SCHOOL OF STUDIES IN ZOOLOGY
JIWAJI UNIVERSITY, GWALIOR

Glycogenesis and Glycogenolysis

Subject : Zoology

Paper : CBCZ -201: Biochemistry

Unit : I

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SOS in Zoology

INTRODUCTION-

- Glucogen is a very large **branched polymer** of glucose residue. Mr about 10^7 Dalton (up to 120,000 glucose residuesglucose units).
- Glycogen is present in the cytosol of animal cells in the form of **granules** ranging in diameter from 10 to 40 nm.
- The two major sites of glycogen storage are **the liver and skeletal muscle**.
- The core of the glycogen particle is a protein (glycogenin, G).
- The polymer is composed of units of glucose linked alpha(1-4) with branches occurring alpha(1-6)approximately every 8-12 residues

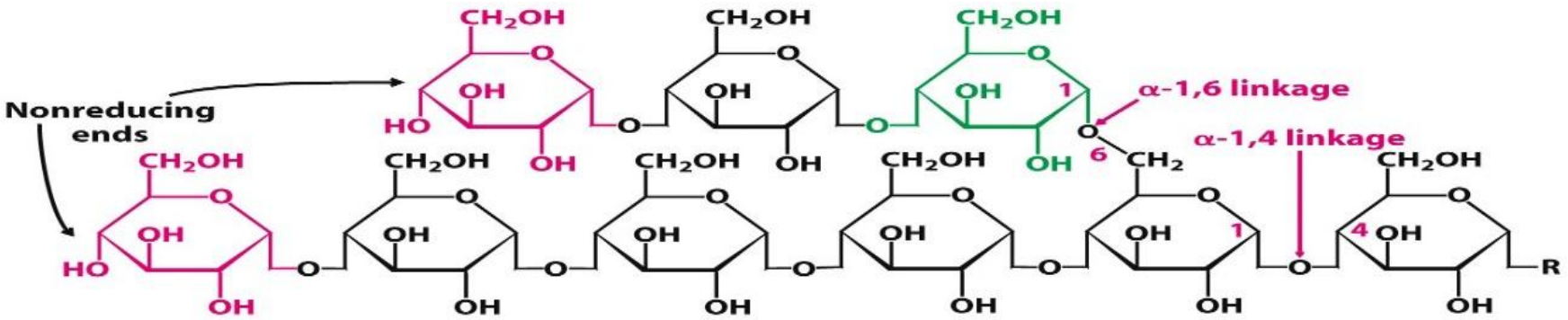
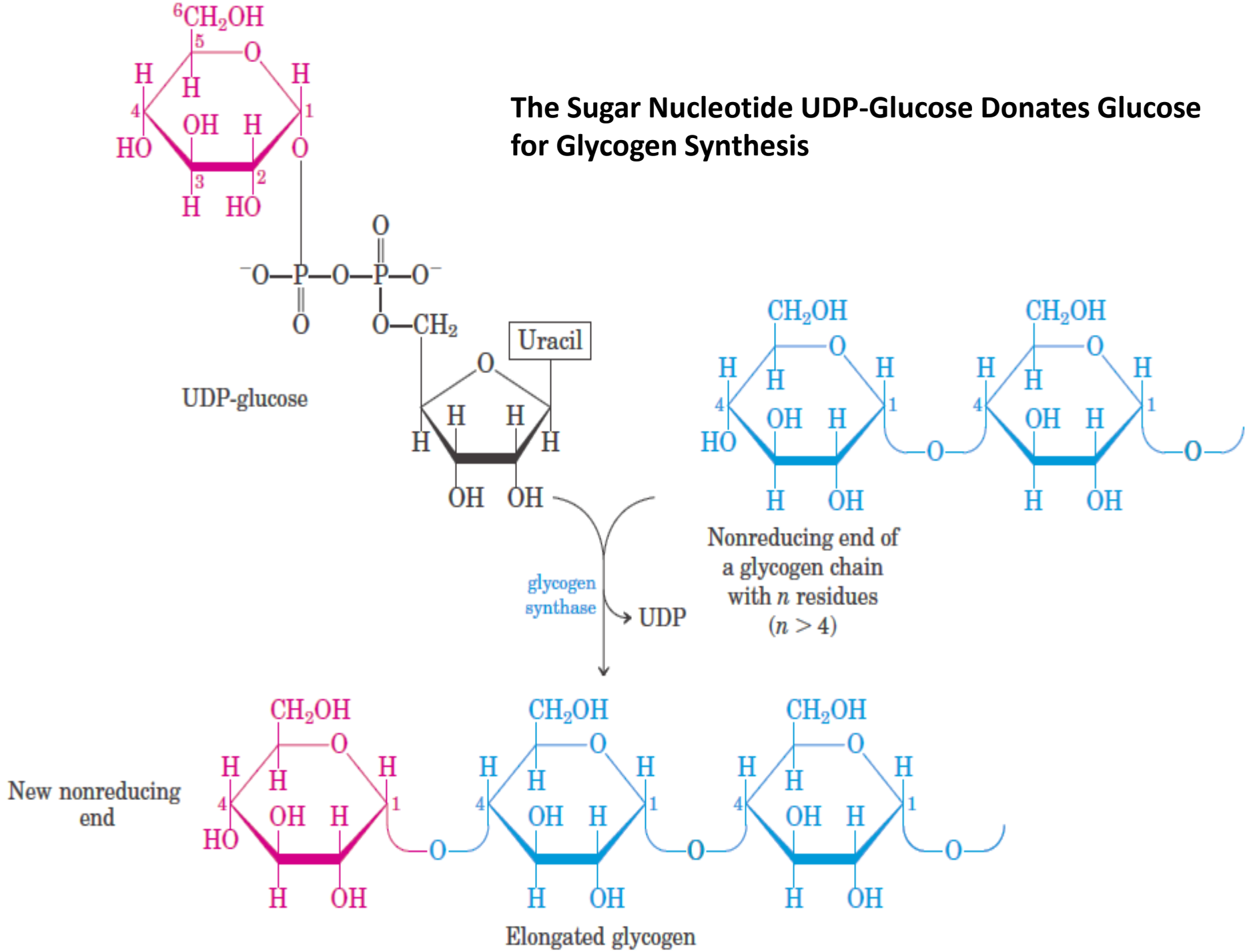


Figure 21.2
Biochemistry, Seventh Edition

Definition of glycogenesis:

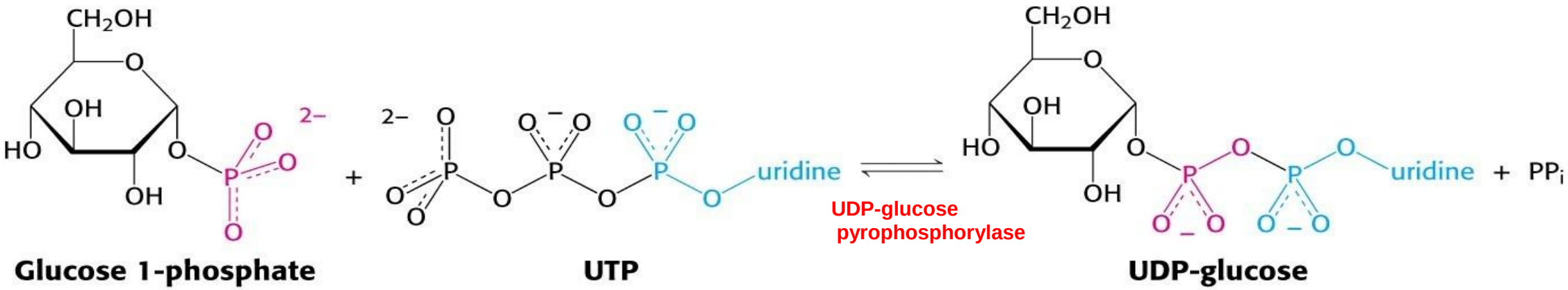
- It is the formation of glycogen, which occurs in all tissues of the body, but in large amount in liver and muscles.
- There are very small amount of glycogen synthesis and storage in the central nervous system; this is why it is completely dependent on blood glucose as a source of energy.
- **Site:** Cytosol of all cells particularly liver and muscles.

The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis



Glycogen synthesis

- A distinct system of enzymes exists for endergonic glycogen synthesis, coupled ultimately to the hydrolysis of ATP.
- Glucose 6-phosphate isomerizes to **glucose 1-phosphate** by the action of phosphoglucomutase.
- **Synthesis of an activated form of glucose (UDP-glucose) :**from glucose 1-phosphate and UTP (uridine triphosphate) in a reaction catalyzed by UDP-glucose pyrophosphorylase



This reaction is reversible, but it is driven by the essentially irreversible and rapid hydrolysis of diphosphate catalysed by inorganic pyrophosphatase.

$$PP_i + H_2O = 2Pi$$

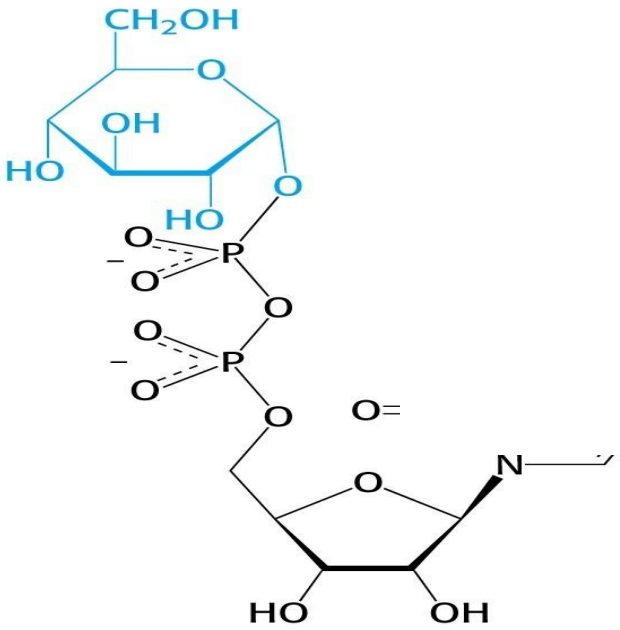
Elongation of glycogen chain

Glycogen synthase – the key regulatory enzyme in glycogenesis

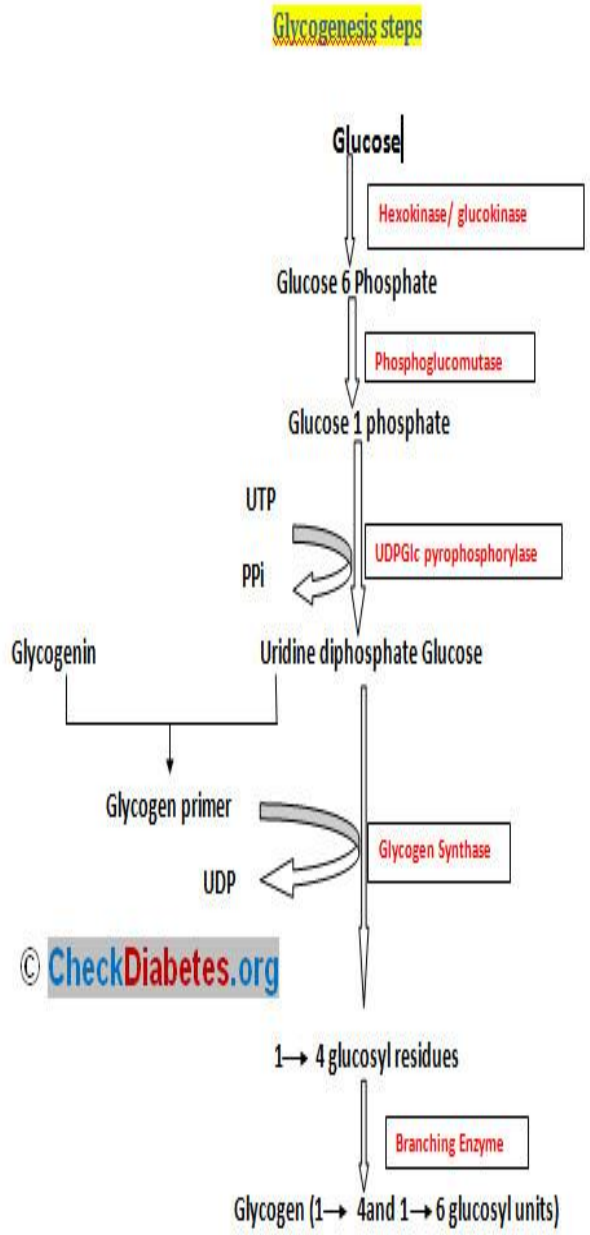
catalyses formation of an α-1,4-glycosidic bonds by the transfer of glucosyl from activated UDP-glucose to an existing chain (a primer

Glycogen synthesis needs a basic molecule on which the glucose residues can be added so that the chain can get elongated. Glycogen fragments which already exist can act as this primer. In glycogen depleted condition, a protein primer called **glycogenin** acts as the flooring to which the glucose molecules from UDP glucose are added like bricks.

Glycogen synthase links between the 1st C atom of the standing glucose residue on the end point of the fragment and 4th carbon of the glucose residue that is being added to the fragment. This forms the 1→ 4 glycogenic link. The enzyme catalysing this step is Glycogen synthase

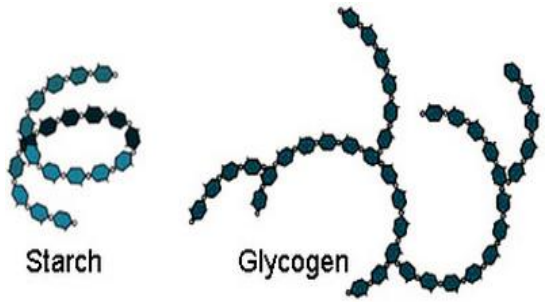


Uridine diphosphate glucose (UDP-glucose)



The branching in glycogen

- After around 8 residues, branching begins and the branches provide more number of activated glucose residual ends for the UDP glucose to get attached to.
- This branching is brought about by branching enzyme called amylo-α(1→4) → α(1→6)-transglucosidase.
- forms α-1,6-linkages that make glycogen a branched polymer.
- Branching is important because it increases the solubility of glycogen and increases the velocity of glycogen synthesis and breakdown (creating a large number of non-reducing ends).
- One such genetic disease is Glycogen storage disorder type 4 called as Anderson disease caused by defective branching enzyme. So the glycogen formed is a linear insoluble structure that accumulates in the cells causing liver and muscle damage



Regulation of Glycogenesis

- Glycogen synthesis is strictly monitored to regulate the blood glucose level. It is activated in well fed state and suppressed in fasting. According to basis of regulation of metabolic process, the factors regulating Glycogenesis are:

1. Availability of substrate

In well-fed state, when the blood glucose level is high, glucose 6 phosphate the substrate for UDP glucose is also high. This allosterically increases Glycogenesis. Also during fasting, the substrate is low and there is need for glucose which causes break down of glycogen which is opposite of Glycogenesis.

2. Hormone:

Glycogen synthase, the key enzyme of Glycogenesis exists in activate (dephosphorylated) and inactive (phosphorylated) form. Hormones like glucagon and epinephrine are diabetogenic i.e. they increase the blood glucose level. Thus they antagonize glycogen synthesis which is an effective way of reducing blood glucose level and storing it for further use.

These hormones succeeds in their function by series of biochemical reactions which results in :

A. phosphorylation of glycogen synthase enzyme rendering it inactive.
B. Insulin is an anti diabetic hormone. It lowers the blood glucose level by stimulating the uptake of glucose by muscle cells and Glycogenesis in liver and muscle.

These phosphorylations are catalysed by the action of **protein kinases**, dephosphorylations by the action of **phosphoprotein phosphatases.** The phosphorylation of both key enzymes depends primarily on the intracellular **concentration of cAMP**.

Glycogen degradation
Glycogen digestion in the gastrointestinal tract

- ❑ is essentially the same as the digestion of amylopectin.
- ❑ Both saliva and pancreatic secretion contain ***α-amylase***, which catalyses **hydrolytic splitting of α-1,4-glucosidic bonds** at random, unless they are near chain ends or branch points.
- ❑ The products are then **maltose, maltotriose** and a mixture of small branched fragments (with 5 - 9 glucose residues) called **α-dextrins**.
- ❑ Those products are **hydrolysed** to **free glucose** by the action of both ***maltase*** and ***saccharase-isomaltase***, found in the plasma membrane of mucosal cells of the duodenum and jejunum.

- *The importance of glycogen in food is not very large, because the glycogen content of meat products is usually negligible due to post-mortem glycogenolysis.*

Breakdown of glycogen (Glycogenolysis): involves

A. release of glucose-1-phosphate (G1P)
B. rearranging the remaining glycogen (as necessary) to permit continued breakdown
C. conversion of G1P to G6P for further metabolism.

❑ **G6P can be:**

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

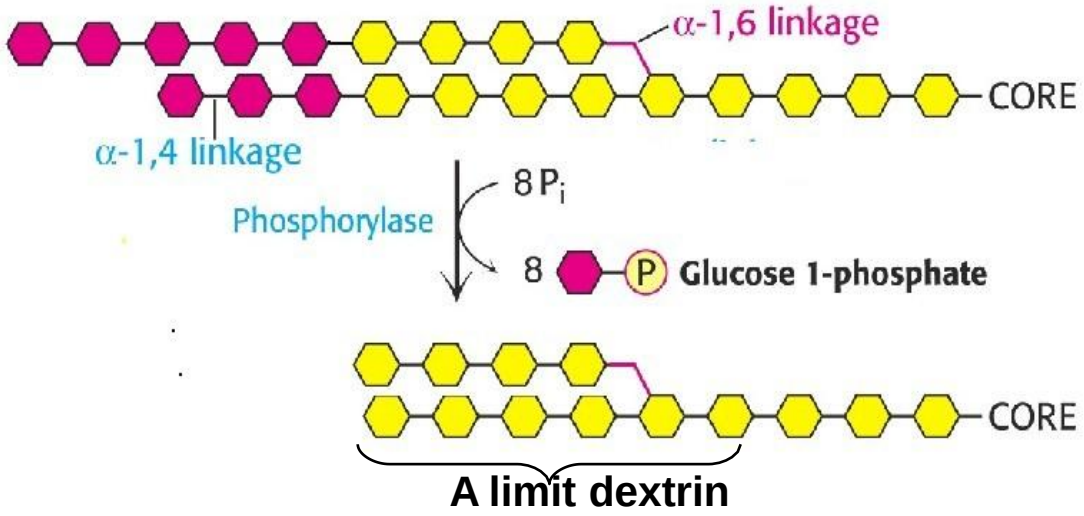
Glycogenolysis: Glycogen breakdown in cells

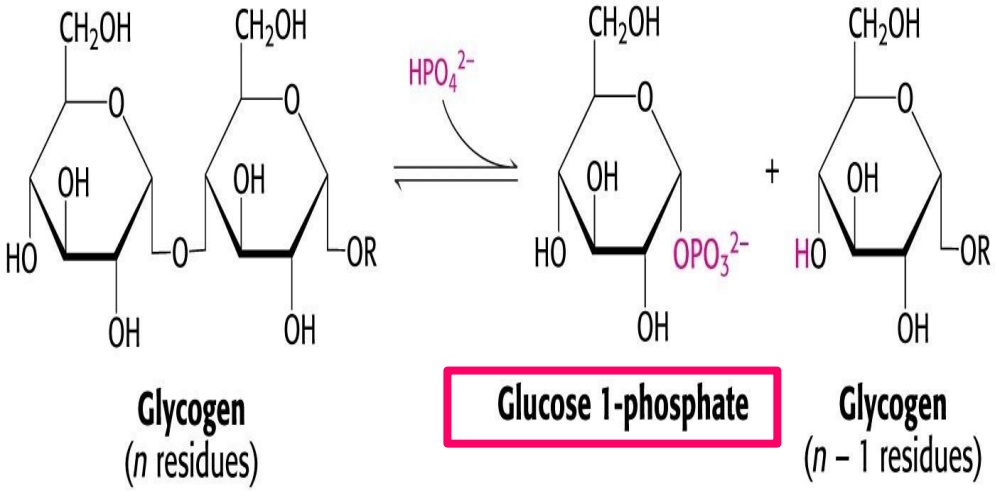
- It occurs in Cytosol of all cells but high activity in liver and muscles.

-Glycogenolysis requires the cooperation of two enzymes – glycogen phosphorylase and
– a debranching enzyme.

Glycogen phosphorylase (phosphorylase)- the key regulatory enzyme in glycogenolysis

-catalyses the sequential phosphorolysis (not hydrolytic splitting) of α-1,4-glycosidic bonds of glycosyl residues from the non-reducing ends, and these only if they are more distant than four residues from abranch point. So its action ends with a production of several molecules of glucose 1-P and a limit dextrin



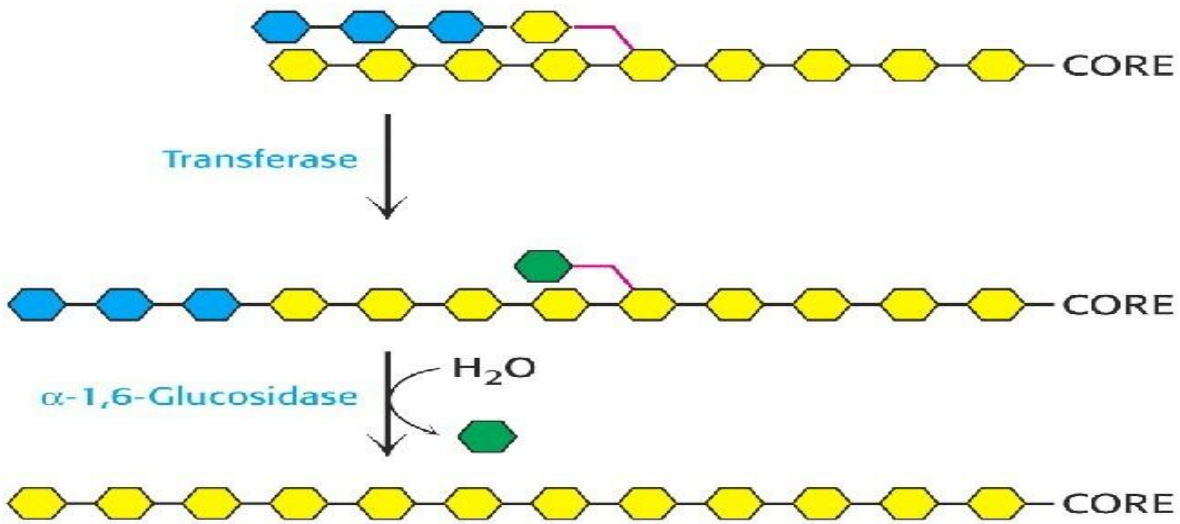


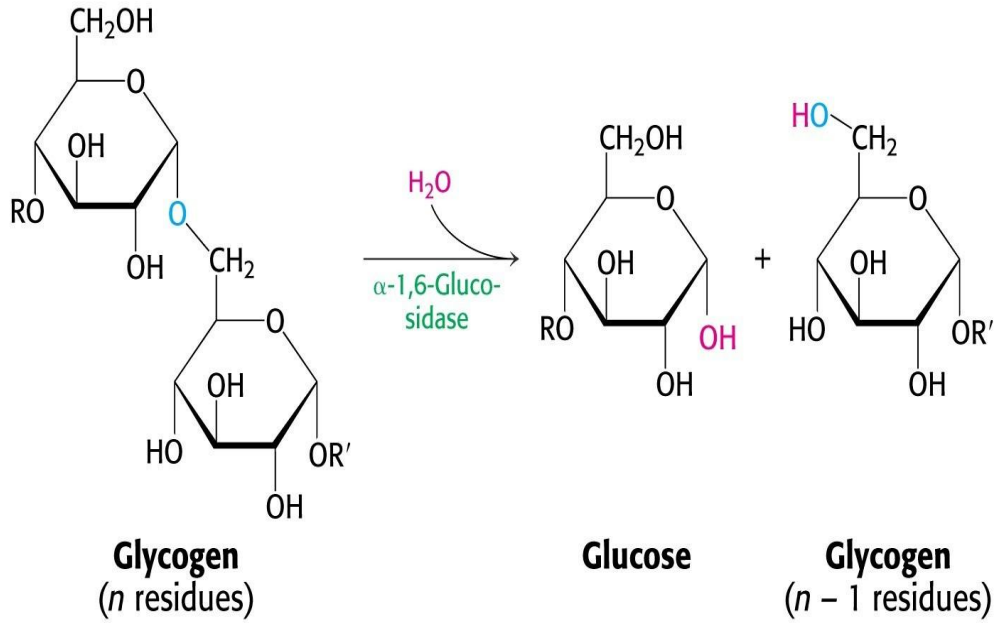
Since ATP is NOT used to put phosphate on G1P, the reaction saves the cell energy. In addition, the phosphate on the G1P helps prevent the molecule from leaving the cell . Glycogen phosphorylase employing the coenzyme PLP.

Glycogen debranching enzyme exhibits two catalytic activities, it is a bifunctional enzyme:

1. The ***transferase*** activity shifts a block of three glucosyl residues from one outer branch to the other.
2. ***α-1,6-glucosidase*** activity : convert alpha(1-6) branches to alpha(1-4); causes **hydrolysis of** the α-1,6-glycosidic bond resulting in the release of a free glucose molecules

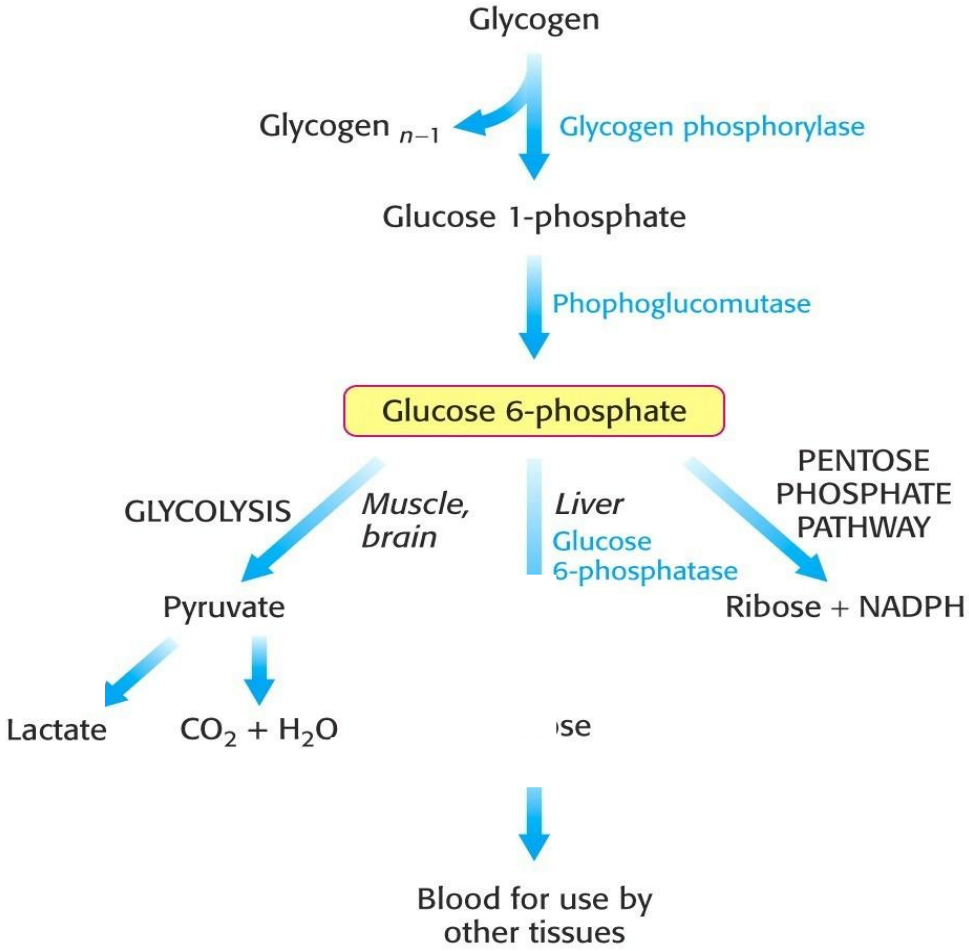
❑ ***The debranching enzyme*** converts the branched structure of a limit dextrin into a linear one:





❑ ***Phosphorylase*** can now attack the remaining α-1,4-linked chain.

- Phosphoglucomutase converts glucose 1-phosphate into glucose 6-phosphate, the intermediate of glycolytic pathway
- phosphoglucomutase is needed to form G1P for glycogen biosynthesis.
- The glucose-6-phosphatase (G6Pase) catalyzes the last step of gluconeogenesis - conversion of G6P to glucose + phosphate. This enzyme is necessary also for release of glucose into the bloodstream from glycogen metabolism (glycogen -> G1P -> G6P -> Glucose).



- It is interesting to note that G6 Phosphatase is ABSENT FROM MUSCLE. This is because muscle does NOT export glucose. the liver, on the other hand, DOES export glucose and thus has abundant supplies of the enzyme. so that when G6P is produced from glycogen breakdown, it can enter glycolysis.

Control of glycogen degradation-

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

4 **cAMP** (increase is evoked by **glucagon and/or adrenaline**)

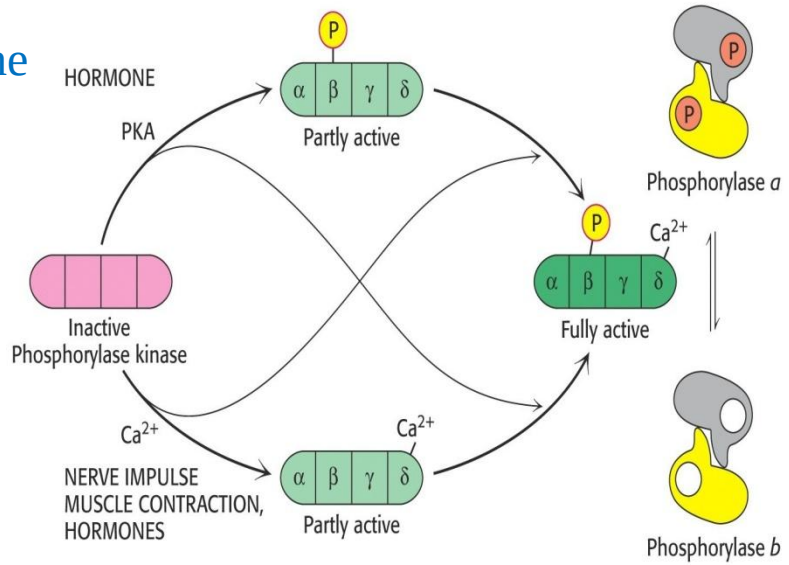
Protein kinase A (**C_2R_2**, inactive) → **Protein kinase A** (2 **C**, active) + $R_2(cAMP)_4$

Phosphorylase kinase (inactive) —(2 ATP, Ca^{2+})→ **Phosphorylase kinase** (-P_2, active)

2 Glycogen phosphorylase ***b*** (dimeric, **inactive**) —(4 ATP, 4 ADP)→ Glycogen **phosphorylase *a*** (tetrameric, phosphorylated , **active**)

Glycogen **phosphorylase *a*** —(4 P_i, 4 H_2O, **Protein phosphatase**)→ 2 Glycogen phosphorylase ***b*** (dimeric, **inactive**)

Activation of phosphorylase kinase by calcium is VERY important in muscle for m contraction



(inactive)

Phosphorylase kinase is activated by:

1. **phosphorylation**
2. **Ca+2**
3. Glucose is negative effector

- Glycogen phosphorylase (GP) is regulated by both allosteric factors and by covalent modification. High energy substrates (ATP, G6P, glucose) inhibit GP, while low energy substrates (AMP, others) activate it.
- the liver GPb form of the enzyme is insensitive to AMP, unlike the muscle GPb.
- Glucose binding to liver GPa causes it to convert into the inactive form. This does not happen in muscle

Glycogen Storage Diseases

- Glycogen storage diseases are groups of inherited disorders characterized by deposition (over-storage) of an abnormal type or quantity of glycogen or failure of storage of glycogen in the tissues.
- They are mainly due to deficiency of one of enzymes of glycogenesis or glycogenolysis, phosphofructokinase, or lysosomal glycosidases.
- these include type I to type VIII glycogen storage diseases.

TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course. **Limit Dextrinosis**
IV Andersen disease	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V. **Tarui's disease**
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.