E-content
M.Sc. Zoology (Semester-II)
Paper: CC7
Unit: 2.3

Topic: Glycogenolysis and Pentose Phosphate Pathway

Dr. Gajendra Kumar Azad
Assistant Professor
Post Graduate Department of Zoology
Patna University, Patna

Glycogenolysis

Glycogen is a polymer of glucose and is a primary carbohydrate storage form in animals. The glycogen is composed of units of glucose linked by α(1, 4) and branches have α(1, 6) occurring approximately every 8-12 residues. Each glycogen molecule have a single reducing and multiple non-reducing ends.

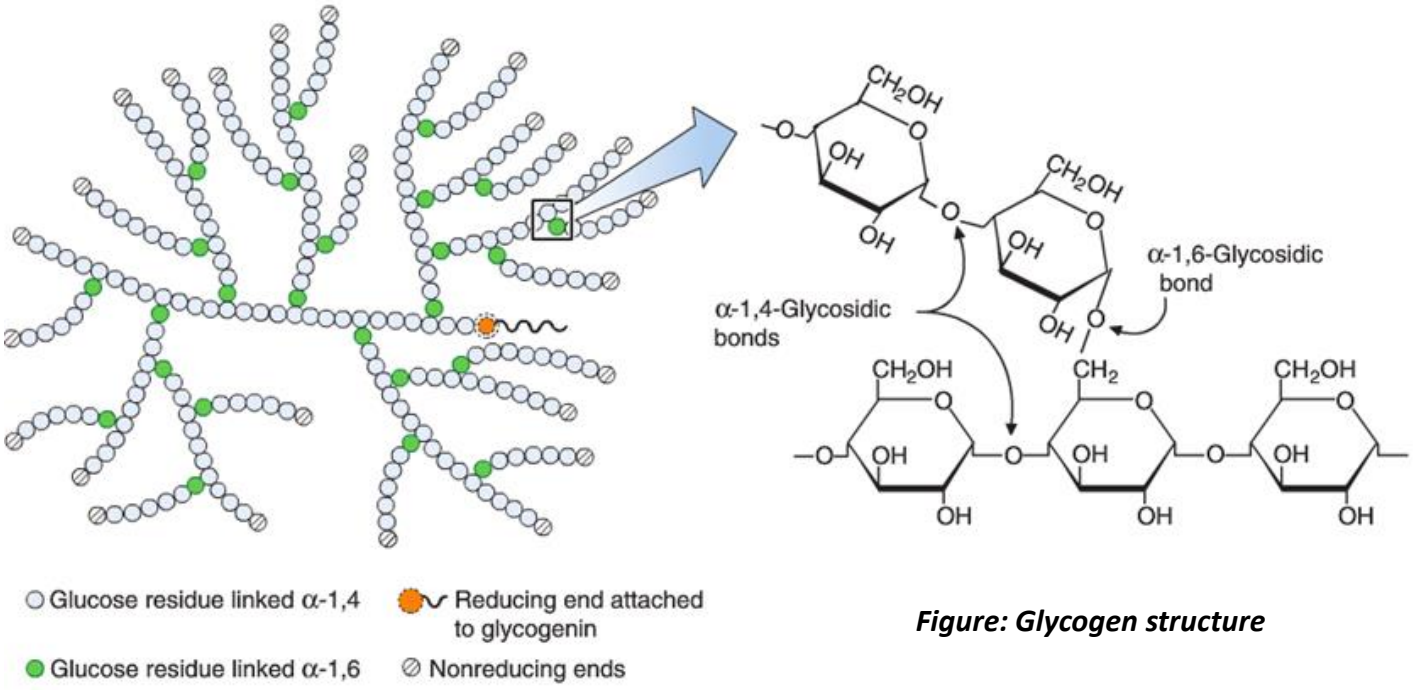


Figure: Glycogen structure

Because glycogen contains so many glucoses, it acts like a battery backup for the body, providing a quick source of glucose when needed and providing a place to store excess glucose when glucose concentrations in the blood rise.

Breakdown of glycogen (glycogenolysis) involves following steps

All steps of glycogenolysis occurs in cytosol

Step 1: Release of glucose 1-phosphate from glycogen

Step 2: Rearrangement of the remaining glycogen molecule

Step 3: Conversion of glucose 1-phosphate to glucose 6-phosphate

Glucose 6-phosphate can have following fates:

1) broken down by glycolysis
2) converted to glucose by gluconeogenesis,
3) oxidized in the pentose phosphate pathway.

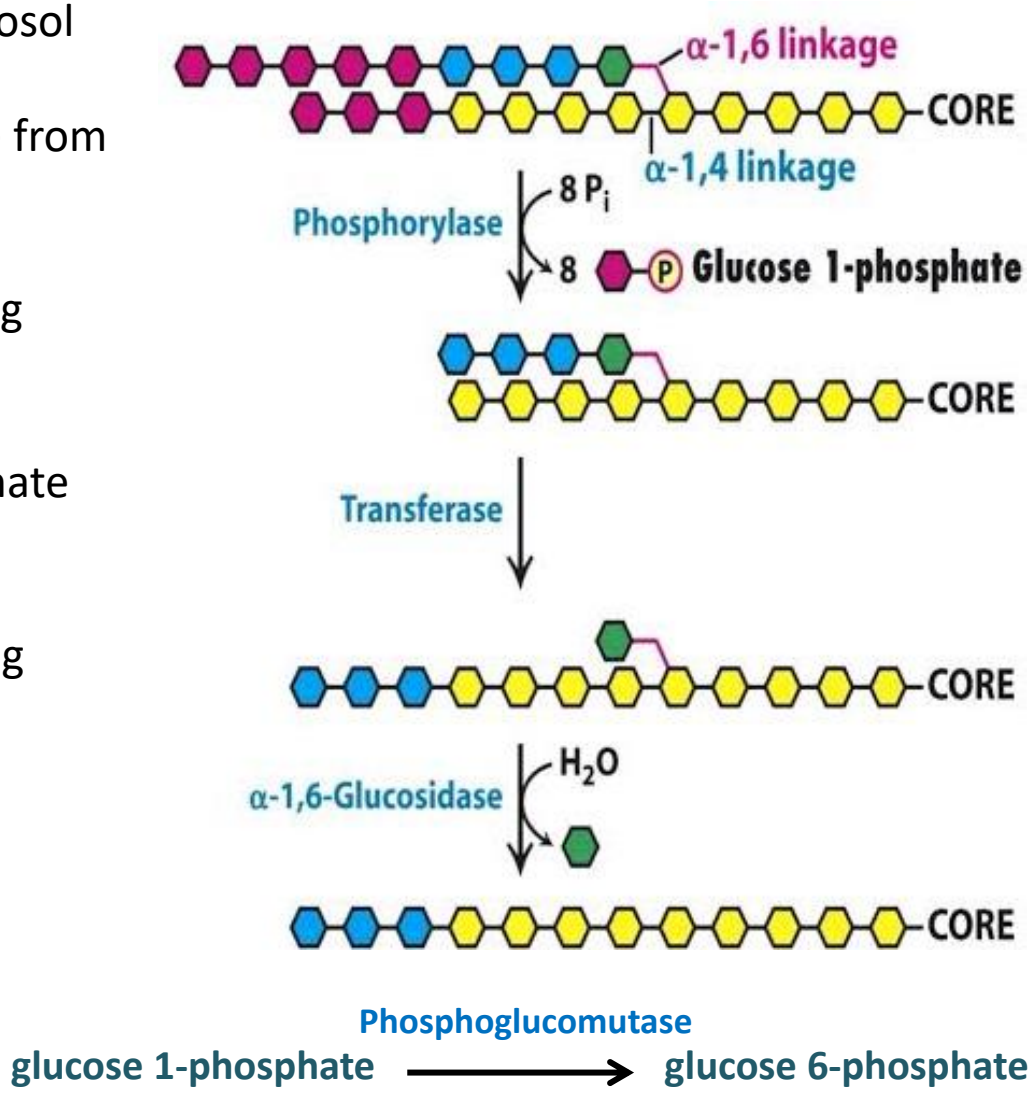
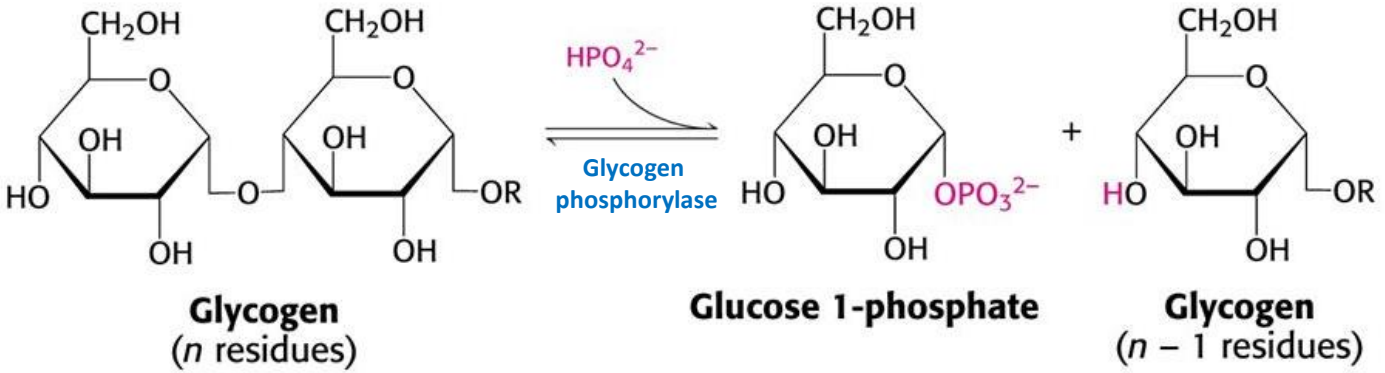


Figure: Steps of glycogenolysis

Step 1: Release of glucose 1-phosphate from glycogen

Glycogen Phosphorylase catalyses breakdown of glycogen into glucose-1-phosphate.

Note that the phosphate does not come from ATP. Since ATP is not used to put phosphate on glucose-1-phosphate, thus this reaction saves energy.



The reaction that produces glucose-1-phosphate from glycogen is a phosphorolysis, not a hydrolysis reaction. The difference is that hydrolysis reactions use water to cleave bigger molecules into smaller ones, but phosphorolysis reactions instead use phosphate for the same purpose.

Glycogen phosphorylase manages to use phosphate to catalyse glycogen breakdown by employing the coenzyme pyridoxal phosphate (PLP).

Step 1: Release of glucose 1-phosphate from glycogen

Glycogen phosphorylase only acts on non-reducing ends of a glycogen chain that are at least 4 glucoses away from a branch point.

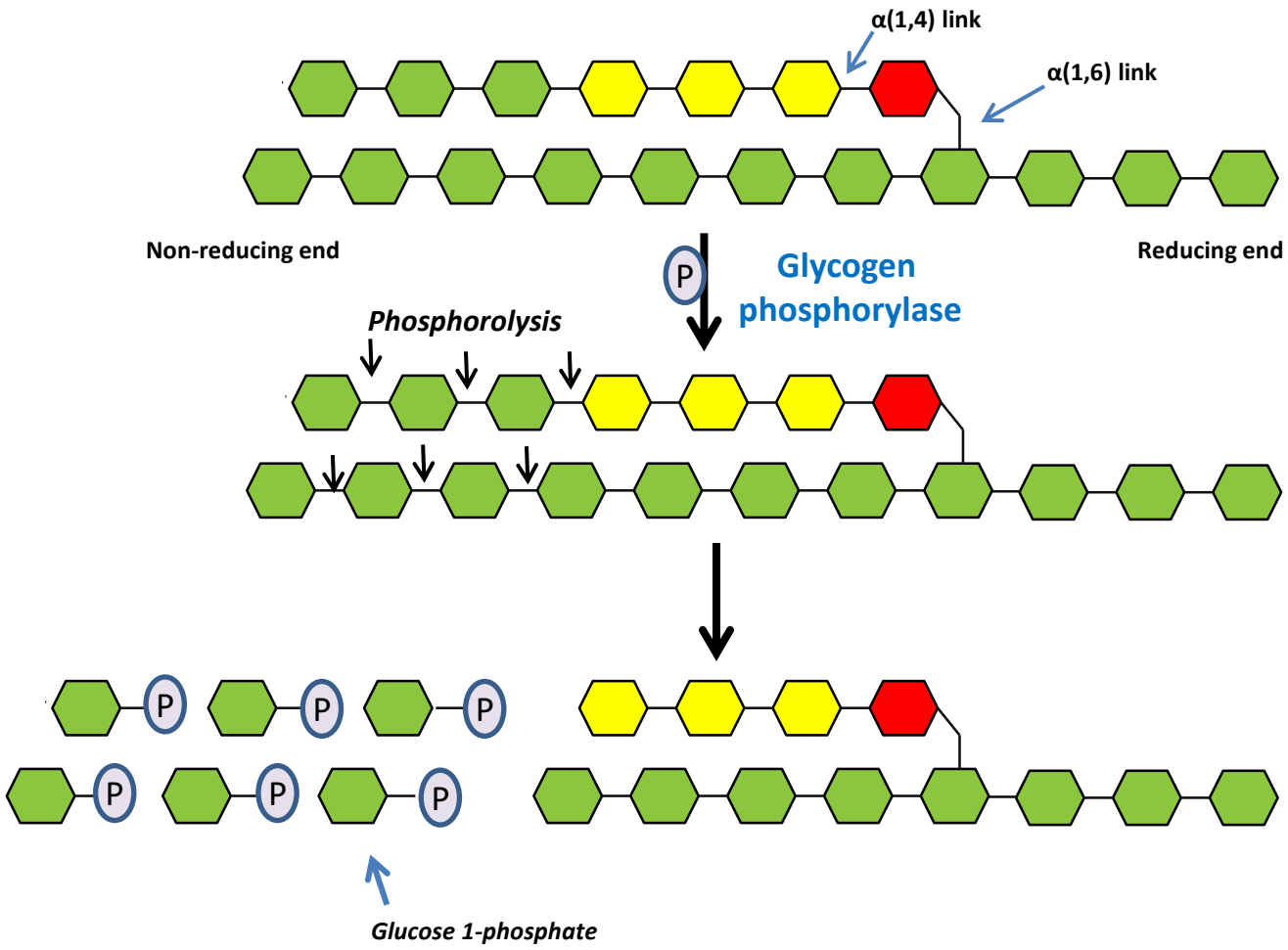


Figure: Glycogen phosphorylase catalyses the release of glucose 1-phosphate from glycogen molecule

Step 2: Rearrangement of the remaining glycogen

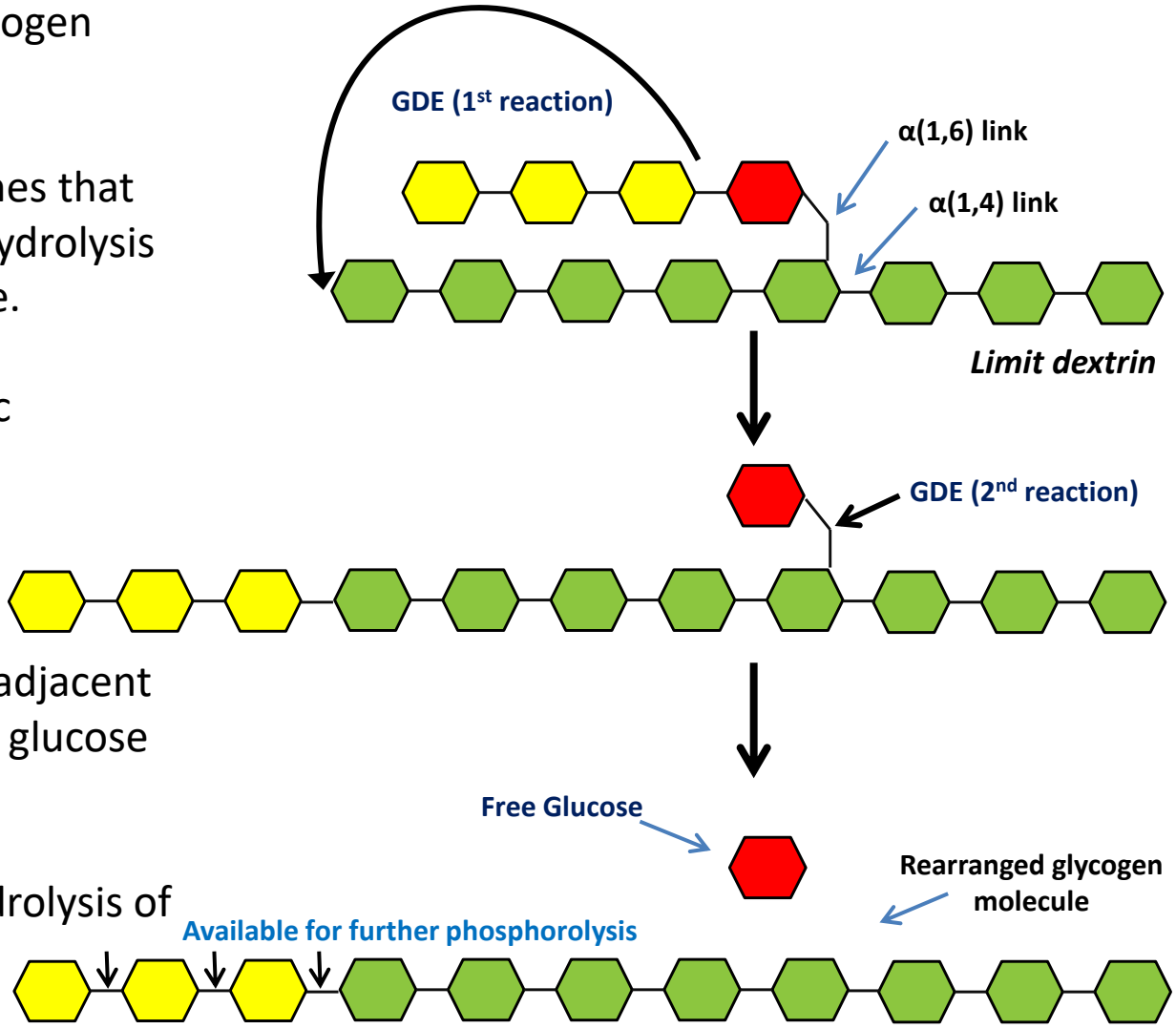
Step two is catalysed by Glycogen Debranching Enzyme (**GDE**).

GDE acts on glycogen branches that have reached their limit of hydrolysis with glycogen phosphorylase.

GDE performs two enzymatic Reactions:

1. GDE transfer rest of the sugar monomer units from a (1,6) branch onto an adjacent (1,4) branch, leaving a single glucose at the (1,6) branch.

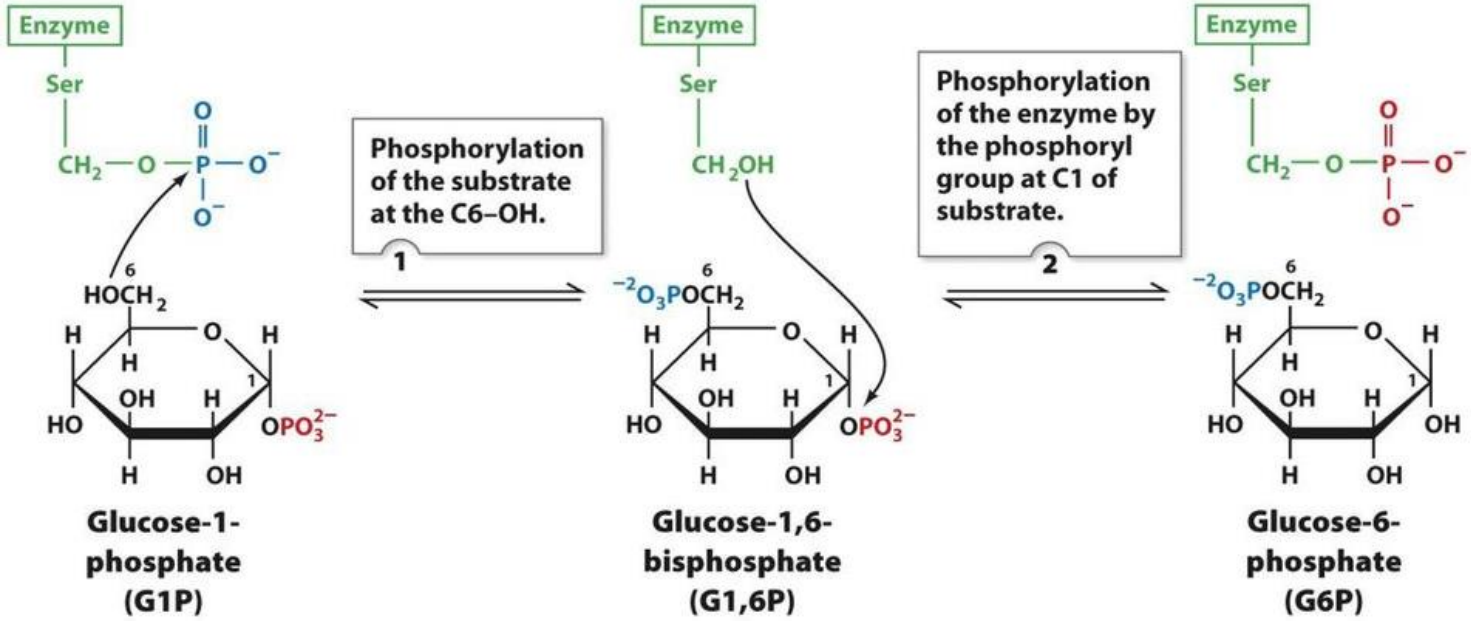
2. GDE also catalyses the hydrolysis of the remaining glucose at the (1,6) branch point to release glucose from glycogen chain.



Step 3: Conversion of glucose 1-phosphate to glucose 6-phosphate

Step 3 is catalysed by Phosphoglucomutase . It converts glucose 1-phosphate to glucose 6-phosphate.

The mechanism of action of phosphoglucomutase involves formation of a transient intermediate of glucose-1,6-bisphosphate before the glucose 6-phosphate is produced.



This reaction is readily reversible, allowing glucose 6-phosphate and glucose 1-phosphate to be interconverted as the concentration of one or the other increases.

Regulation of Glycogenolysis

Glycogenolysis is precisely controlled by multiple mechanisms. The focus of this control is the enzyme glycogen phosphorylase.

Regulation of glycogen phosphorylase:
Its activity is regulated by mainly three mechanisms

1. Allosteric
2. Calcium influence
3. Hormonal

Regulation of glycogen phosphorylase also depends on the tissue in which it is found. Here, we will discuss glycogen phosphorylase regulation in liver and muscle tissues.

The liver maintain the glucose homeostasis of the organism as a whole, however the muscle uses glucose to produce energy for itself.

Regulation of Glycogen Phosphorylase in muscle

In muscle, glycogen phosphorylase exists in two forms , phosphorylase –a (GPa) an active form and Phosphorylase-b (GPb) an inactive form.

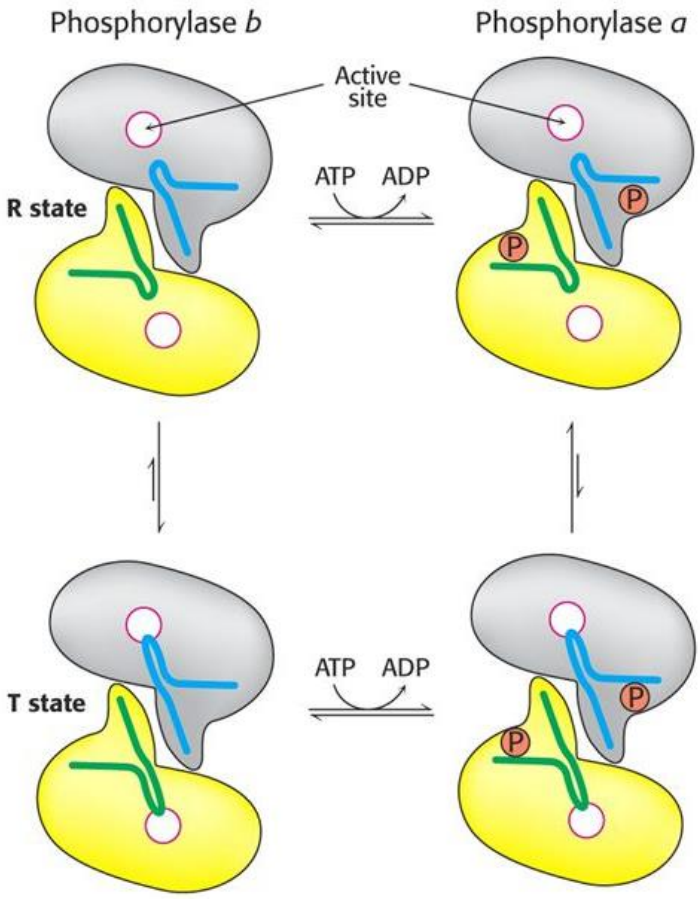
GPa and GPb differ chemically only in that GPa is phosphorylated (two phosphates), but GPb is not.

GPb is converted to GPa by phosphorylation by an enzyme known as **phosphorylase kinase**.

Both Gpa and GPb exist in an active relaxed (R) state and less active or tensed (T) state.

The equilibrium for GPa favors the R state and the equilibrium for GPb favors the T state.

Conversions between the T and R states of GPb involve allosteric interactions. GPb can convert from the T state to the GPb R state by binding AMP. Thus, a low energy state of the cell can activate GPb.



Regulation of Glycogen Phosphorylase in muscle

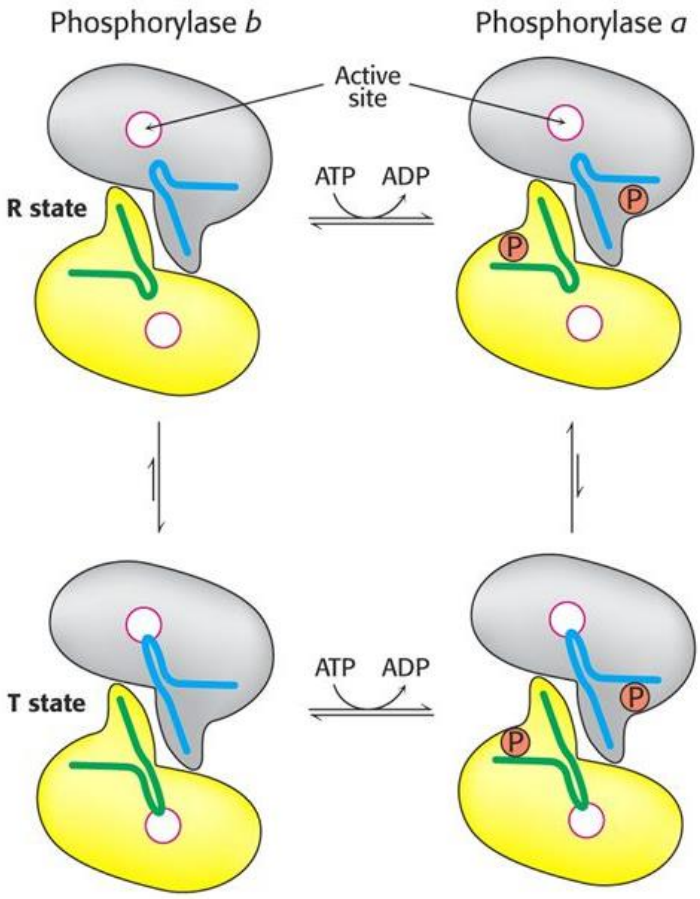
When cells are in high energy state i.e., ATP and/or glucose 6-phosphate (G6P) are abundant in the cell then they binds to GPb (instead of AMP) and favors the T state (inactive).

Binding of ATP or G6P to GPb thus favors the inactive state of GPb.

On the other hand the GPa is NOT affected by AMP, ATP, or G6P and is usually found in the R state (active).

When we begin exercise, most of the glycogen phosphorylase is in the GPb T state. As AMP builds up from the use of ATP, GPb is converted from the T to the R state.

Further exercise results in hormonal stimulation that leads to phosphorylation of GPb to form GPa.

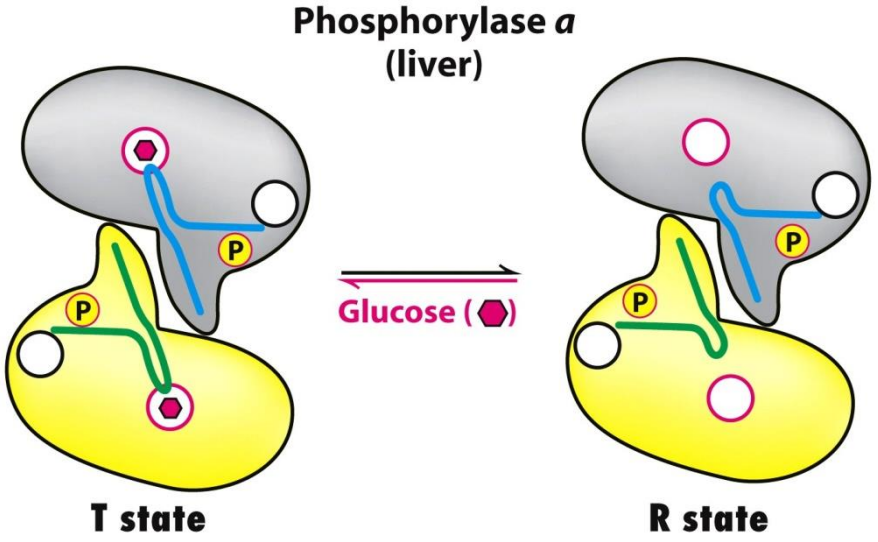


Regulation of Glycogen Phosphorylase in liver

The Glycogen phosphorylase present in liver is an isozyme to the one found in muscle. It catalyses the same chemical reaction like muscle.

The subtle changes in liver glycogen phosphorylase cause GPa to have a property that muscle glycogen phosphorylase does not - namely that GPa is allosterically inhibited by the accumulation of glucose.

Glucose binding to liver GPa causes it to convert into the T form (inactive). This does not happen in muscle and is an important control in the liver, allowing it to shut down when glucose accumulates faster than it is needed.



In addition, the GPb form of the enzyme is insensitive to AMP, unlike the muscle GPb.

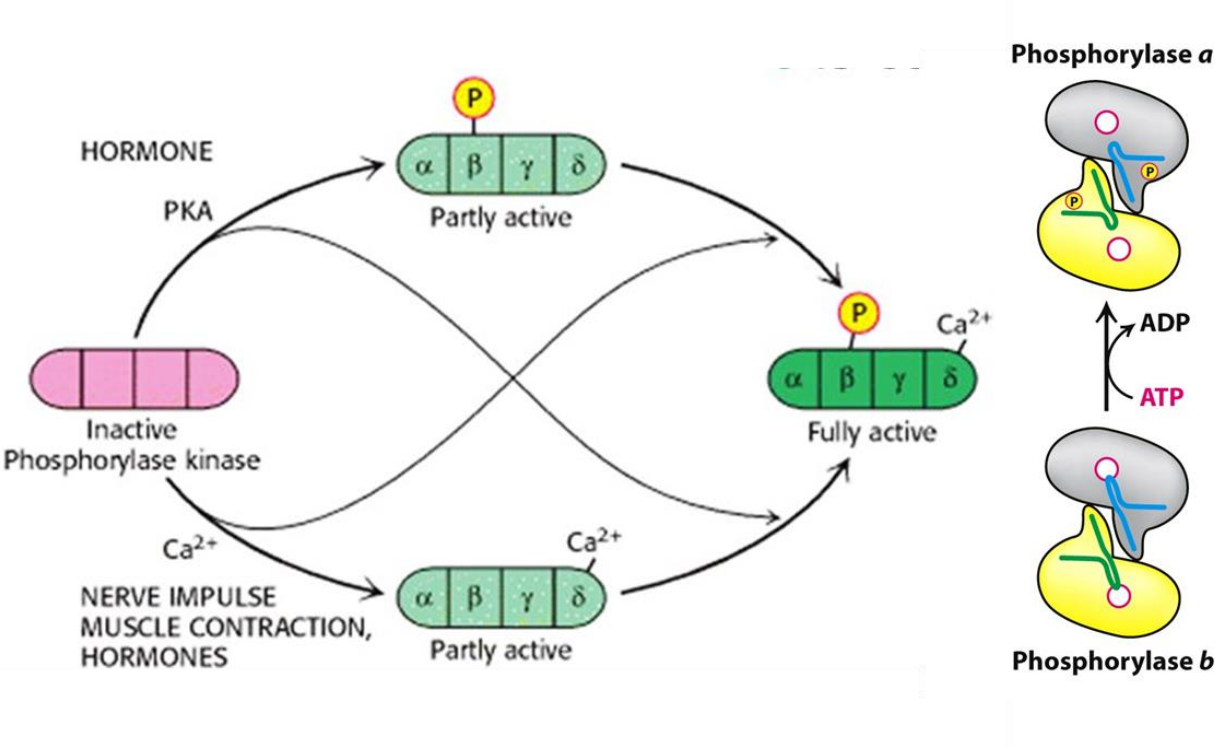
Regulation of Glycogen Phosphorylase

Interconversion of GPa and GPb is accomplished by the enzyme **Phosphorylase Kinase**, which transfers phosphates from 2 ATPs to GPb to form GPa.

Phosphorylase kinase is present as inactive, partly active and fully active form. The enzyme can be activated by two ways:

a) Through phosphorylation by Protein Kinase A (PKA).

b) By binding with calcium.



Calcium triggers muscular contraction as well as activates phosphorylase kinase. Thus, the same ion that stimulates muscular contraction also activates phosphorylase kinase, which activates glycogen phosphorylase, which releases glucose 1-phosphate from glycogen, which can be used to make ATP to support muscular contraction.

Hormonal Regulation of Glycogen Phosphorylase

Glycogen phosphorylase is also regulated by hormones in both the liver and muscle cells.

The enzyme phosphorylase kinase is activated by PKA.

PKA is, of course, activated by cAMP, which is, in turn produced by adenlyate cyclase after activation by a G protein.

G proteins are activated by binding of ligands to its 7TM receptors. The ligands are epinephrine and glucagon.

Epinephrine exerts it greatest effects on muscle and glucagon works preferentially on the liver.

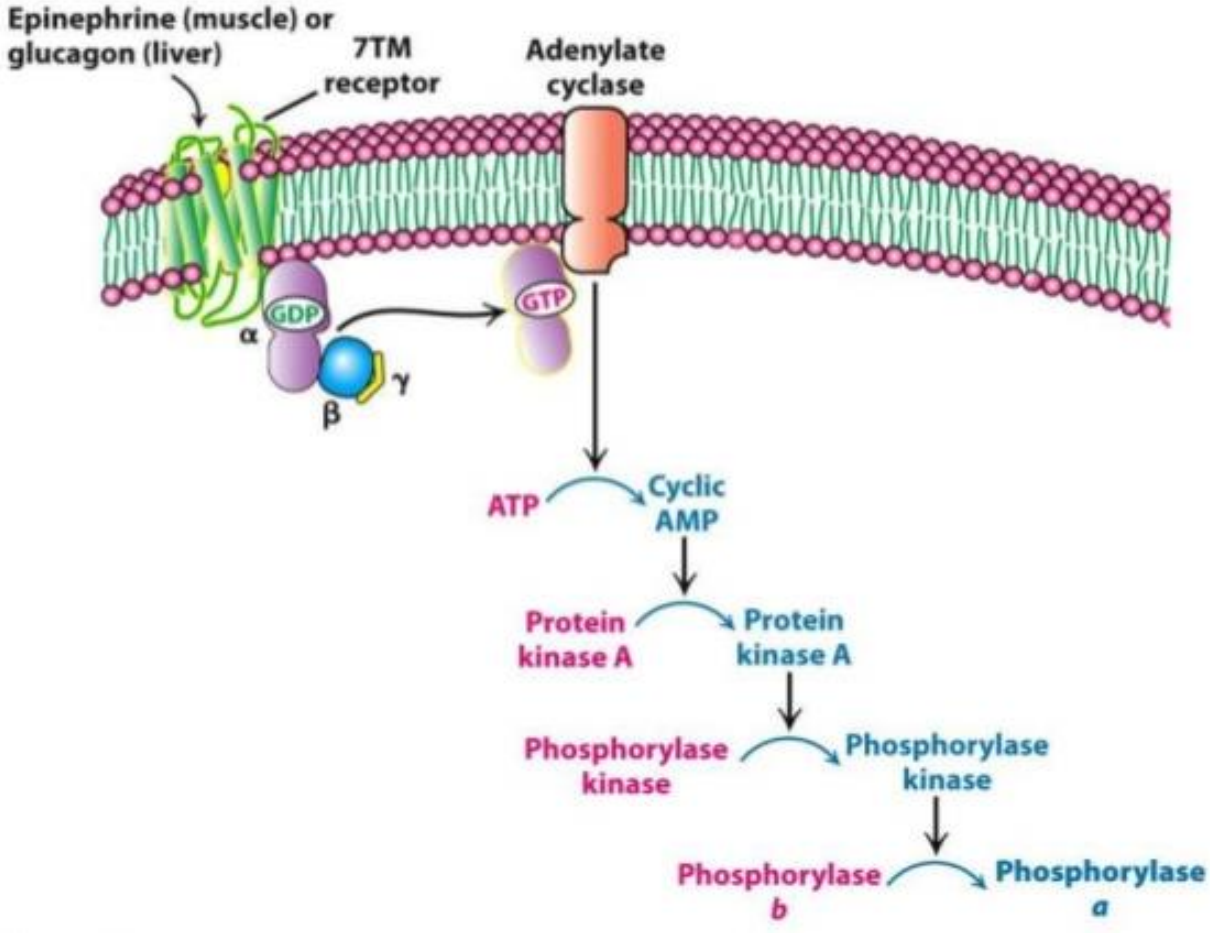


Fig: Hormone mediated signalling to activate glycogen phosphorylase

Turning Off Glycogen Breakdown

Turning OFF signals is as important, as turning them ON.

The steps in the glycogen breakdown regulatory pathway can be reversed at several levels.

1. First, The ligand can leave the receptor.

2. Second, the G proteins have an inherent GTPase activity that serves to turn them off over time.

3. Third, cells have phosphodiesterase for breaking down cAMP.

4. Fourth, an enzyme known as ‘protein phosphatase’ can remove phosphates from phosphorylase kinase (inactivating it) and from GPa, converting it to the much less active GPb.

Summary of Glycogenolysis

Breakdown of glycogen requires the interplay of several enzymes.

Phosphorylase and Debranching enzymes facilitates the breakdown of glycogen to glucose monomers.

The activity of phosphorylase is regulated by allosteric and phosphorylation events.

Epinephrine and glucagon signal the need for glycogen breakdown.

References

[1]***Lehninger Principles of biochemistry***

[2]***Lubert Stryer Biochemistry***

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Hexose Monophosphate Pathway
Or
Pentose Phosphate Pathway
Or
Phosphogluconate pathway

Pentose Phosphate Pathway

In most animal tissues, the major catabolic fate of glucose 6-phosphate is glycolytic breakdown to pyruvate. However, glucose 6-phosphate does have other catabolic fate that produces specialised products needed for cells.

One such fate is the oxidation of glucose 6-phosphate to pentose phosphates by the pentose phosphate pathway (also called phosphogluconate pathway or the hexose monophosphate pathway)

The pentose phosphate pathway occurs in cytoplasm and plays important role in:

1. It provides a way for our cells to oxidise glucose to create NADPH.

2. NADPH is used as reducing agents in various intracellular processes including
   a) Fatty acid biosynthesis, b) Nucleotide biosynthesis
   c) Cholesterol biosynthesis, d) Neurotransmitter biosynthesis
   e) Detoxification reactions

3. It provides a way to breakdown pentose sugar obtained from the diet.

4. It provide a way to synthesise pentose sugar (ribose) that are incorporated into important biomolecules such as DNA, RNA, ATP, NADH, $FADH_2$ and coenzyme A.

Pentose Phosphate Pathway

The pentose phosphate pathway has two phases

1. **Oxidative phase**
2. **Non-oxidative phase**

In oxidative phase the *NADPH* and *ribose 5-phosphate* is produced.

In nonoxidative phase, the ribose 5-phosphate is converted back to *glucose 6-phosphate*.

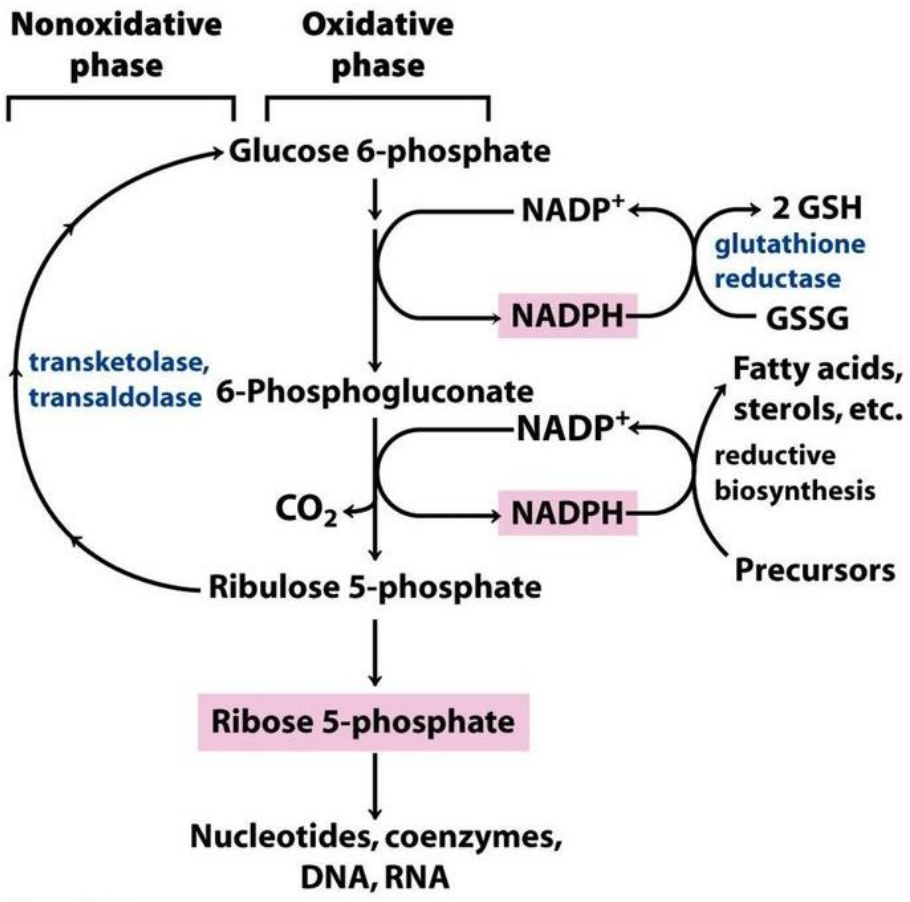


Fig: General scheme of the pentose phosphate pathway

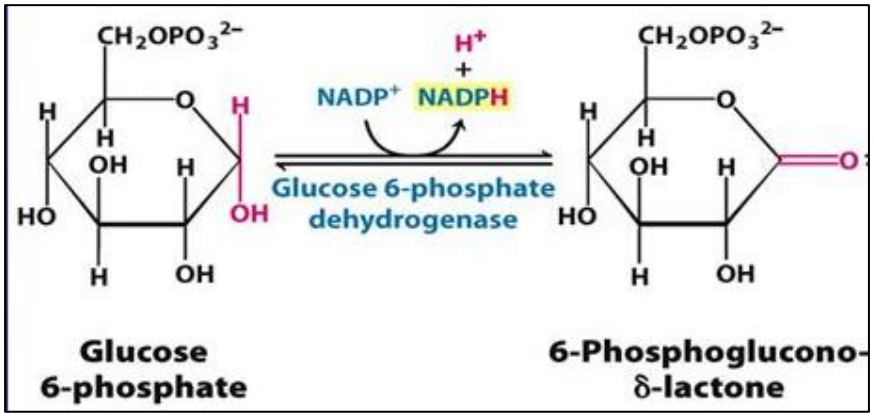
Oxidative phase of pentose phosphate pathway

The oxidative phase is comprised of 4 steps:

Step 1: Oxidation of glucose 6-phosphate
Step 2: Hydrolysis of 6-phosphoglucono-δ-lactone
Step 3: Oxidative decarboxylation of 6-phosphogluconate
Step 4: Isomerisation of ribulose 5-phosphate

Step 1: Oxidation of glucose 6-phosphate

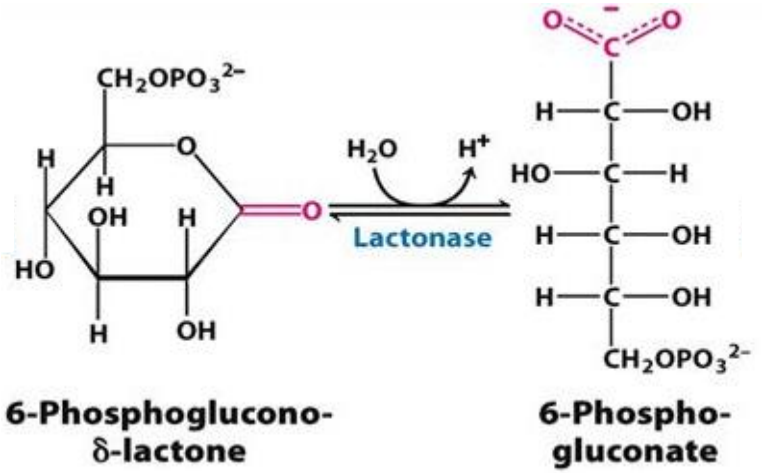
- Catalysed by glucose 6-phosphate dehydrogenase
- This reaction generates first NADPH
- The product formed is 6-phosphoglucono-δ-lactone which is an intramolecular ester



Oxidative phase of pentose phosphate pathway

Step 2: Hydrolysis of 6-phosphoglucono-δ-lactone

- This step is catalysed by lactonase enzyme
- It is a hydrolysis reaction to open the ring structure
- The product formed is 6-phosphogluconate

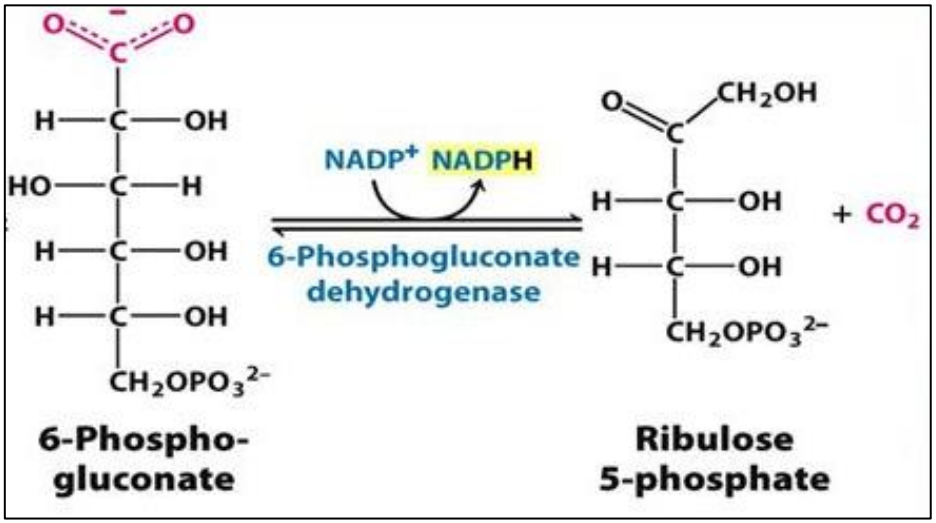


6-Phosphoglucono-δ-lactone **6-Phospho-gluconate**

Oxidative phase of pentose phosphate pathway

Step 3: Oxidative decarboxylation of 6-phosphogluconate

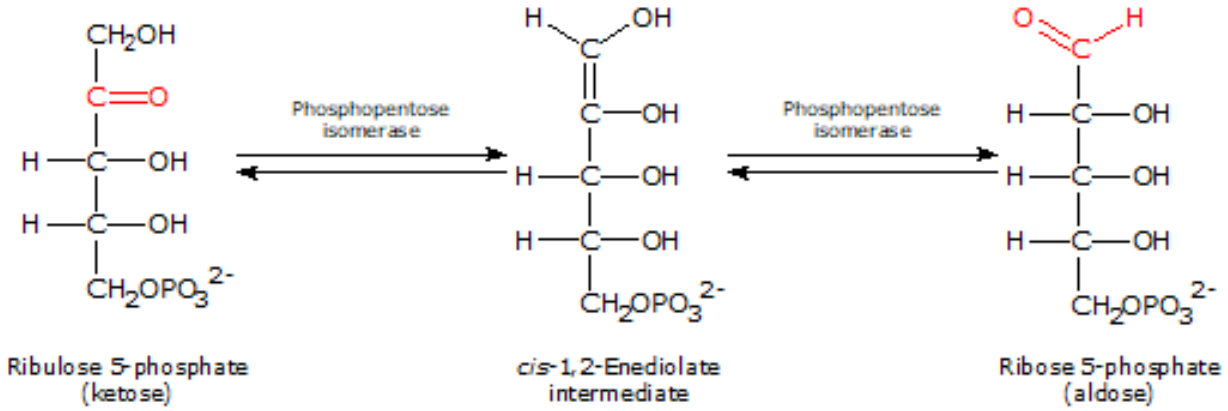
- This step is catalysed by 6-phosphogluconate dehydrogenase enzyme
- This reaction generates second NADPH
- One carbon is removed from 6 carbon chain in the form of CO_2 to yield 5-carbon, ribulose 5-phosphate.



Oxidative phase of pentose phosphate pathway

Step 4: Isomerisation of ribulose 5-phosphate

- This is the final step of oxidative phase catalysed by phosphopentose isomerase
- It is a typical ketose to aldose conversion.



Overall reaction of Oxidative phase of pentose phosphate pathway is:

Glucose 6-phosphate + 2NADP+ + H_2O → ribose 5-phosphate + 2NADPH + CO_2 + 2H^+

Nonoxidative phase of pentose phosphate pathway

Many cell types need NADPH for reductive biosynthesis processes much more than they need ribose 5-phosphate. In these cases, ribose 5-phosphate is recycled back to glucose 6-phosphate via glycolytic intermediates.

Nonoxidative phase is comprised of two steps:

Step 1: Conversion of Ribose 5-phosphate to Xylulose 5-phosphate

Step 2: Series of rearrangements of the carbon skeleton catalysed by transketolase and transaldolase enzymes

a) C5 + C5 ⇌ **C3 + C7**

b) **C3 + C7** ⇌ **C6** + **C4**

c) **C4** + C5 ⇌ **C6** + **C3**

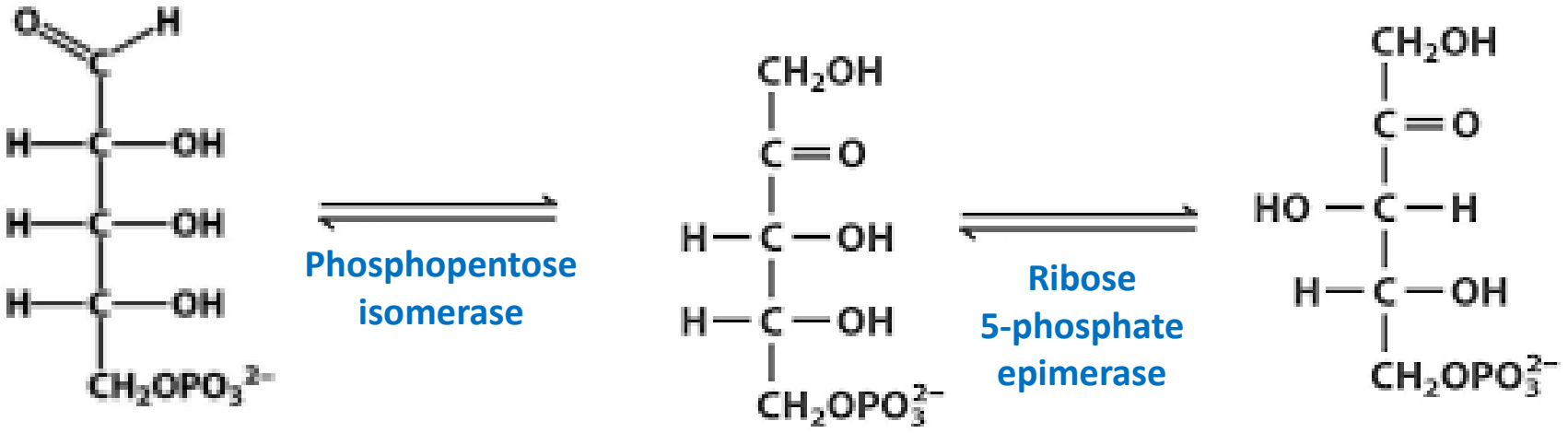
Nonoxidative phase of pentose phosphate pathway

Step 1: Conversion of Ribose 5-phosphate to Xylulose 5-phosphate

Involves two steps:

a) the ribose 5-phosphate is converted into ribulose 5-phosphate by phosphopentose isomerase

b) ribulose 5-phosphate is converted to xylulose 5-phosphate by Ribose 5-phosphate epimerase



Ribose 5-phosphate **Ribulose 5-phosphate** **Xylulose 5-phosphate**

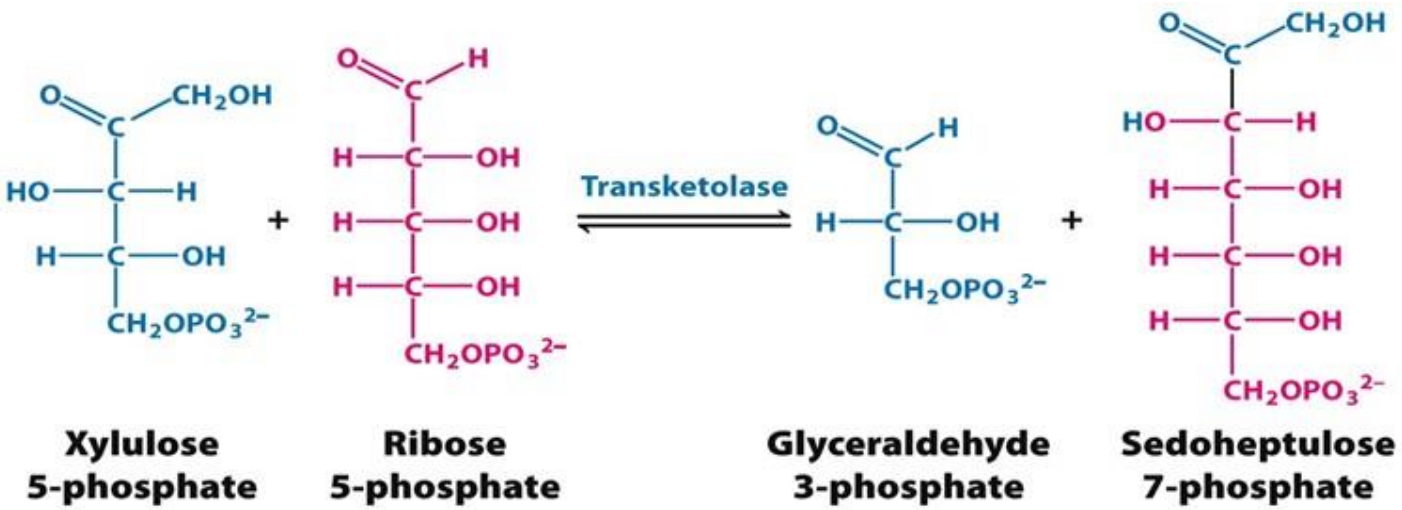
Nonoxidative phase of pentose phosphate pathway

Step 2: Carbon skeleton rearrangement

a) C5 + C5 ⇌ **C3 + C7**

The first rearrangement occurs between two 5-carbon sugar phosphate mediated by transketolase. Transketolase catalyses the transfer of two-carbon fragment from a ketose donor to an aldose acceptor.

Here, transketolase transfer C1 and C2 of xylulose 5-phosphate to ribose 5-phosphate forming 7-carbon product sedoheptulose 7-phosphate. The remaining 3-carbon fragment from xylulose is glyceraldehyde 3-phosphate



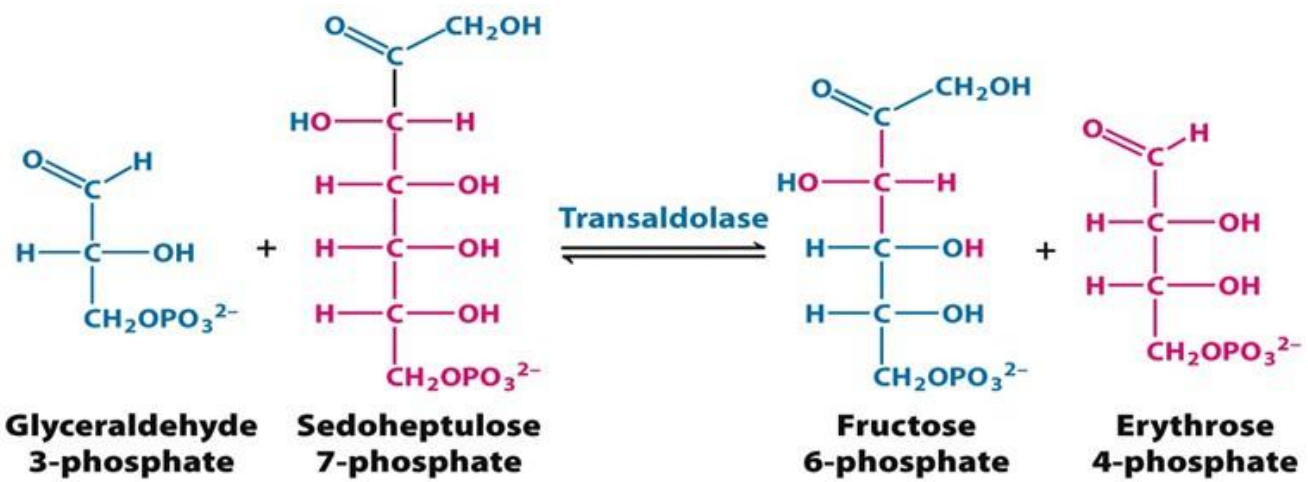
Nonoxidative phase of pentose phosphate pathway

Step 2: Carbon skeleton rearrangement

b) **C3 + C7** ⇌ **C6** + **C4**

The second rearrangement occurs between the product of first rearrangement reaction that is between sedoheptulose 7-phosphate and glyceraldehyde 3-phosphate. The reaction is mediated by transaldolase.

A three carbon fragment is removed from sedoheptulose 7-phosphate and condensed with glyceraldehyde 3-phosphate, forming fructose 6-phosphate and erythrose 4-phosphate. Fructose 6-phosphate produced in this step is a glycolytic intermediate. Erythrose 4-phosphate participates in next reaction.



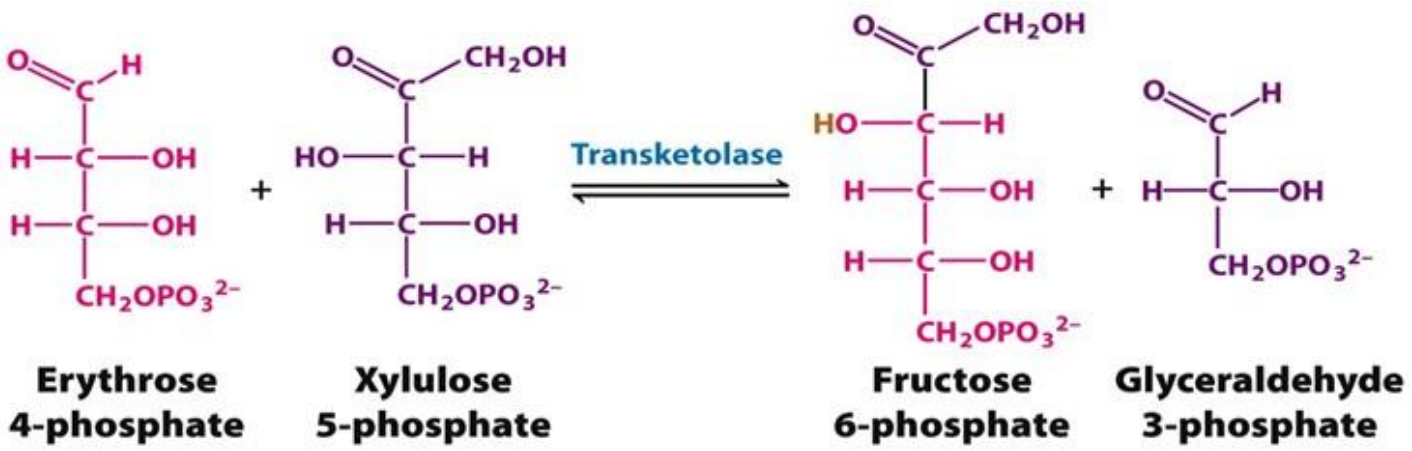
Nonoxidative phase of pentose phosphate pathway

Step 2: Carbon skeleton rearrangement

c) **C4** + C5 ⇌ **C6** + **C3**

The third rearrangement occurs between erythrose 4-phosphate (obtained from second rearrangement reaction) and xylulose 5-phosphate (from step 1) This reaction is mediated by transketolase.

This rearrangement reaction forms fructose 6-phophate and glyceraldehyde 3-phosphate. Both end products are glycolytic intermediates.



Nonoxidative phase of pentose phosphate pathway

The net result of the rearrangement s reactions is the formation of two hexoses and one triose from three pentoses.

3 C5 ⇌ 2 C6 + C3

Hexose: fructose 6-phosphate
Triose: glyceraldehyde 3-phosphate

Finally, the fructose 6-phosphate and glyceraldehyde 3-phosphate can follow gluconeogenesis steps to produce glucose 6-phosphate.

In this way, by nonoxidative phase of pentose phosphate pathway recycles ribose 5-phosphate back to glucose 6-phosphate via glycolytic intermediates.

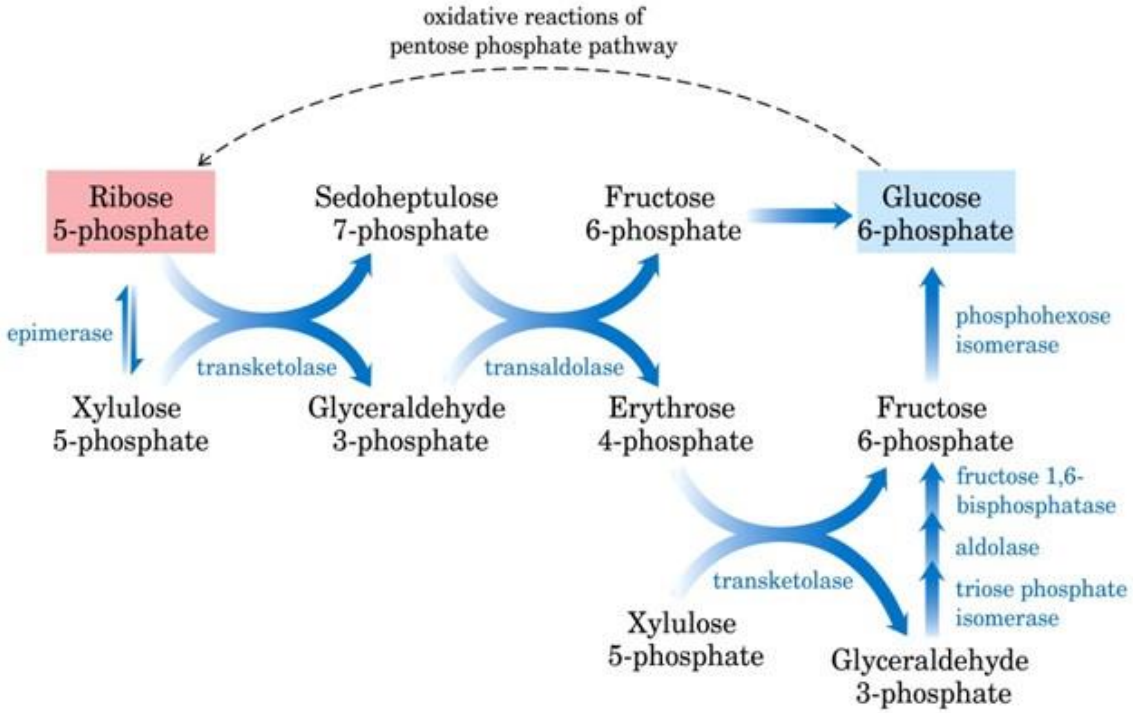


Fig: Nonoxidative reactions of the pentose phosphate pathway

Summary of pentose phosphate pathway

Table 20.3 Pentose phosphate pathway

Reaction	Enzyme
Oxidative phase	
Glucose 6-phosphate + $NADP^+$ ⟶ 6-phosphoglucono-δ-lactone + NADPH + H^+	Glucose 6-phosphate dehydrogenase
6-Phosphoglucono-δ-lactone + H_2O ⟶ 6-phosphogluconate + H^+	Lactonase
6-Phosphogluconate + $NADP^+$ ⟶ ribulose 5-phosphate + CO_2 + NADPH + H^+	6-Phosphogluconate dehydrogenase
Nonoxidative Phase	
Ribulose 5-phosphate ⇌ ribose 5-phosphate	Phosphopentose isomerase
Ribulose 5-phosphate ⇌ xylulose 5-phosphate	Phosphopentose epimerase
Xylulose 5-phosphate + ribose 5-phosphate ⇌ sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate	Transketolase
Sedoheptulose 7-phosphate + glyceraldehyde 3-phosphate ⇌ fructose 6-phosphate + erythrose 4-phosphate	Transaldolase
Xylulose 5-phosphate + erythrose 4-phosphate ⇌ fructose 6-phosphate + glyceraldehyde 3-phosphate	Transketolase

References

[1]*Lehninger Principles of biochemistry*

[2]*Lubert Stryer Biochemistry*

End