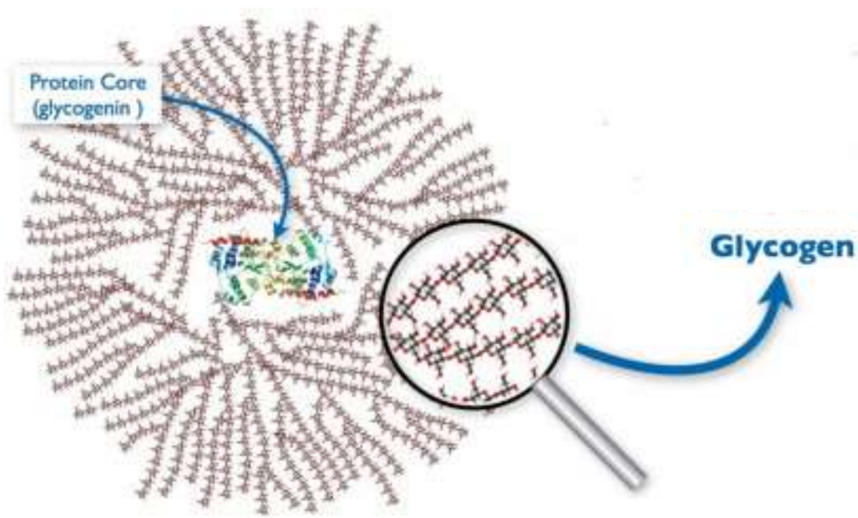
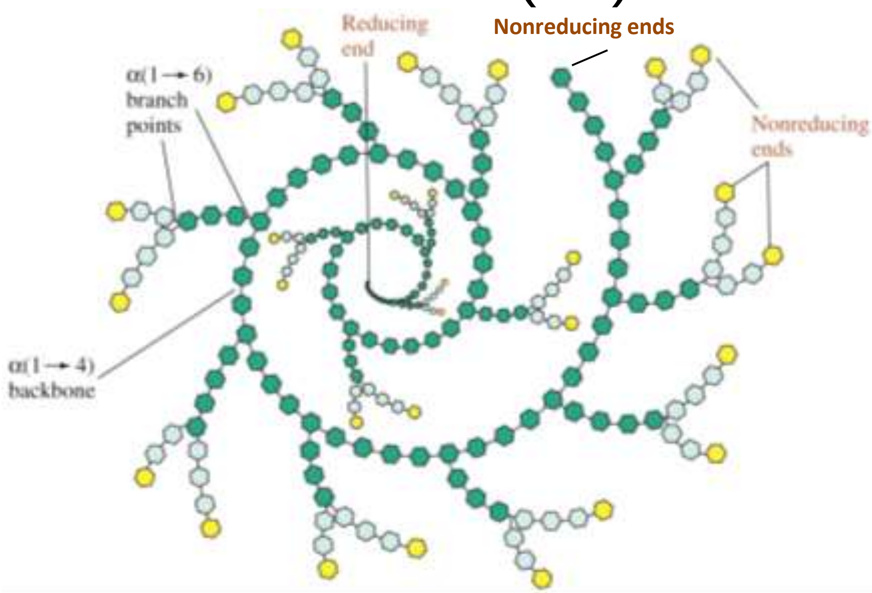
Glycogen Metabolism

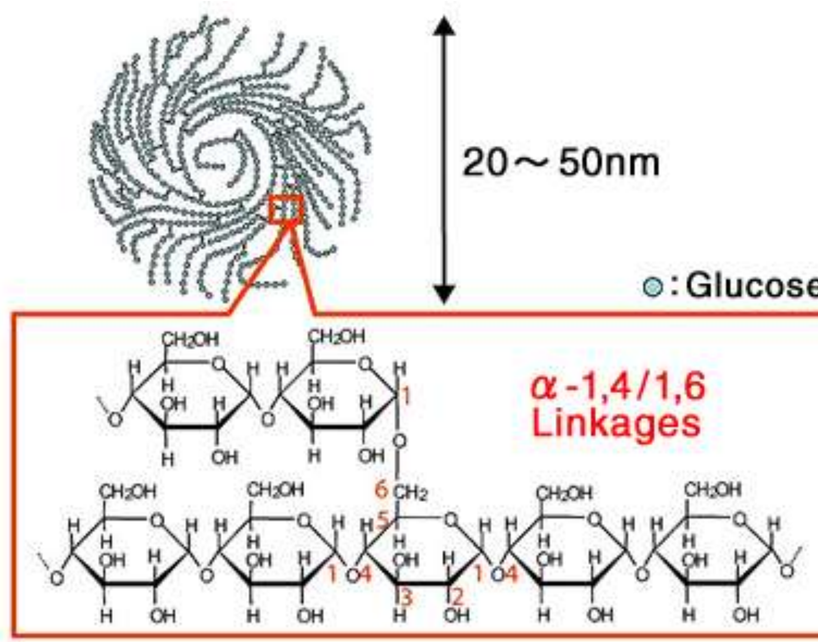


Dr. Nesrin Mwafi
Biochemistry & Molecular Biology Department
Faculty of Medicine, Mutah University

Glycogen Structure

- Glycogen is a readily **mobilized** storage form of glucose in animals and human
- It is a homoglycan or homopolysaccharide consists of glucose subunits most of them are linked by α-1,4-glycosidic bonds
- Glycogen is a highly branched polymer with branch points occurring every 8-14 residues created by α-1,6-glycosidic bonds
- Glycogen consists of only one reducing end consisting of free anomeric carbon (C1)



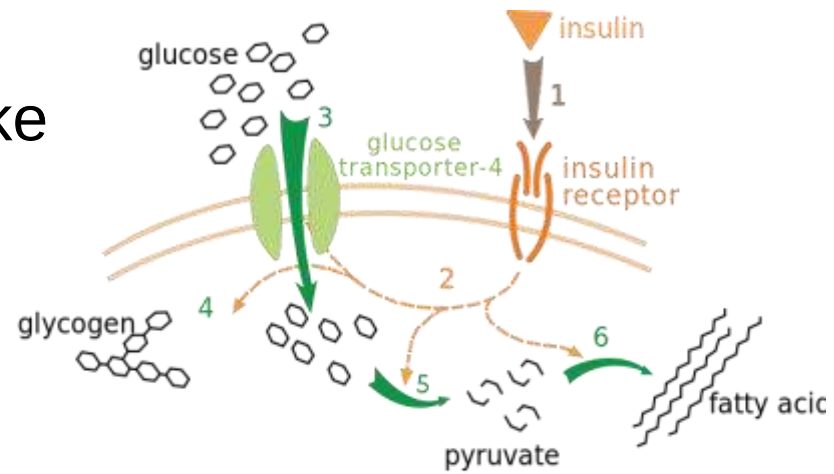


Glycogen Metabolism

- Mainly found in skeletal muscle (up to 1-2% of muscle mass) and liver cells (up to 10% of liver mass). It is found in the cytosol as granules ranging in diameter from 10-40 nm
- Other tissues particularly the brain require a constant supply of blood glucose for survival
- Glycogen in synthesized (glycogenesis) when blood glucose is high and glycogen is degraded (glycogenolysis) releasing glucose into the blood stream when blood glucose is low (normal blood glucose level is 80-100 mg/dl)
- This balance between the need and availability is called metabolic homeostasis

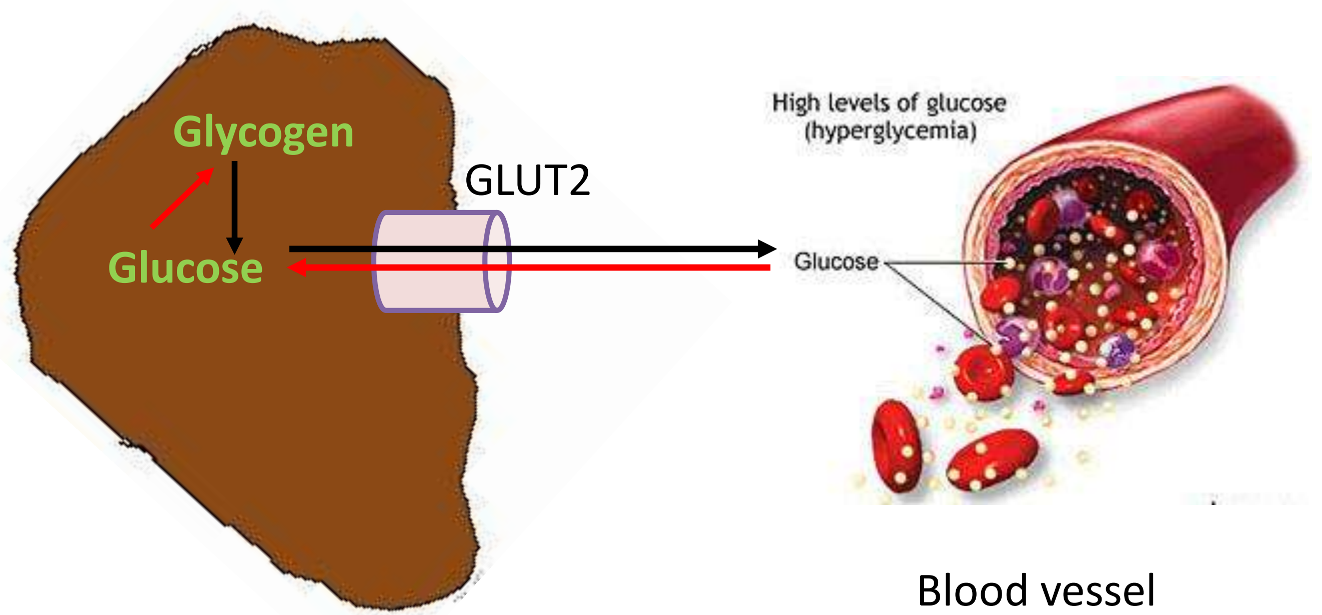
Glucose Transporter Protein

- Glucose transporters (GLUTs) are transmembrane proteins which facilitate the transport of glucose across plasma membrane
- To date, 12 GLUTs genes have been identified in human genome which are expressed in various tissues
- For example, GLUT4 is found primarily in adipose tissues, skeletal and cardiac muscles. It is regulated by insulin (insulin dependent). So insulin stimulates adipose and muscles to express more GLUT4 proteins on the cell membrane after CHO rich meal. Consequently, the glucose uptake by these cells is enhanced. This will stimulate glycogenesis in muscles and fatty acids synthesis in adipose tissue



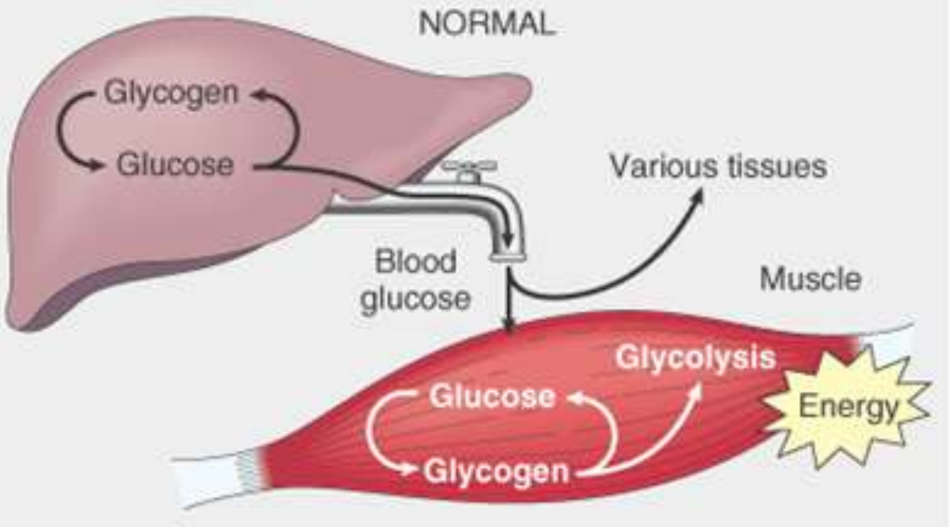
Glucose Transporter Protein

- GLUT3 expressed mostly in neurons
- GLUT2 is a bidirectional transporter expressed mainly in liver and pancreatic β-cells. It does not relay on insulin for facilitated diffusion (glucose uptake)



Glycogen Metabolism

- In liver, glycogen synthesis and degradation processes are controlled to maintain blood-glucose level within the normal range in order to meet the energetic needs of the organism as whole
- In muscle, glycogen synthesis and degradation processes are regulated to meet the energetic needs of the muscle itself



Glycogenesis

- Glycogenesis is the process of glycogen synthesis in which glucose molecules are added to chains of glycogen for storage. It occurs in the cytosol of the cell.
- This process is stimulated by the insulin hormone, a peptide hormone secreted by beta cells in the pancreas
- Glycogenesis takes place when blood glucose level is sufficiently high (e.g. after a CHO-rich meal) to allow excess glucose to be stored in liver and muscle cells
- The glycogenesis requires an activated form of glucose "uridine diphosphate glucose or UDP-glucose" generated by the reaction of UTP with glucose-1-phosphate. UDP-glucose is a substrate for glycogen biosynthesis (glycogen synthase)

Glycogenesis

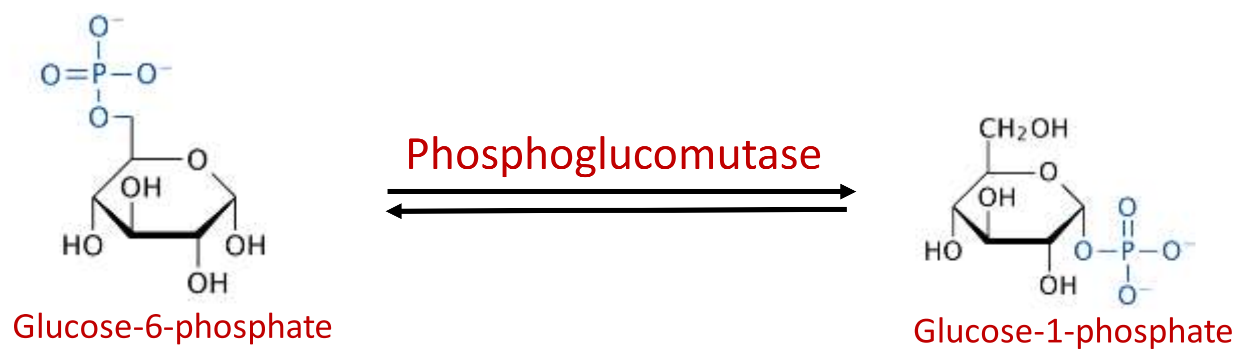
- Glycogenesis pathway consists of three phases:
  1. Biosynthesis of UDP-glucose
  2. The glycogen synthase reaction and the formation of glycogen primer (the first 8 glucose residues in the core chain)
  3. Formation of branches

❖ **Biosynthesis of UDP-glucose:** this pathway consists of three steps

- **Step 1:** the intracellular glucose is phosphorylated by hexokinase (glucokinase in liver and pancreas) to produce glucose-6-phosphate

Glycogenesis

- **Step 2:** G6P is isomerized to G1P by phosphoglucomutase in a reversible reaction

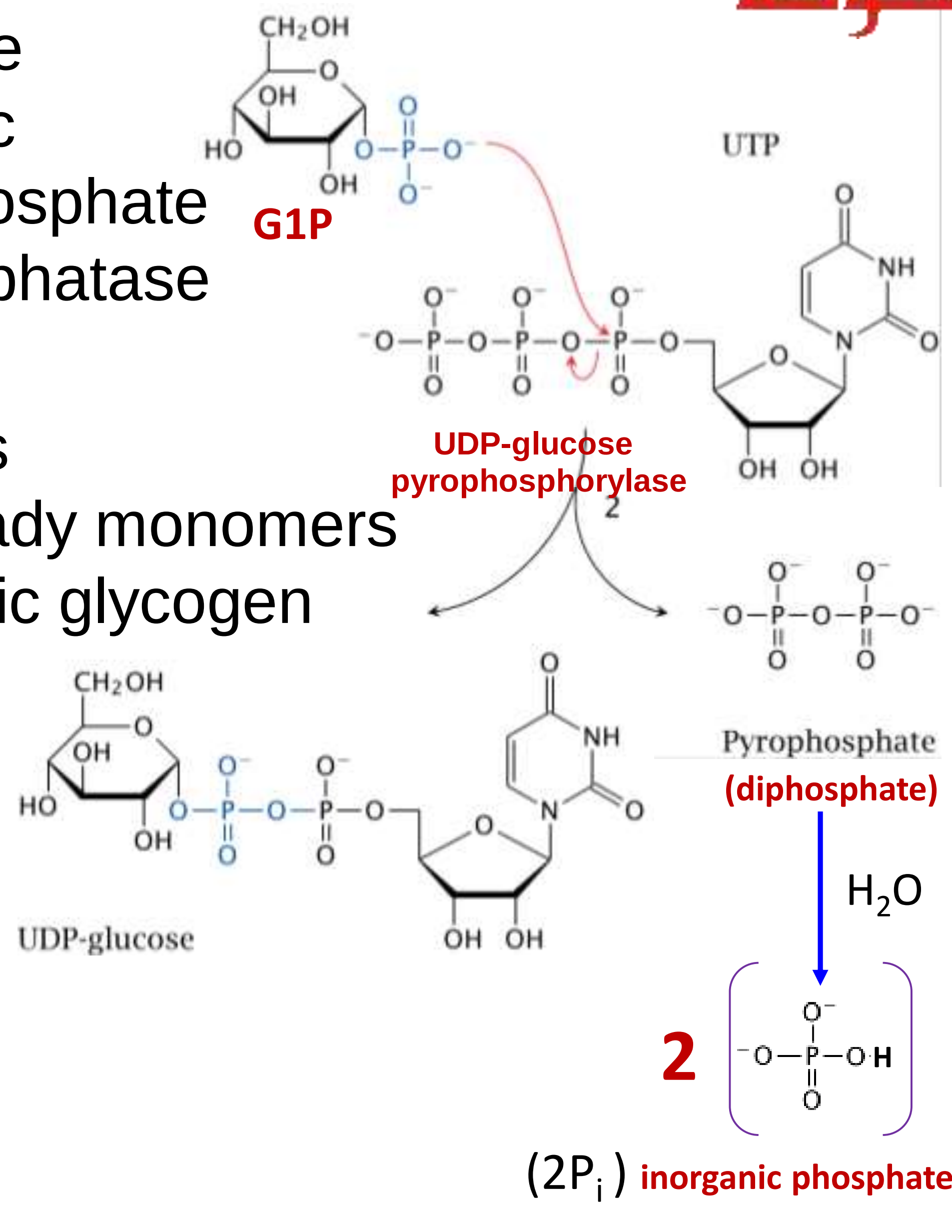


- **Step 3:** an important intermediate in glycogen synthesis is UDP-glucose which is synthesized from G1P in a reversible reaction catalyzed by the enzyme **UDP-glucose pyrophosphorylase** which transfer an UMP to G1P releasing pyrophosphate (PP_i)

Glycogenesis

- The reaction is drawn to the right by the rapid enzymatic cleavage of PP_i to orthophosphate $2P_i$ catalyzed by pyrophosphatase (hydrolysis rxn)
- The activated glucose units (UDP-glucose) are now ready monomers to be added to the polymeric glycogen

  (substrate for glycogen synthase enzyme)



Glycogenesis

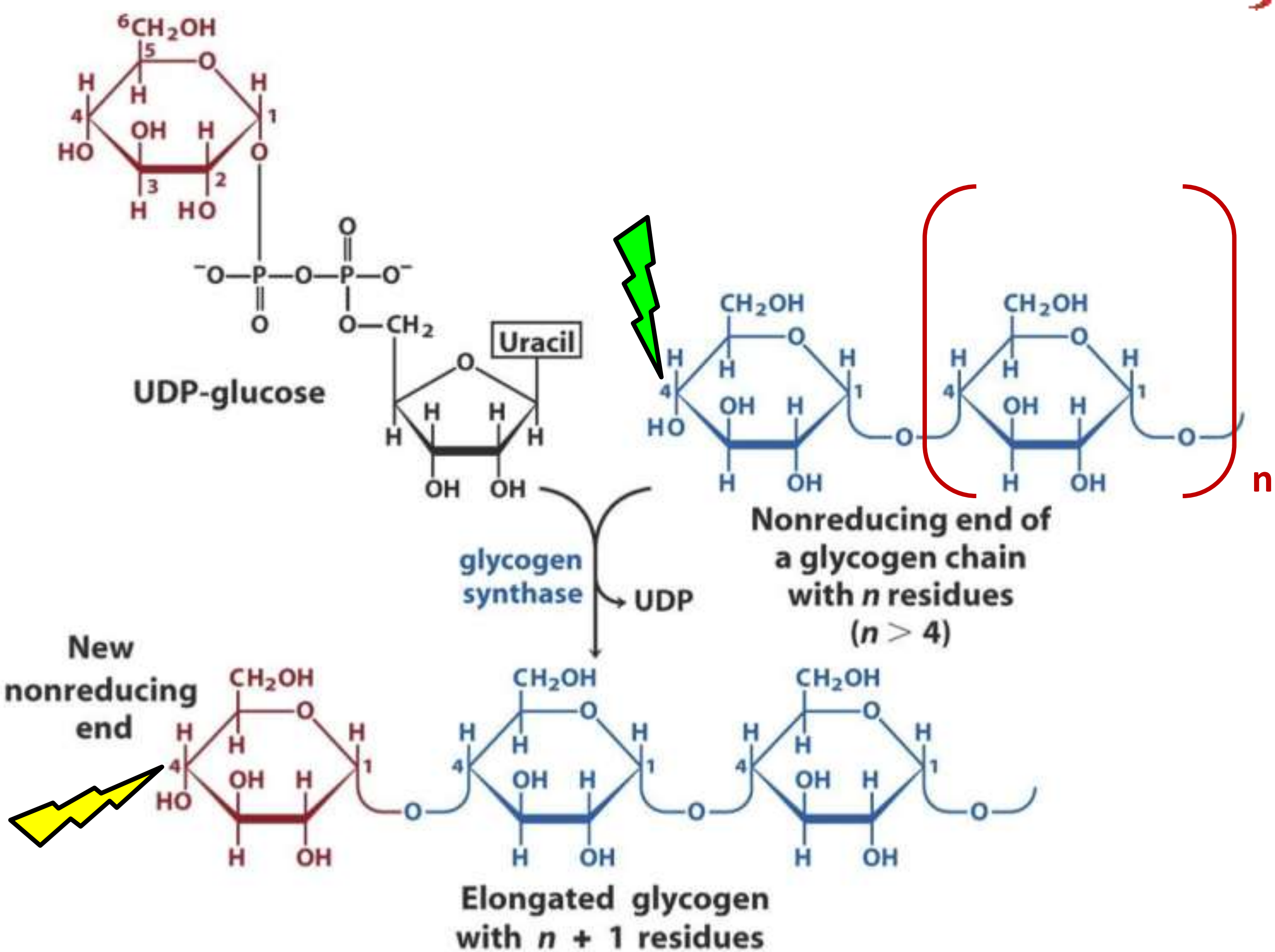
❖ The Glycogen Synthase reaction (the second phase)

- UDP-glucose units are the immediate donors of glucosyl residues added to the non-reducing end of either:

  1. Primer or glycogen core (8 Glu residues)
  2. Glycogen branch consists of at least 4 glucose units in length ($n \geq 4$)

- α-1,4-glycosidic bond is formed between C1 of the transferred glucosyl moiety and C4 of the terminal glucose residue of the elongated chain (non-reducing end)

Glycogenesis



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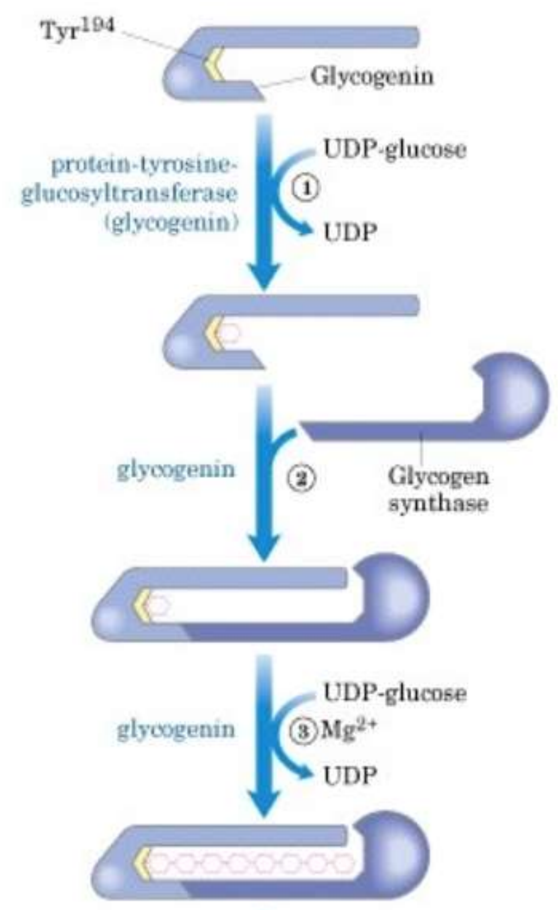
- How is a new/nascent glycogen molecule initiated?

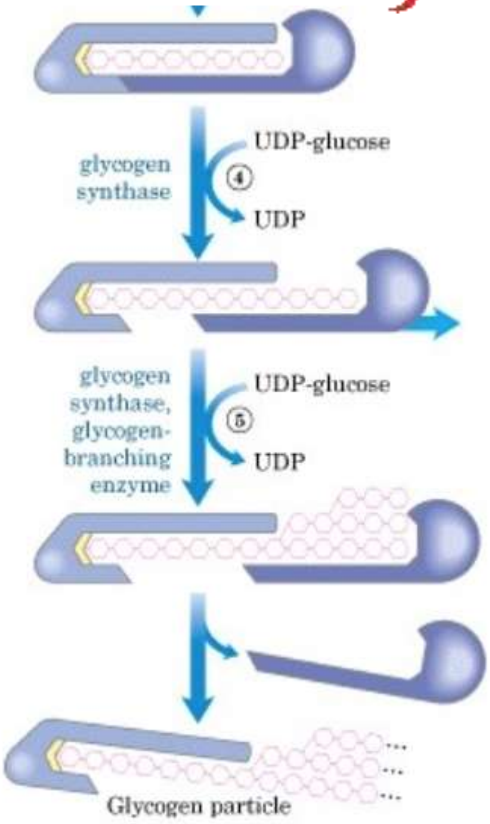
Glycogen Synthesis Initiation

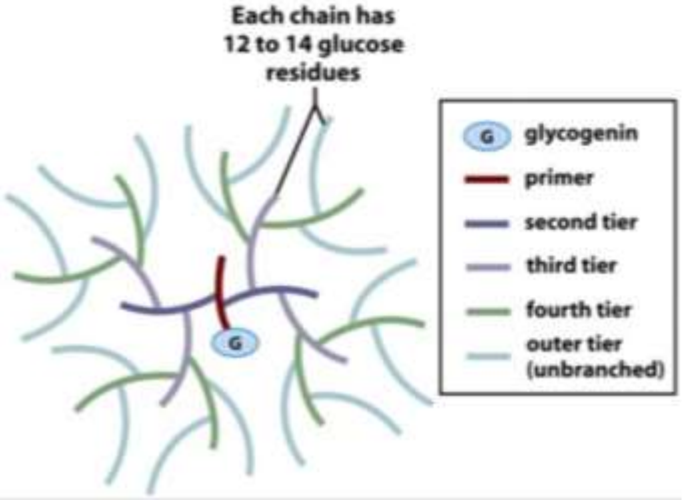
- Step 1: the first glucose is attached to tyrosine residue of a protein called glycogenin
- Step 2: glycogenin forms a tight complex with glycogen synthase
- Step 3: the chain is extended by sequential addition of up to 7 glucose residues autocatalyzed by glycogenin itself (α-1,4-glycosidic bond)
- Step 4: at this point, glycogen synthase dissociates and starts to extend the linear glycogen chain



Glycogen Synthesis Initiation

- Step 5: the combined action of glycogen synthase and branching enzyme completes the glycogen particle
- Step 6: glycogen synthase dissociates from the newly synthesized glycogen molecule while the glycogenin remains covalently attached to reducing end

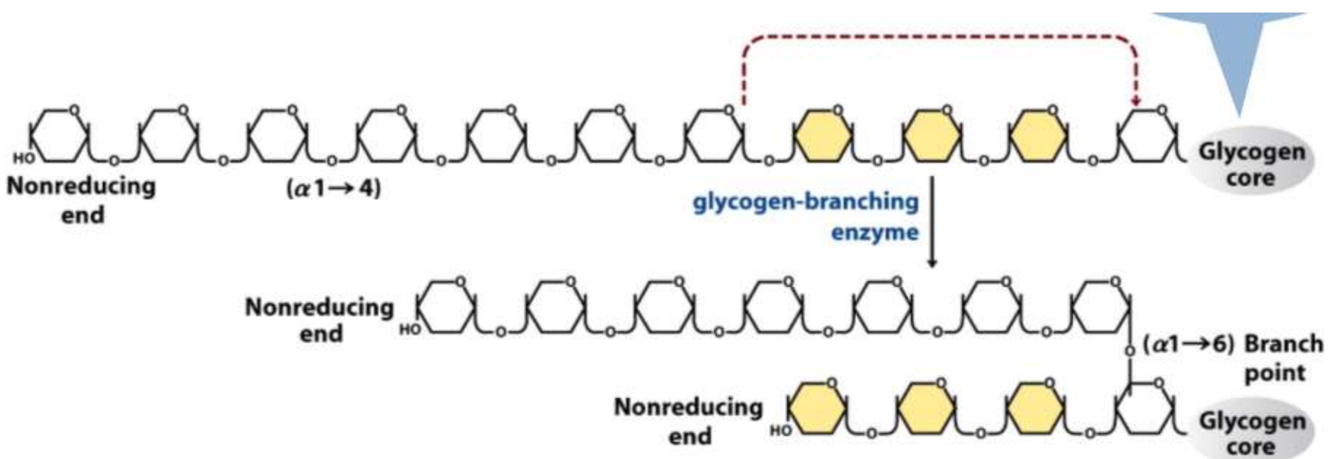




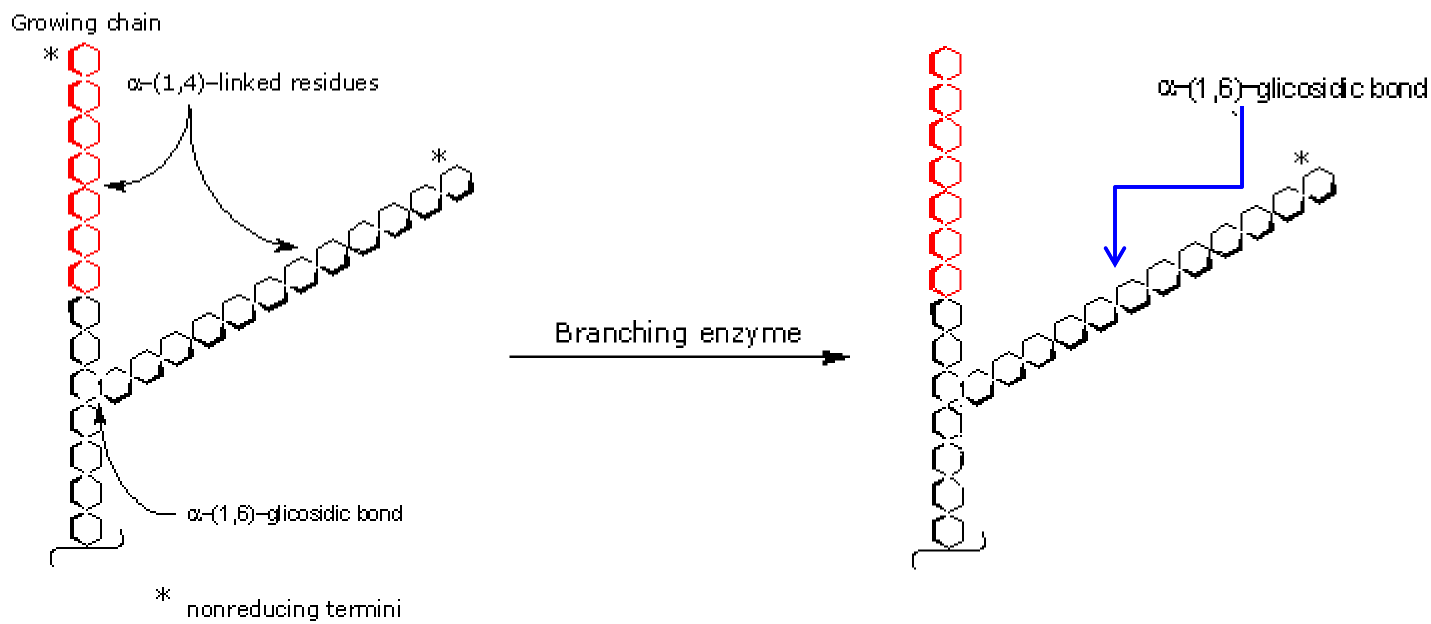
Glycogen Branch Point

❖ Formation of branches (the third phase)

- Step 1: the ($\alpha_{1\rightarrow6}$) bonds found at the branch points of glycogen are formed by glycogen branching enzyme which catalyzes the transfer of small fragment (6-7 glucosyl residues) from the non-reducing end of a branch having **at least eleven residues.**
- Step 2: further glucosyl residues may be added to the new branch by glycogen synthase



Glycogenesis

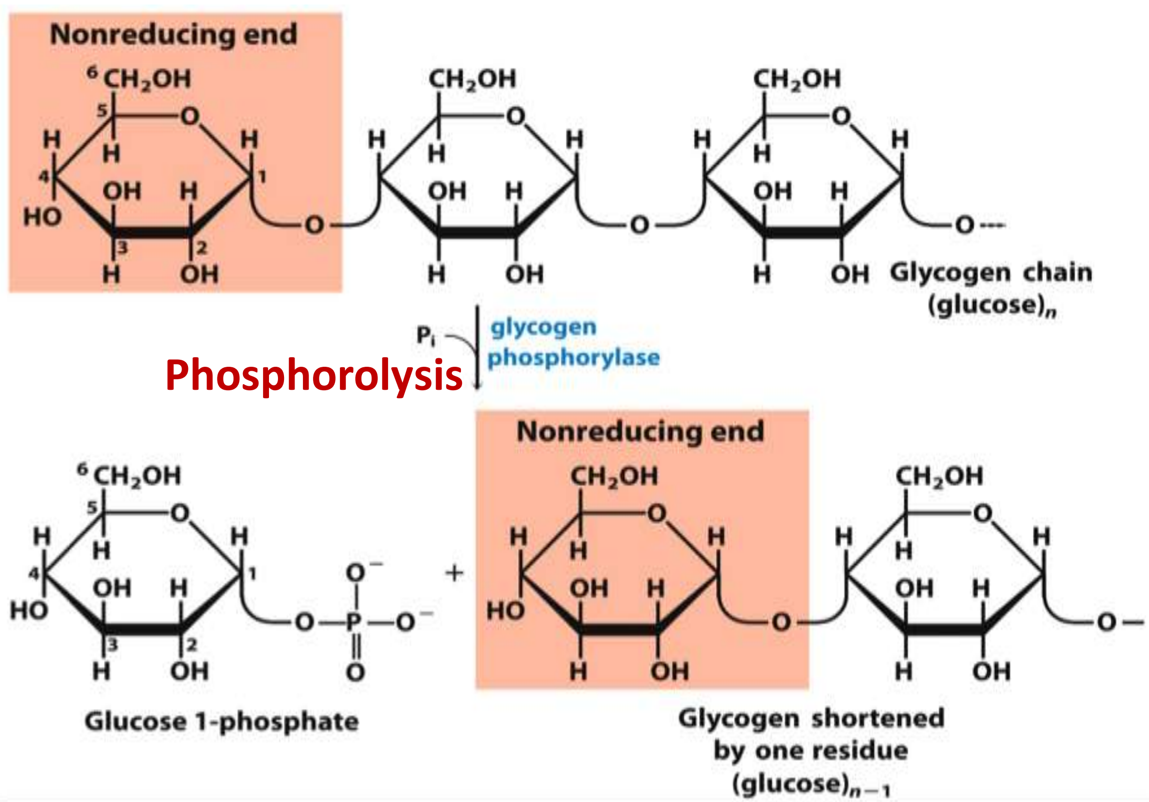


Glycogenolysis

- Glycogenolysis occurs in the cytosol of the cells primarily in liver (and any glycogen containing tissues like muscles)
- Glycogenolysis or glycogen mobilization is the breakdown of glycogen$_{(n)}$ into usable energy by sequential phosphorolytic cleavages of ($\alpha_{1\rightarrow4}$) glycosidic bonds catalyzed by glycogen phosphorylase. Each time, this enzyme cleaves single bond starting from the non-reducing ends of branches releasing one G1P unit while leaving glycogen$_{(n-1)}$ polymer

Glycogenolysis

- Phosphorylase enzyme catalyzes the phosphorolysis step "the cleavage of the bond by the addition of inorganic phosphate P_i"
- Although this cleavage reaction is slightly disfavored under standard conditions but it proceeds in this direction due relatively to high intracellular levels of inorganic phosphate (P_i)

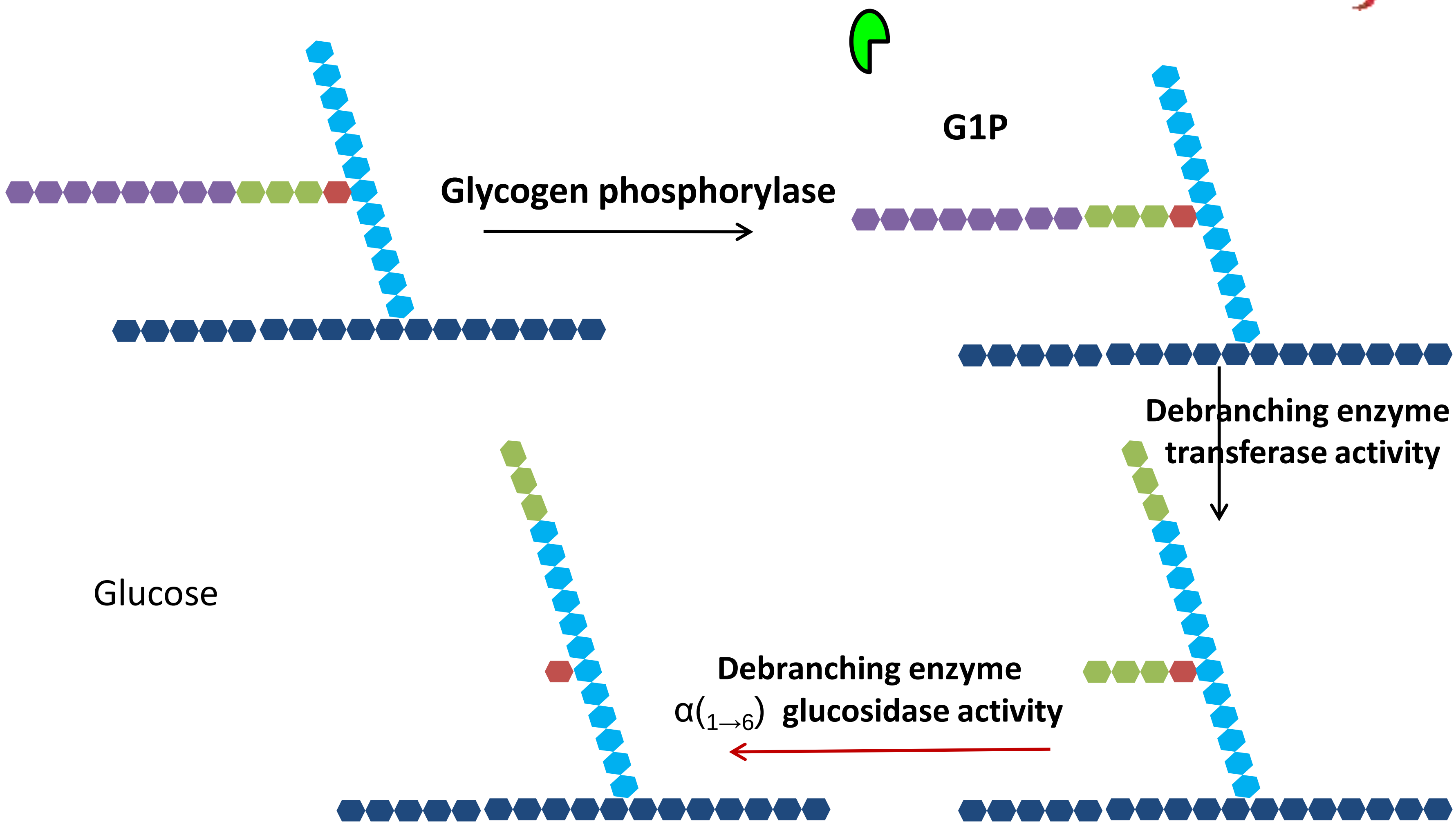


Glycogenolysis

- A second enzyme called debranching enzyme removes the branch points in two steps:

1. First "the transferase activity": the enzyme removes intact trisaccharide moiety (3 glucose units) and transfers it to the end of some other outer branch
2. Second " the ($\alpha_{1\rightarrow6}$) glucosidase activity": the enzyme removes the last glucose unit attached to the chain by ($\alpha_{1\rightarrow6}$) glycosidic bond

Glycogenolysis



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- The end result of this debranching process is the release of one glucose moiety each time
- Therefore, the end products of glycogenolysis are G1P (the major product) and glucose

Glycogenolysis

- G1P is reversibly converted via phosphoglucomutase to G6P. G6P can then be converted to glucose by glucose-6-phosphatase which is found in liver but absent from muscle and brain tissues
- Glucose released into blood from liver is distributed to other tissues in need for energy
- In muscles and brain, G6P joins the glycolysis for energy production