CC7_Unit 2.3

Glycolysis and Gluconeogenesis

Glucose occupies a central position in the metabolism of plants, animals and many microorganisms. In animals, glucose has four major fates as shown in figure 1.

The organisms that do not have access to glucose from other sources must make it. Plants make glucose by photosynthesis. Non-photosynthetic cells make glucose from 3 and 4 carbon precursors by the process of gluconeogenesis.

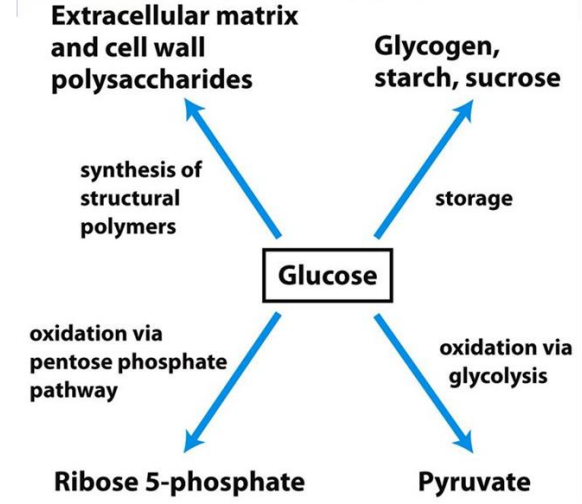

Figure 1: Major pathways of glucose utilisation

Glycolysis is the process of enzymatic break down of one molecule of glucose (6 carbon) into two pyruvate molecules (3 carbon) with the concomitant net production of two molecules of ATP.

The complete glycolytic pathway was elucidated by 1940, largely through the pioneering cotributions of Gustav Embden, Otto Meyerhof, Carl Neuberg, Jcob Parnad, Otto Wrburg, Gerty Cori and Carl Cori. Glycolysis is also known as Embden-Meyerhof pathway.

- Glycolysis is an almost universal central pathway of glucose catabolism.
- Glycolysis is anaerobic process. During glycolysis some of the free energy is released and conserved in the form of ATP and NADH.
- Anaerobic microorganisms are entirely dependent on glycolysis.
- In most of the organisms, the pyruvate formed by glycolysis is further metabolised via one of the three catabolic routes. 1) Under aerobic conditions, glucose is oxidized all the way to $C0_2$ and H_2O. 2) Under anaerobic conditions, the pyruvic acid can be fermented to lactic acid or to 3) ethanol plus CO_2 as shown in figure 2.
- Glycolytic breakdown of glucose is the sole source of metabolic energy in some mammalian tissues and cells (RBCs, Brain, Renal medulla and Sperm cell).

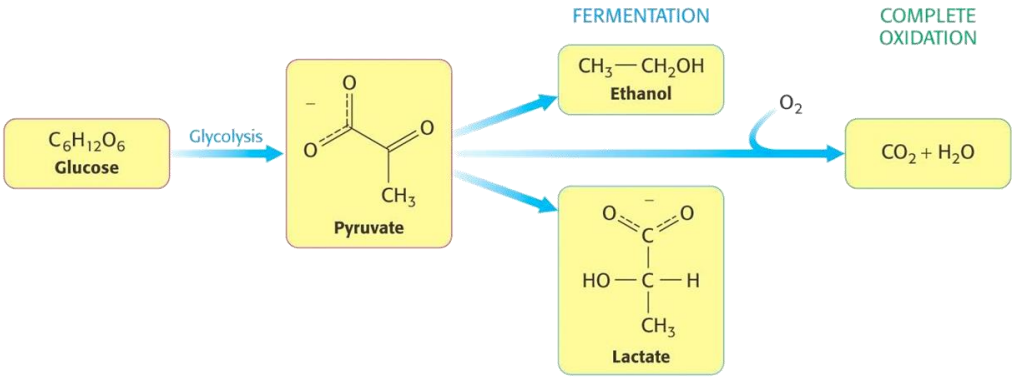

Figure 2. Three possible catabolic fate of pyruvate formed in glycolysis

Glycolysis occurs in TEN steps.

The breakdown of six carbon glucose into two molecules of the three carbon pyruvate occurs in a series of 10 enzyme catalyzed reactions as summarised in figure 3.

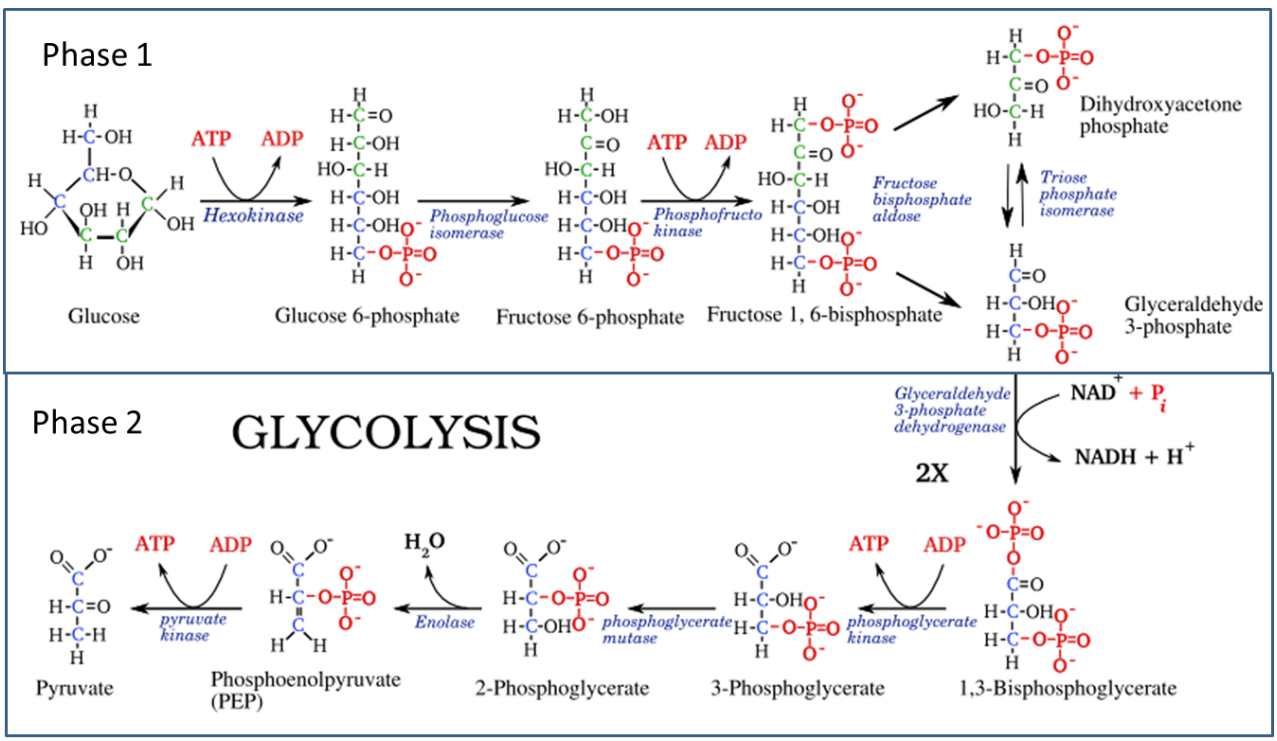

Figure 3: The two phase of glycolysis. Phase1- for each molecule of glucose, two molecules of glyceraldehyde 3-phosphate is formed. Phase 2- glyceraldehyde 3-phosphate is converted to pyruvate.

The process of glycolysis are divided into two phases as shown in figure 4.

1. Preparatory phase (phase 1)
2. Payoff phase (phase 2)

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1. **Preparatory phase (phase 1)**
2. **Payoff phase (phase 2)**

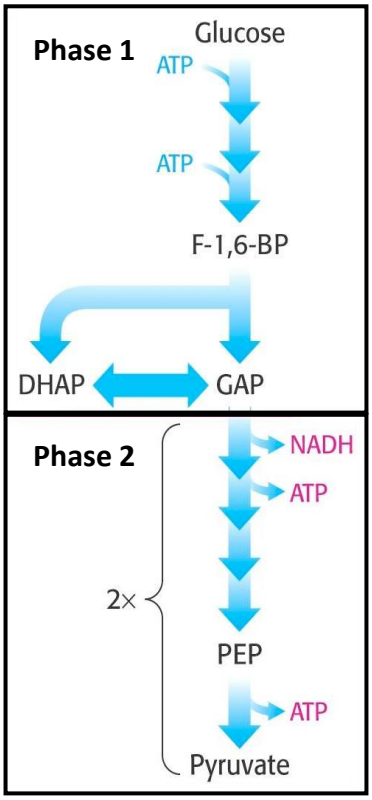


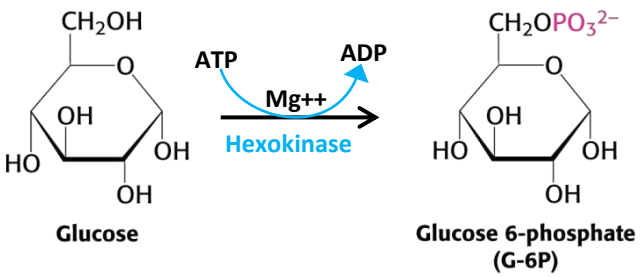
Figure 4: Glycolysis is comprised of two phase.
Phase 1: Preparatory phase
Phase 2: Payoff phase

1. Preparatory phase:

In preparatory phase of glycolysis, two molecule of ATP are invested and hexose chain is cleaved into two triose phosphates. The energy is invested in the process of phosphorylation of glucose. The first five reactions constitute the preparatory phase.

Step I: Phosphorylation of glucose

Glucose is phosphorylated at -OH group of C6 in which one molecule ATP is consumed. The reaction is catalysed by the enzyme Hexokinase in the presence of Mg++ ion. This step is irreversible under intracellular condition. Hexokinase can also catalyse the phosphorylation of other hexoses such as D-fructose and D-mannose. Hexokinase is present in nearly all organisms. The human genome encodes four different hexokinase (I to IV), all of which catalyses the same reaction.



Step I

The binding of glucose to hexokinase changes its confirmation form open to close as shown in figure 5. The phosphorylation keeps the metabolite (glucose) inside the cell. Phosphorylated species in general cannot freely diffuse across any membrane.

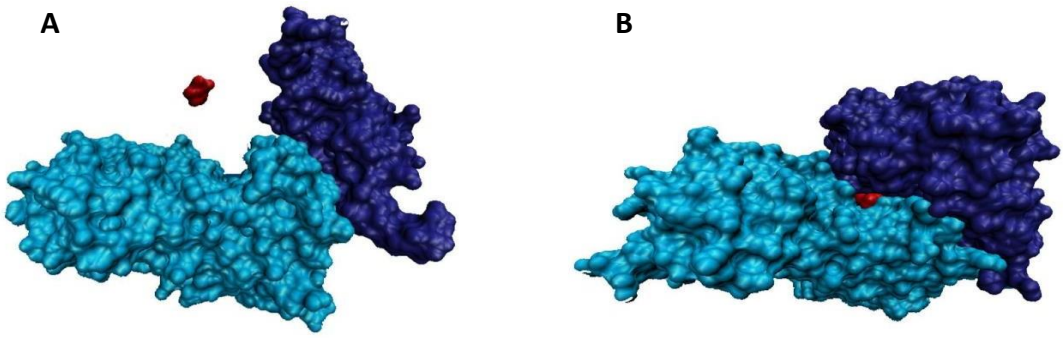
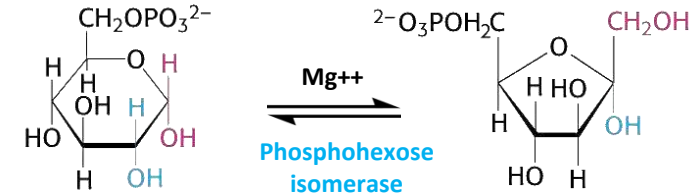


Figure 5. Human glucokinase. A. Human glucokinase in the open conformation. B. Human glucokinase in the closed conformation bound to substrate. Note the huge change in conformation on substrate binding.

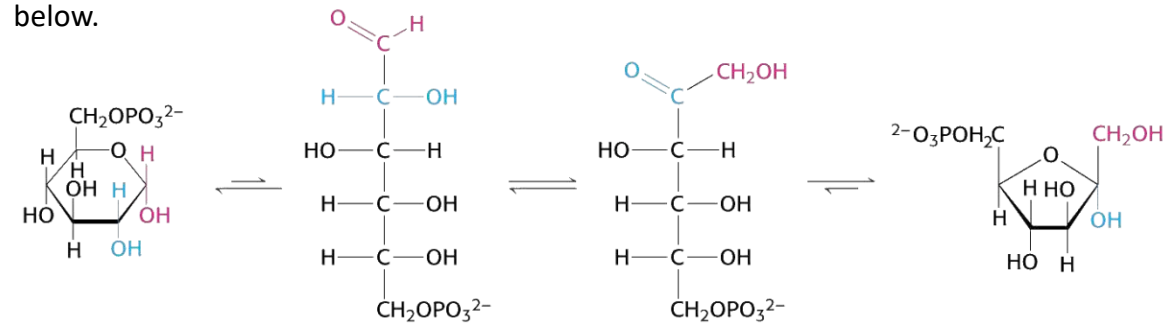
Step II: Isomerization of glucose-6 phosphate to fructose-6- Phosphate:

This reaction is catalysed by the enzyme phosphoglucose isomerase (phosphohexose isomerase).



Glucose 6-phosphate (G-6P) **Step II** **Fructose 6-phosphate (F-6P)**

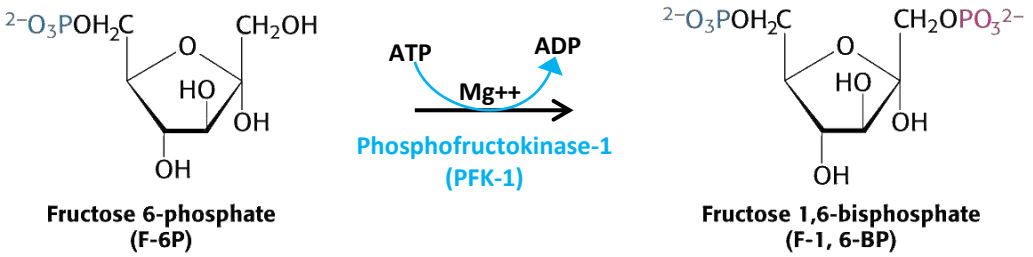
This enzyme catalyses the reversible isomerisation of glucose 6-phosphate, an aldose, to fructose 6-phospahte, a ketose. This reaction can proceeds readily in either direction and involves an enediol intermediate. The mechanism for this reaction involves the opening of the glucose ring and conversion of aldose to ketose as shown below.



Glucose 6-phosphate (G-6P) **Glucose 6-phosphate** (Open chain form) **Fructose 6-phosphate** (Open chain form) **Fructose 6-phosphate (F-6P)**

Step III: Phosphorylation of Fructose-6-phosphate to Fructose 1, 6-Bisphosphate.

This reaction is catalysed by Phosphofructokinase (PFK) in the presence of Magnesium ion, in which fructose-6-phosphate is converted into fructose-1,6-bisphosphate. One molecule of ATP is consumed.



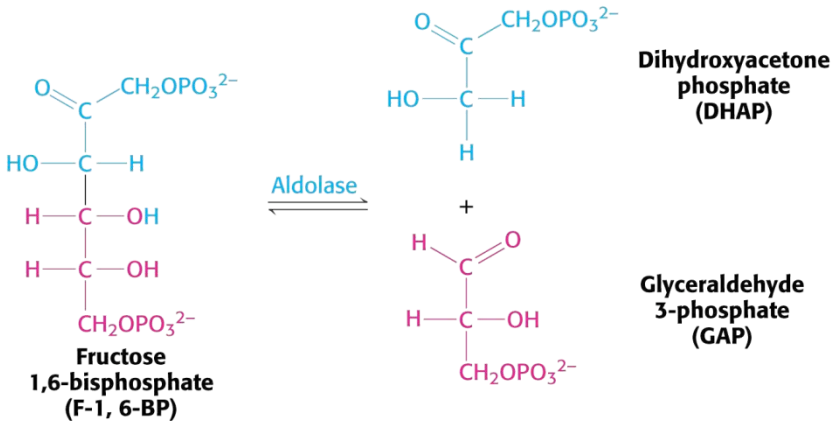
Fructose 6-phosphate (F-6P)

Fructose 1,6-bisphosphate (F-1, 6-BP)

PFK-1 reaction is essentially irreversible under cellular conditions, and it is the first 'committed' step in the glycolytic pathway; glucose 6-phosphate and fructose 6-phosphate have other possible fate, but fructose 1, 6-phosphate is targeted for glycolysis. PFK-1 activity is regulated by allosteric mechanisms such as its activity is reduced when cells have high ATP levels.

Step IV: Cleavage of Fructose 1,6-bisphosphate

The enzyme Aldolase (fructose 1,6-diphosphate aldolase) cleave fructose 1,6-bisphosphate to yield two different triose phosphates, glyceraldehyde 3-phosphate, an aldose, and dihydroxyacetone phosphate, a ketose.



Fructose 1,6-bisphosphate (F-1, 6-BP)

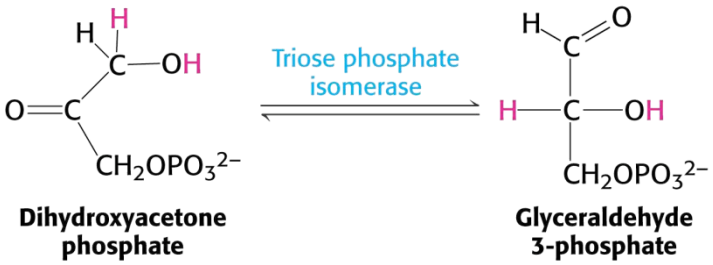
Dihydroxyacetone phosphate (DHAP)

Glyceraldehyde 3-phosphate (GAP)

Aldolase enzymatic reaction is readily reversible in nature.

Step V: Conversion of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate.

Only glyceraldehyde-3-phosphate can be directly degraded into the subsequent steps of glycolysis. The other product, dihydroxyacetone phosphate, is rapidly and reversibly converted to glyceraldehyde-3-phosphate by the enzyme triose phosphate isomerase.



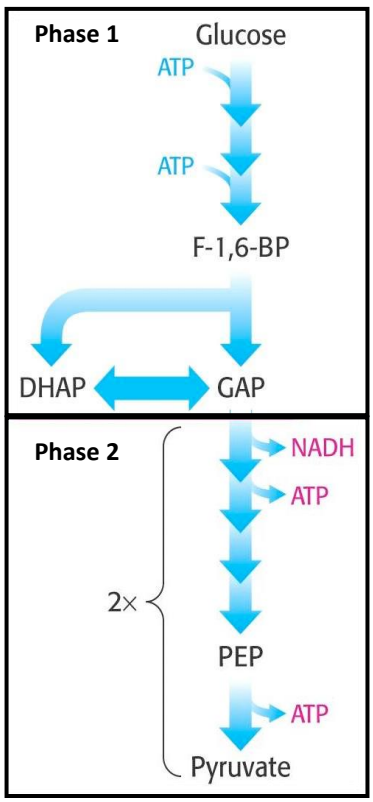
Dihydroxyacetone phosphate **Glyceraldehyde 3-phosphate**

After the triose phosphate isomerase reaction, the two halves of the glucose have both yielded glyceraldehyde 3-phosphate.

This reaction completes the preparatory phase of glycolysis. The hexose molecule has been phosphorylated at C1 and C6 and then cleaved to form two molecules of glyceraldehyde 3-phosphate.

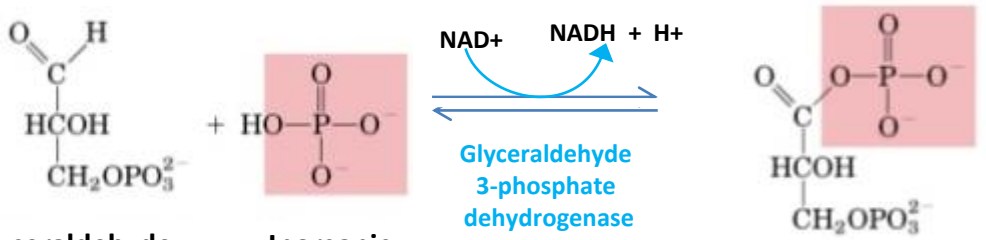
2. Payoff phase:

In payoff phase (phase 2) of glycolysis, some of the chemical energy of glucose is conserved in the form of ATP and NADH. The preparatory phase have yielded two molecules of glyceraldehyde 3-phosphate from one molecule of glucose. In payoff phase the conversion of two molecules of glyceraldehyde 3-phosphate to two molecules of pyruvate is accompanied by the formation of four molecule of ATP from ADP. However, the net yield of ATP per molecule of glucose degraded is only two, because two molecules were invested in preparatory phase of glycolysis to phosphorylate the two ends of hexose molecule. The remaining five reactions constitutes payoff phase.



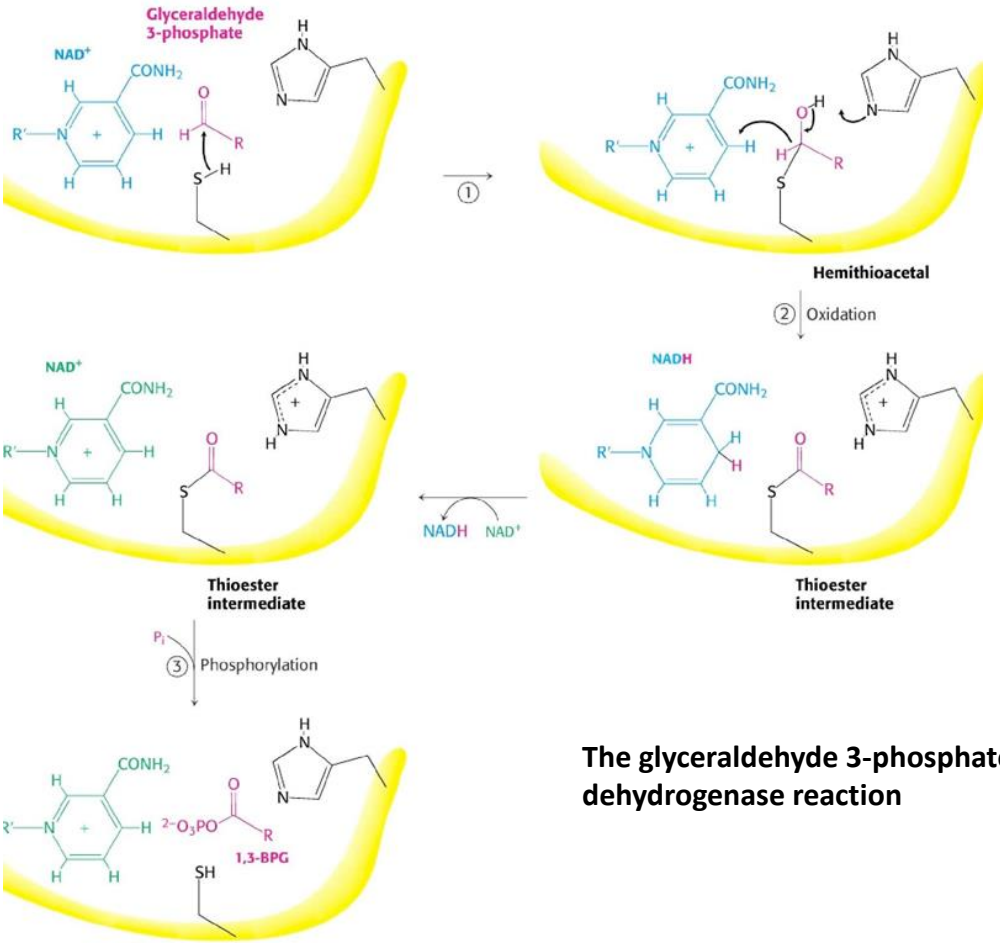
Step VI: Oxidation of glyceraldehyde-3-phosphate:

The first step of payoff phase is the oxidation of glyceraldehyde-3-phosphate into 1,3-bisphosphoglycerate in the presence of enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). In this reaction one molecule of NADH is released.



Glyceraldehyde 3-phosphate + **Inorganic phosphate** → **1,3-Bisphosphoglycerate**

The aldehyde group of glyceraldehyde 3-phosphate is oxidised to a carboxylic acid anhydride with phosphoric acid. The mechanism involves covalent catalysis using a cysteine in the active site of glyceraldehyde 3-phosphate dehydrogenase enzyme with NAD^+ serving as the oxidant as shown in figure below.

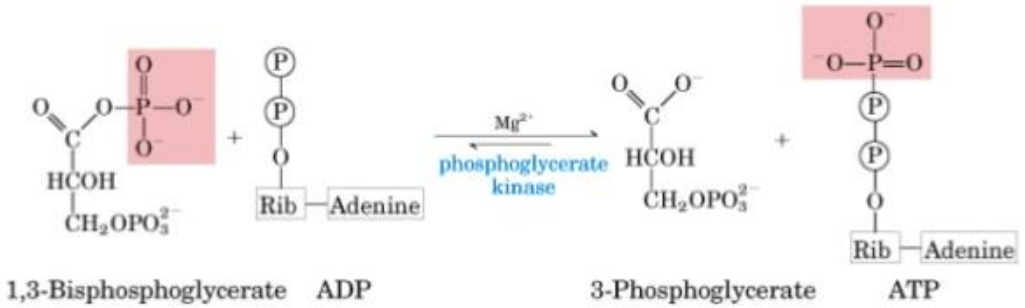


The glyceraldehyde 3-phosphate dehydrogenase reaction

The amount of NAD+ in a cell is by far smaller than the amount of glucose metabolised in a few minutes. Therefore, the NADH formed during this step is continuously recycled to NAD+.

Step VII: Transfer of phosphoryl group from 1,3-bisphosphoglycerate to ADP

The enzyme phosphoglycerate kinase (PGK) transfer phosphoryl group from 1,3 bisphosphate glycerate to ADP forming ATP and 3-phospholycerate. This reaction is an example of substrate level phosphorylation in which phosphoryl group is transfer from substrate i.e., 1,3-bisphosphoglycerate to ADP to form ATP.



PGK catalyzes the first step in the pathway where **net ATP** is produced. There are two ATPs produced from one C6 sugar, as the two-C3 fragments undergo this reaction.

The step VI and VII of glycolysis together constitute an energy-coupling process in which 1, 3- bisphospoglycerate is a common intermediate. The sum of these two reaction is

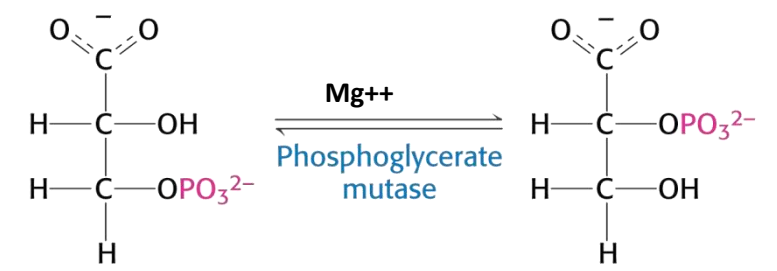
Glyceraldehyde 3-phosphate + ADP + Pi + NAD+ ⇌ **3-phopshoglycerate + ATP + NADH + H+**

The outcome of this reversible coupled reaction is that the energy released on oxidation of an aldehyde to a carboxylate group is conserved by the coupled formation of ATP from ADP and Pi.

Step VIII: Conversion of 3-phosphoglycerate to 2-phoshoglycerate

The enzyme phosphoglycerate mutase catalyses reversible shift of phosphoryl group between C2 and C3 of phosphoglycerate. Mg++ is essential for this reaction.

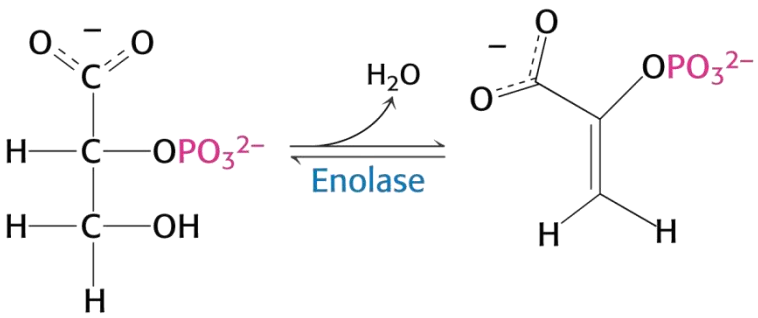
The mechanism for PGM goes through a covalent, phosphorylated histidine intermediate.



3-Phosphoglycerate **2-Phosphoglycerate**

Step IX: Dehydration of 2-phosphoglycerate (Removal of H2O from 2-phosphoglycerate)

Enolase promote reversible removal of a molecule of water from 2-phosphoglycerate forming Phosphoenolpyruvete (PEP).

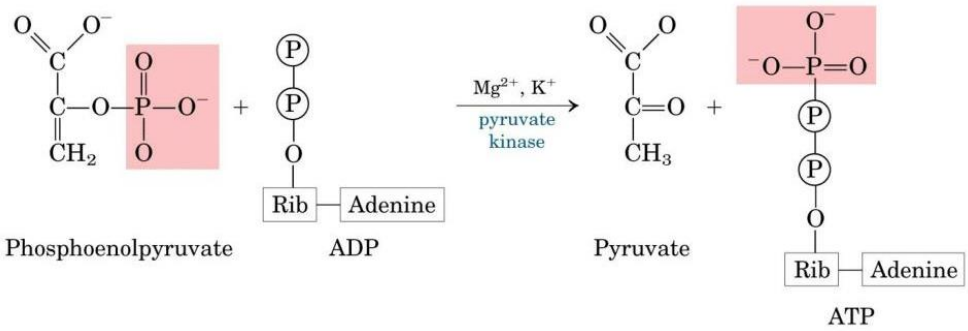


2-Phosphoglycerate **Phosphenolpyruvate**

The mechanism of the enolase reaction involves an enolic intermediate stabilised by Mg++ ion.

Step X: Transfer of phosphoryl group from PEP to ADP

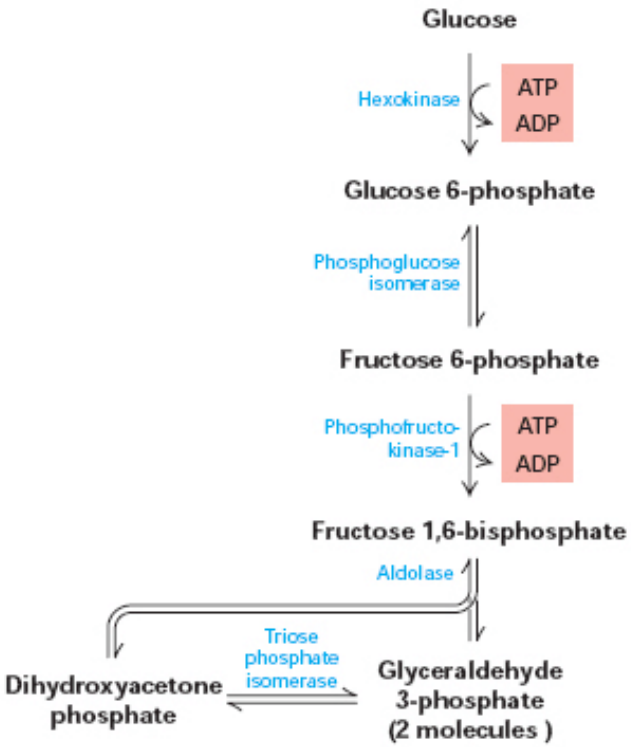
This reaction is catalyzed by the enzyme pyruvate kinase (PK) in the presence of K+ and Mg++ or Mn++ ions. This is also a substrate level phosphorylation in which phosphoryl group is transferred from PEP to ADP forming ATP and Pyruvate. PK catalyses the irreversible step in which 2 ATPs are made (two-C3s). This is the first time that we now have net ATP production.



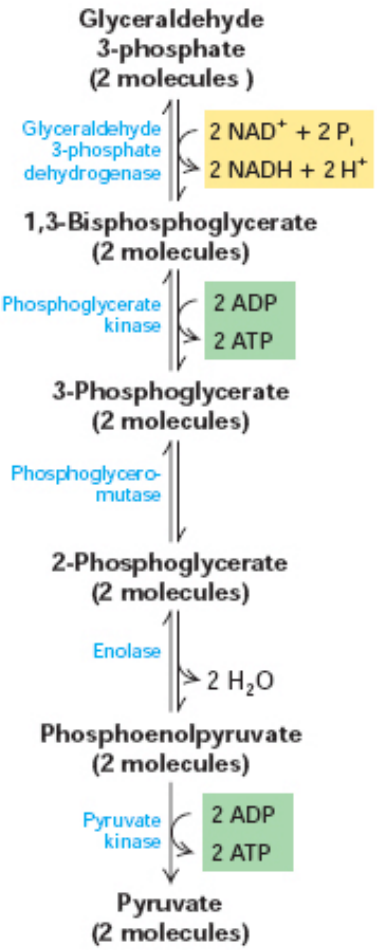
In this substrate level phosphorylation, the product pyruvate first appears in its enol form which then tautomerize rapidly and non-enzymatically to its keto form.

Summary of Glycolysis

Phase 1: Preparatory Phase



Phase 2: Payoff phase



Thermodynamics of Glycolysis:

In glycolysis, one molecule of glucose is break down into two molecules of pyruvate releasing 2 ATP and 2 NADH. The overall equation of aerobic glycolysis is

Glucose + 2NAD+ + 2ATP +2Pi → 2pyruvate + 2ATP + 2NADH + 2H2O + 2H+

Thermodynamics of the steps in the glycolysis pathway are shown in table below.

Enzyme	Step	$\Delta G^{o\prime}$ (kJ/mol)	ΔG (kcal/mol) *
Hexokinase (HK)	1	-16.7	-8.0
Phosphoglucose isomerase (PGlu I; PGI)	2	+1.7	-0.6
Phosphofructokinase (PFK1)	3	-14.2	-5.3
Aldolase	4	23.8	-0.3
Triose phosphate isomerase (TIM)	5	+7.5	+0.6
Glyceraldehyde-3-phosphate dehydrogenase (GAPDH)	6	+6.3	-0.4
Phosphoglycerate kinase (PGK)	7	-18.8	+0.3
Phosphoglycerate mutase (PGly M; PGM)	8	+4.7	+0.2
Enolase	9	+1.7	-0.8
Pyruvate kinase (PK)	10	-31.4	-4.0

* ΔG values are calculated from $\Delta G^{o\prime}$ and known concentrations of reactants under standard physiological conditions.

Table. Standard free energy ($\Delta G^{o\prime}$) and free-energy changes (ΔG) for each reaction in the glycolysis pathway.

Regulation of glycolysis:

Two major needs of the cell influence the flow of material from glucose to pyruvate:

- The need for ATP (energy).
- The need for building blocks for biosynthesis.

The adjustment of rate of glycolysis is achieved at multiple levels including ATP Consumption, NADH regeneration, and allosteric regulation of enzymes.

Level of control	Response time
Allosteric	milliseconds
Phosphorylation	seconds
Transcriptional	hours

In metabolic pathways, control is focused on those steps in the pathway that are irreversible. In glycolysis, the reactions catalyzed by hexokinase, PFK and pyruvate kinase are virtually irreversible and acts as regulatory components.

TABLE 16.3 Reactions of glycolysis

Step	Reaction	Enzyme	Reaction type	$\Delta G^{\circ\prime}$ in kcal mol^{-1} (kJ mol^{-1})	ΔG in kcal mol^{-1} (kJ mol^{-1})
1	Glucose + ATP ⟶ glucose 6-phosphate + ADP + H^+	Hexokinase	Phosphoryl transfer	−4.0 (−16.7)	−8.0 (−33.5)
2	Glucose 6-phosphate ⇌ fructose 6-phosphate	Phosphoglucose isomerase	Isomerization	+0.4 (+1.7)	−0.6 (−2.5)
3	Fructose 6-phosphate + ATP ⟶ fructose 1,6-bisphosphate + ADP + H^+	Phosphofructokinase	Phosphoryl transfer	−3.4 (−14.2)	−5.3 (−22.2)
4	Fructose 1,6-bisphosphate ⇌ dihydroxyacetonephosphate + glyceraldehyde 3-phosphate	Aldolase	Aldol cleavage	+5.7 (+23.8)	−0.3 (−1.3)
5	Dihydroxyacetone phosphate ⇌ glyceraldehyde 3-phosphate	Triose phosphate isomerase	Isomerization	+1.8 (+7.5)	+0.6 (+2.5)
6	Glyceraldehyde 3-phosphate + P_i + NAD^+ ⇌ 1,3-bisphosphoglycerate + NADH + H^+	Glyceraldehyde 3-phosphate dehydrogenase	Phosphorylation coupled to oxidation	+1.5 (+6.3)	+0.6 (+2.5)
7	1,3-Bisphosphoglycerate + ADP ⇌ 3-phosphoglycerate + ATP	Phosphoglycerate kinase	Phosphoryl transfer	−4.5 (−18.8)	+0.3 (+1.3)
8	3-Phosphoglycerate ⇌ 2-phosphoglycerate	Phosphoglycerate mutase	Phosphoryl shift	+1.1 (+4.6)	+0.2 (+0.8)
9	2-Phosphoglycerate ⇌ phosphoenolpyruvate + H_2O	Enolase	Dehydration	+0.4 (+1.7)	−0.8 (−3.3)
10	Phosphoenolpyruvate + ADP + H^+ ⟶ pyruvate + ATP	Pyruvate kinase	Phosphoryl transfer	−7.5 (−31.4)	−4.0 (−16.7)

Note: ΔG, the actual free-energy change, has been calculated from $\Delta G^{\circ\prime}$ and known concentrations of reactants under typical physiologic conditions. Glycolysis can proceed only if the ΔG values of all reactions are negative. The small positive ΔG values of three of the above reactions indicate that the concentrations of metabolites in vivo in cells undergoing glycolysis are not precisely known.

1. Regulation of hexokinase:

Hexokinase activity is regulated by high concentration of glucose 6-phosphate. Under high glucose 6-phosphate state, the hexokinase activity us inhibited by negative feedback loop by the product itself. In liver cells, the isozyme of hexokinase, called glucokinase regulates glycolysis by phosphorylating the glucose. Glucokinase phosphorylates glucose only when it is abundant in the cell because this enzymes affinity for glucose is 50-times lower than hexokinase. The role of glucokinase is to provide glucose 6-phosphate for the synthesis of glycogen and for the formation of fatty acid and it only happens when glucose concentration is abundant in the cell.

2. Regulation of Phosphofructokinase (PFK):

The reaction catalysed by Phosphofructokinase is the rate limiting step or most important control point of mammalian glycolysis. It is regulated by two mechanism.

a) Allosteric regulation: ATP and citrate are allosteric inhibitor of phosphofructokinase. Therefore glycolysis stops in cells having large amount of ATP and citrate (High energy condition). AMP and ADP are allosteric activator and they get accumulated in cell when energy content is depleted and these condition activates PFK and promote glycolysis.

High levels of ATP allosterically inhibits the PFK. ATP binds to allosteric site and lowers the PFK affinity for fructose 6-phosphate. Further, AMP diminishes and citrate enhances the inhibitory effect of ATP.

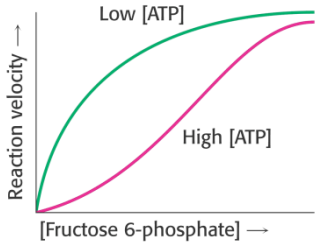


Figure: Allosteric regulation of PFK

b) Activation of PFK:

Fructose 2,6-bisphosphate is potent activator of PFK while Fructose 1,6-bisphosphate is inhibitor of PFK. The increased concentration of fructose 6-phosphate accelerates the synthesis of fructose 2,6-bisphosphate. Fructose 2,6-bisphosphate binds with PFK and increases its affinity for fructose 6-phsphate and thereby glycolysis is accelerated. This process is called feed forward stimulation.

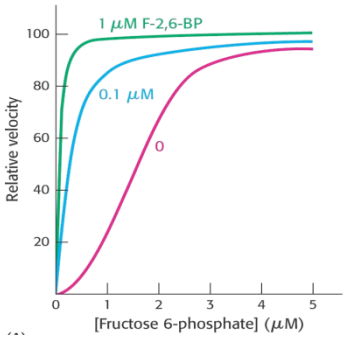


Figure: Activation of PFK by Fructose 2, 6-bisphosphate

Regulation of Pyruvate Kinase:

This enzymes controls the last step of glycolysis and therefore regulates the outflow from this pathway. ATP allosterically inhibit pyruvate kinase to slow glycolysis when energy state is high. Alanine also allosterically inhibits pyruvate kinase. When glucose level is down, it promotes phosphorylation of pyruvate kinase which diminishes its activity and dephosphorylation occurs when glucose level increases.

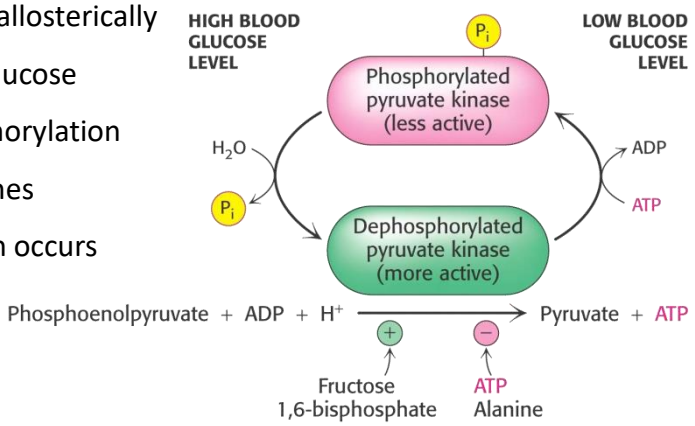


Figure: Control of catalytic activity of pyruvate kinase

Gluconeogenesis

The biosynthesis of glucose from noncarbohydrate precursors is called gluconeogenesis. This process is required to maintain a constant level of glucose (prevent hypoglycemia). Some cells such as brain cells and red blood cells are primarily dependent on glucose for their energy requirements. For humans, the average consumption of glucose by brain is about 120 grams per day. Further, it cannot store energy in the from of glycogen and also not sensitive for insulin regulation. Therefore, brain must have glucose for energy! Hence, the glucose is constantly made from noncarbohydrate source to maintain constant levels of glucose. The gluconeogenic pathways converts pyruvate into glucose. The noncarbohydrate precursors of glucose are converted into pyruvate or enters the pathway at later intermediates such as oxaloacetate and dihydroxyacetone phosphate.

The major noncarbohydrate precursors are-

1. Pyruvate
2. Lactate
3. Glucogenic amino acids
4. Glycerol

Major sites of gluconeogenesis:

1. Liver (90%)
2. Kidney (10%)

The net reaction of gluconeogenesis is

2 pyruvate + 2 NADH + 4ATP + 2GTP + 6H2O + 2 H+ → Glucose + 2 NAD+ + 4 ADP + 2 GDP + 6 Pi

Reactions of gluconeogenesis take place in the cytosol except for, pyruvate carboxylase (mitochondria) and Glucose-6-phosphatase (endoplasmic reticulum). These two important enzymes of gluconeogenesis pathways prevent direct competition of gluconeogenesis and glycolysis by compartmentalization.

Steps of gluconeogenesis

The various steps of gluconeogenesis is mentioned in the table below. First, we will discuss the conversion of pyruvate to glucose.

The reactions of gluconeogenesis beginning with pyruvate

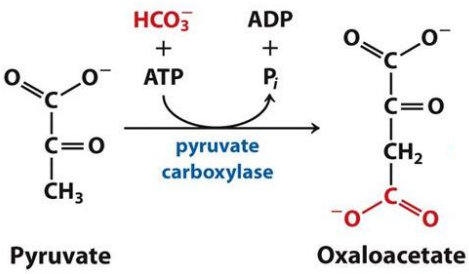
Number	Reaction
1	Pyruvate + CO_2 + ATP → oxaloacetate + ADP + P_i
2	Oxaloacetate + GTP ⇌ phosphoenolpyruvate + CO_2 + GDP
3	Phosphoenolpyruvate + H_2O ⇌ 2-phosphoglycerate
4	2-Phosphoglycerate ⇌ 3-phosphoglycerate
5	3-Phosphoglycerate + ATP ⇌ 1,3-bisphosphoglycerate + ADP
6	1,3-Bisphosphoglycerate + NADH + H^+ ⇌ glyceraldehyde-3-phosphate + NAD^+ + P_i
7	Glyceraldehyde-3-phosphate ⇌ dihydroxyacetone phosphate
8	Glyceraldehyde-3-phosphate + dihydroxyacetone phosphate ⇌ fructose-1,6-bisphosphate
9	Fructose-1,6-bisphosphate + H_2O → fructose-6-phosphate + P_i
10	Fructose-6-phosphate ⇌ glucose-6-phosphate
11	Glucose-6-phosphate + H_2O ⇌ glucose + P_i

Gluconeogenesis: Steps 1 & 2-conversion of pyruvate to phosphoenolpyruvate

These two steps are required to bypass pyruvate kinase and proceeds through an oxaloacetate intermediate.

Gluconeogenesis: Step 1-conversion of pyruvate to oxaloacetate

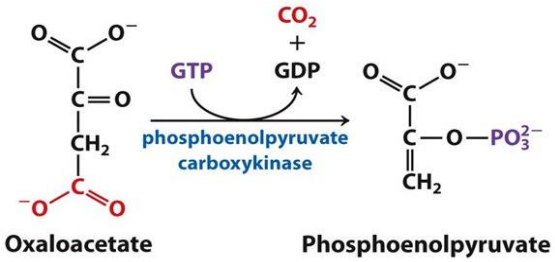
The irreversible carboxylation reaction is performed by pyruvate carboxylase enzyme and during this step one ATP molecule is consumed to synthesize C-C bond. This step occurs in mitochondria because the enzyme pyruvate carboxylase is a mitochondrial protein.



Gluconeogenesis: Step 2-conversion of oxaloacetate to phosphoenolpyruvate

Oxaloacetate is synthesized in the mitochondria by pyruvate kinase and is shuttled into the cytosol where it is converted into phosphoenolpyruvate. In order for oxaloacetate to leave the mitochondria, it must be reduced to malate. In cytosol, malate is then reoxidized to oxaloacetate.

Step 2 is catalyzed by phosphoenolpyruvate carboxykinase (PEPCK) is enzyme. The reaction is comprised of decarboxylation and group transfer reaction (phosphoryl transfer) and requires GTP molecule.



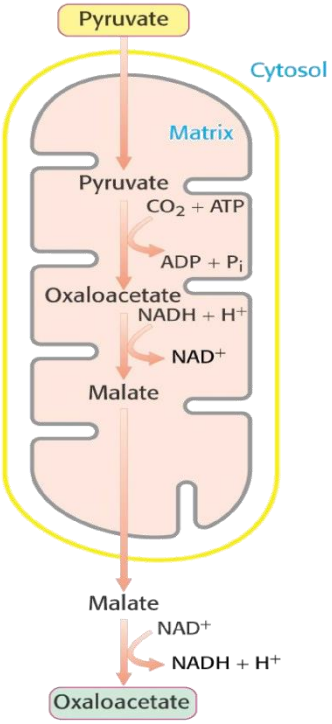


Fig: Transportation of oxaloacetate from mitochondria to cytosol

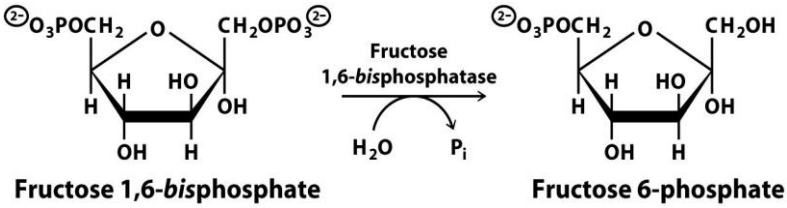
Gluconeogenesis: Steps 3-8: reverse of glycolysis

Step 3 -8 are reverse reactions of glycolysis by the same glycolytic enzymes. None of these steps requires energy. *Step 8* produces fructose-1,6-bisphosphate from triose phosphates.

Gluconeogenesis: Step 9-conversion of fructose-1, 6-bisphosphate to fructose 6-phosphate

This step is catalysed by fructose-1,6-bisphosphatase enzyme which essentially perform the reverse reaction catalysed by phosphofructokinase during glycolysis.

This is a hydrolysis reaction and is irreversible.



Gluconeogenesis: Step 10- Reverse of glycolysis

This step yields glucose 6-phosphate

Gluconeogenesis: Step 11- conversion of glucose 6-phosphate to glucose

This step occurs in endoplasmic reticulum. Therefore, glucose 6-phopshate is transported from the cytoplasm into the ER by GLUT7 transporter. GLUT7 is only found in liver, kidney, pancreas, and small intestine.

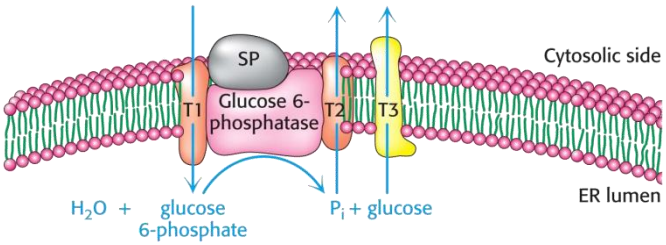
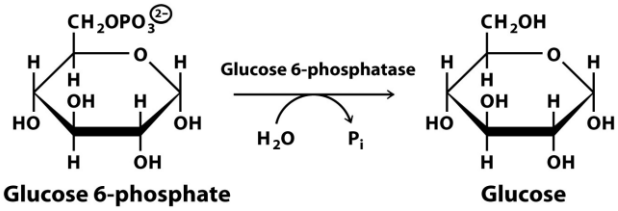


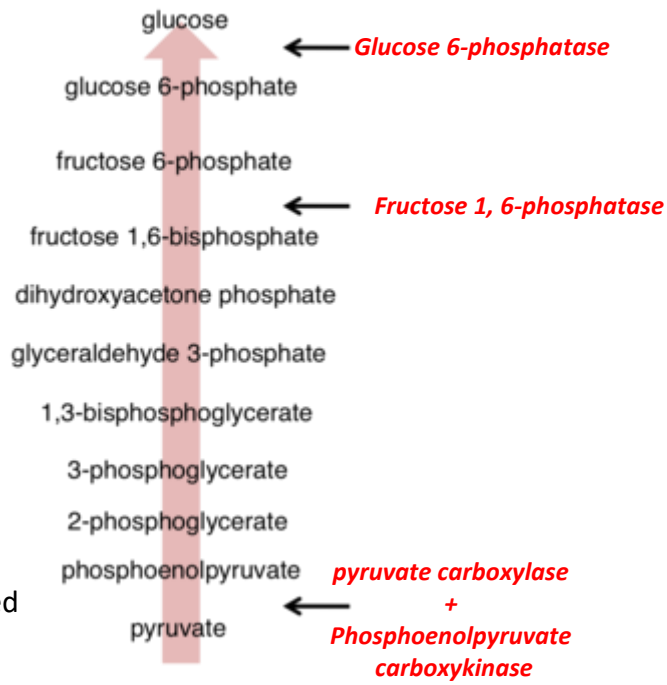
Fig: Transportation of glucose 6-phosphate into the ER



The conversion of glucose 6-phosphate to glucose is performed by glucose 6-phosphatase. This step is also irreversible hydrolysis reaction. In this way the glucose is synthesized from pyruvate by gluconeogenesis pathway.

Summary of gluconeogenesis (steps 1-11)

The conversion of pyruvate to glucose follows most of the steps of the glycolysis pathway in reverse order. The key regulatory steps of gluconeogenesis are Highlighted (red font). These three steps are irreversible steps of glycolysis; therefore, in gluconeogenesis they are performed by different enzymes.



Noncarbohydrate precursors of gluconeogenesis

Gluconeogenesis is the biosynthesis of glucose from noncarbohydrate precursors. The noncarbohydrate precursors of glucose are first converted into pyruvate or enters the pathway at later intermediates such as oxaloacetate and dihydroxyacetone phosphate and eventually converted to glucose as described (steps 1-11).

The major noncarbohydrate precursors of gluconeogenesis are-

1. Pyruvate (already discussed)
2. Lactate
3. Glucogenic amino acids
4. Glycerol (from triacylglyceride hydrolysis)

2. Lactate: Conversion of lactate to pyruvate

Lactate are produced by active muscle cells when the rate of glycolysis exceeds the rate of oxidative mechanisms. This lactate is transported to liver and converted back to pyruvate and then to glucose. The metabolic conversion of glucose to lactate and from lactate to glucose is known as Cori cycle named after Carl and Geti Cori.

In Cori Cycle, lactate accumulated in the muscle cells is taken up by liver. The liver performs gluconeogenesis to convert lactate back to glucose. The conversion of lactate to pyruvate is catalysed by lactate dehydrogenase enzyme.

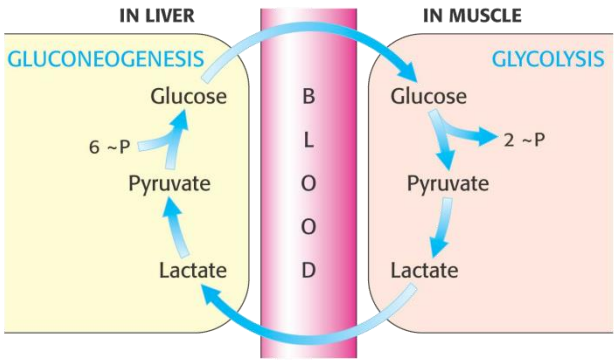
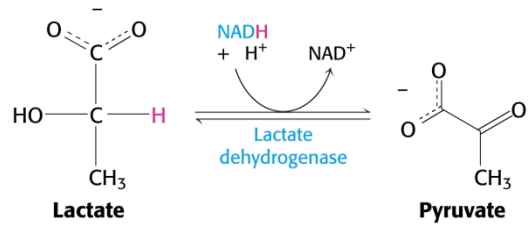


Fig: Cori cycle



3. Glucogenic amino acids: Glucogenic amino acids are those amino acids whose carbon skeleton can be used to form glucose molecules. Glucogenic amino acids contributes to gluconeogenesis by two ways (as shown in figure)

a) Some amino acids can converted directly to pyruvate.

b) Few amino acids are converted to TCA intermediates that in turn metabolises to oxaloacetate.

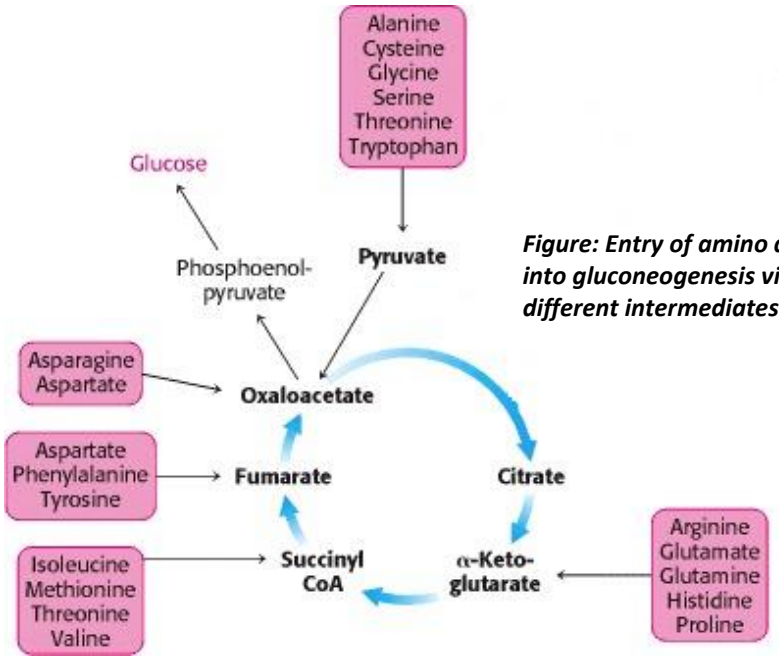
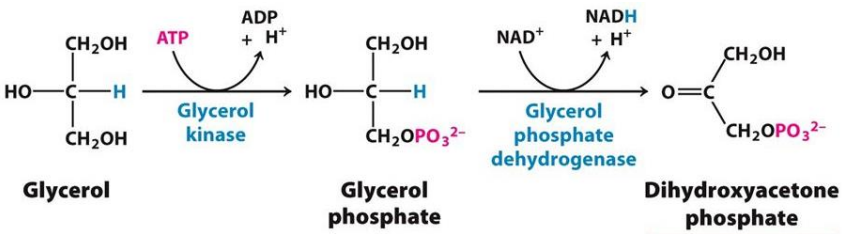


Figure: Entry of amino acids into gluconeogenesis via different intermediates

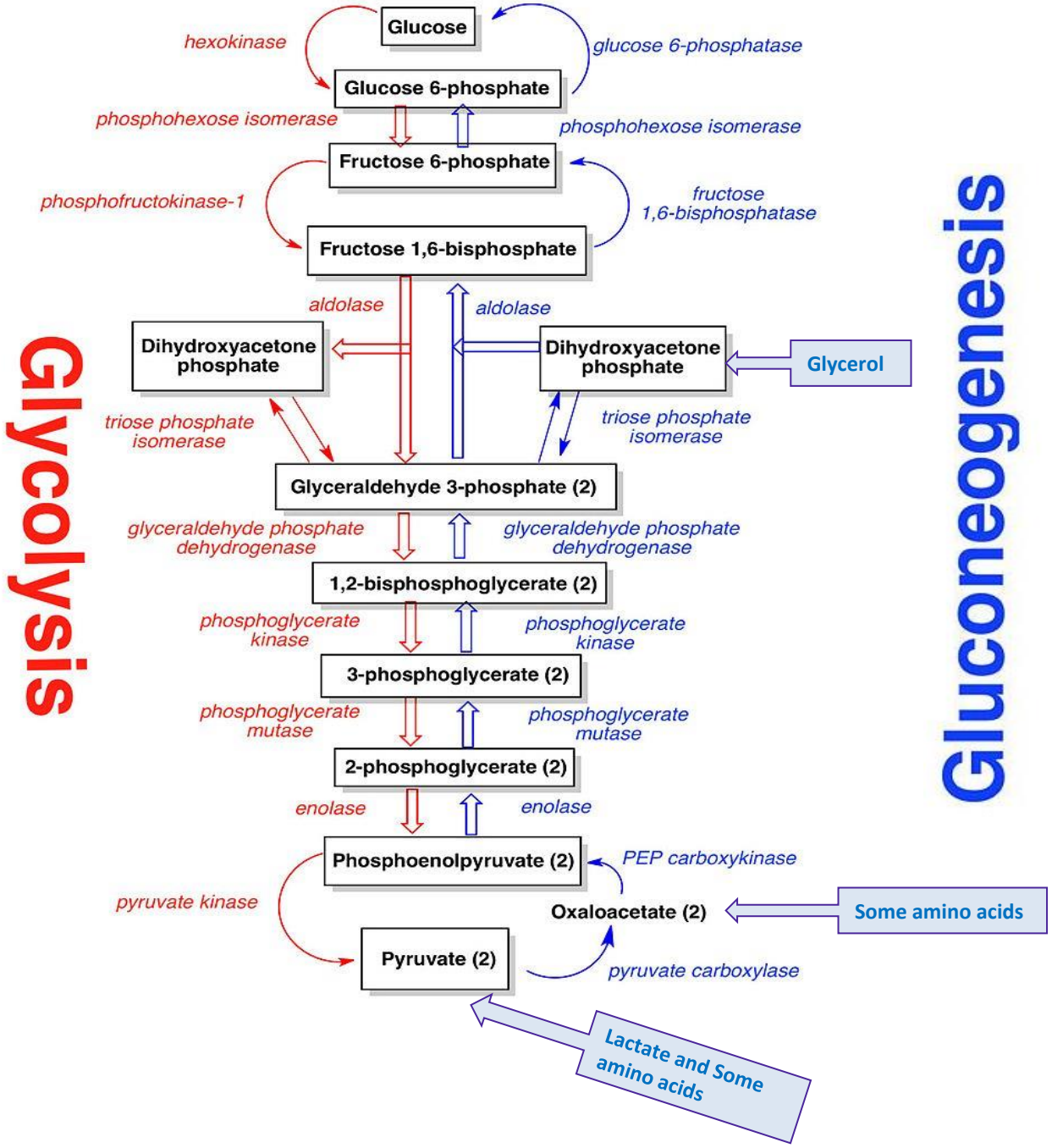
4. Glycerol

The hydrolysis of triacylglycerol in fat cells yield glycerol and fatty acids. Glycerol may enters the gluconeogenic pathway at dihydroxyacetone phosphate (DHAP) intermediate. In the fasting state glycerol released from lipolysis of adipose tissue triacylglycerol is used solely as a substrate for gluconeogenesis in the liver and kidneys.



Glycerol is converted to glycerol 3-phosphate by the enzyme glycerol kinase and then to DHAP by glycerol phosphate dehydrogenase. The glycerol kinase is absent in adipose tissues hence the formed glycerol is transported to liver and participates in gluconeogenesis.

Summary of glycolysis and gluconeogenesis



References

[1]*Lehninger Principles of biochemistry*

[2]*Lubert Stryer Biochemistry*