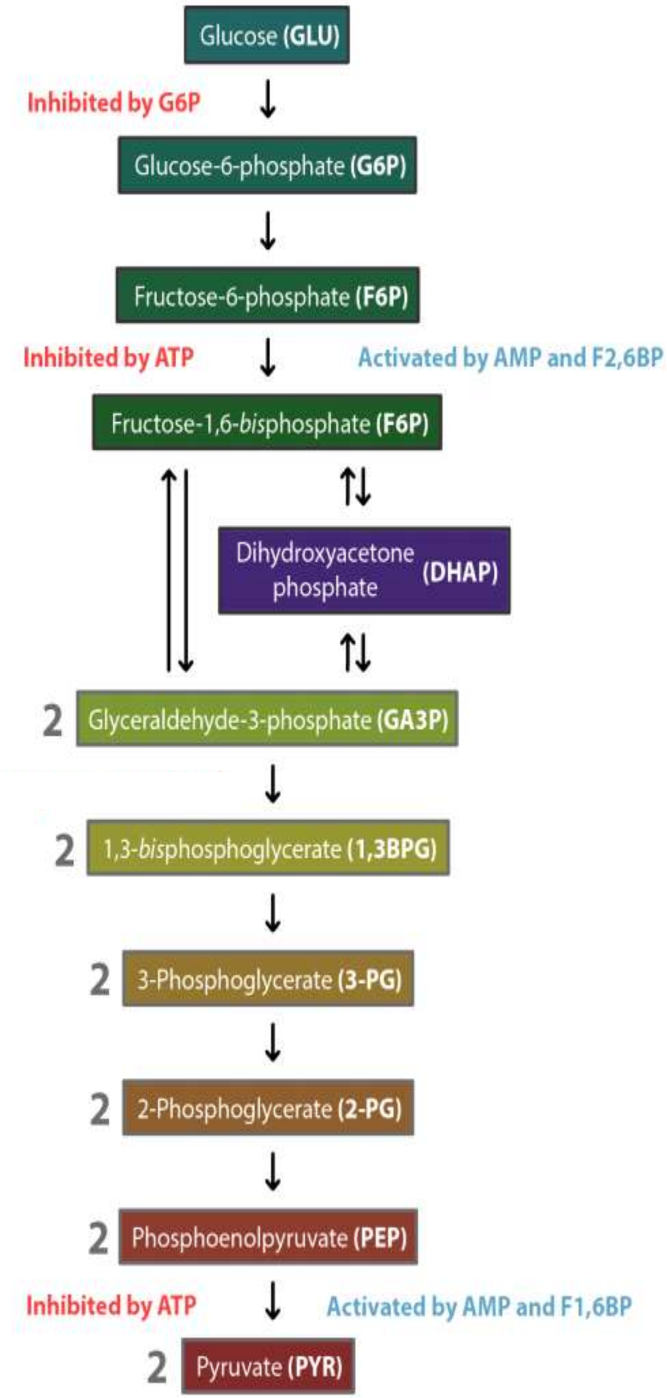
Feeder Pathways for Glycolysis



Regulation

- Regulation occurs at three enzymatic points.
- Three reactions of glycolysis are so exergonic as to be essentially irreversible.
- These reactions are catalyzed by hexokinase, PFK-1, and pyruvate kinase.

$\underbrace{\text{Glucose} \rightleftharpoons G_6P}_{\text{hexokinase}}$
$\underbrace{F_6P \rightleftharpoons F_1,6\,BP}_{\text{phosphofructokinase (PFK)}}$
$\underbrace{\text{PEP} \rightleftharpoons \text{pyruvate.}}_{\text{pyruvate kinase}}$



Regulation of Glycolysis

1. **Hexokinase** is inhibited by glucose 6- phosphate. This enzyme prevents the accumulation of glucose 6-phosphate due to product inhibition.

2. **Phosphofructo kinase (PFK)** is the most important regulatory enzyme in glycolysis. PFK is an allosteric enzyme regulated by allosteric effectors ATP, citrate & H+ ions (low pH) are the most important allosteric inhibitors. Fructose 2 ,6-bisphosphate, ADP, AMP & Pi are the allosteric activators.

3. **Pyruvate kinase PK** Inhibited by ATP & activated by F1,6-BP.

   - Pyruvate kinase is active

     (a) in dephosphorylated state & inactive

     (b) in phosphorylated state.

   - Inactivation of pyruvate kinase is brought about by cAMP-dependent protein kinase. The hormone glucagon inhibits hepatic glycolysis by this mechanism.

Thank You