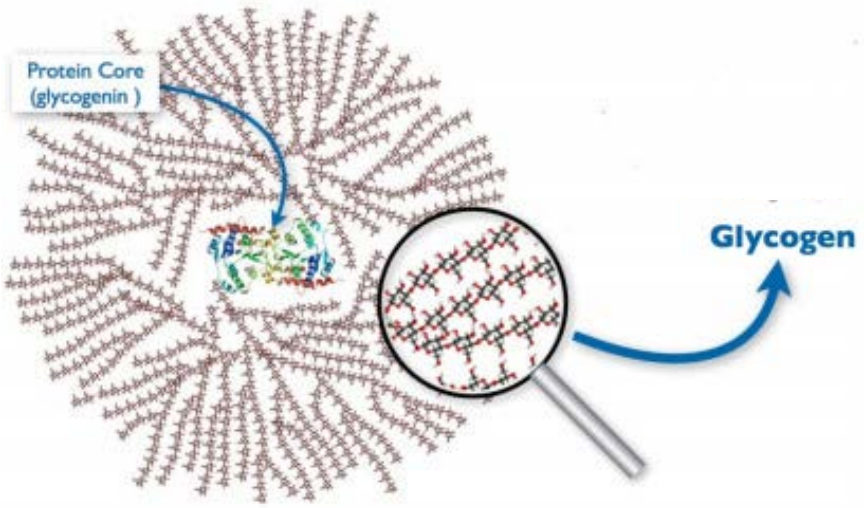
Glycogen Metabolism



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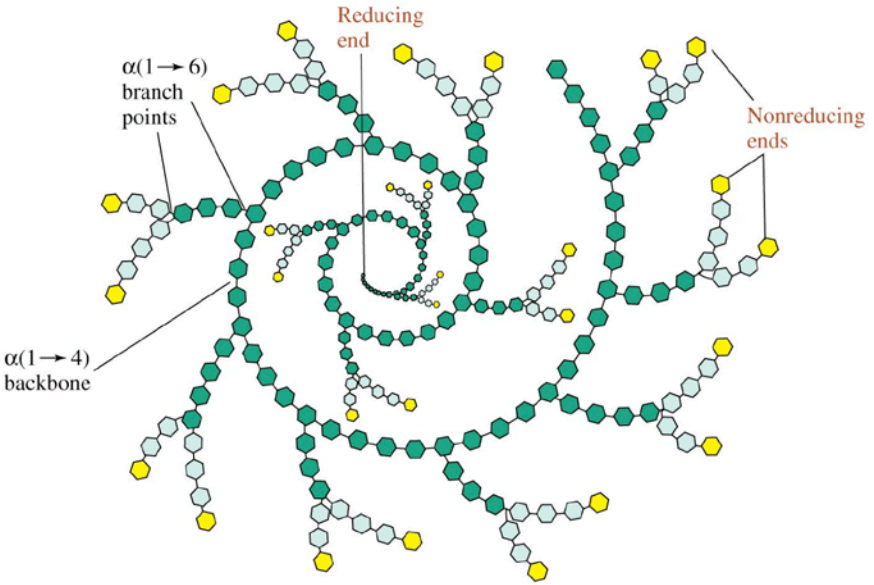
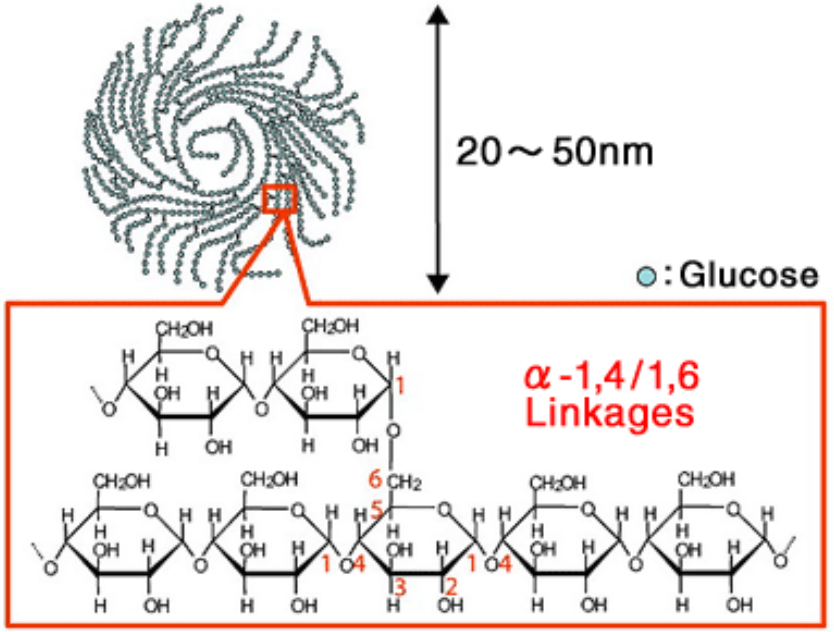
Glycogen Structu

1-start with reducing end (have free anomeric carbon atom
2-branch end →non reducing end

- 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

brain can store small amount glycogen for its own use not for other cell

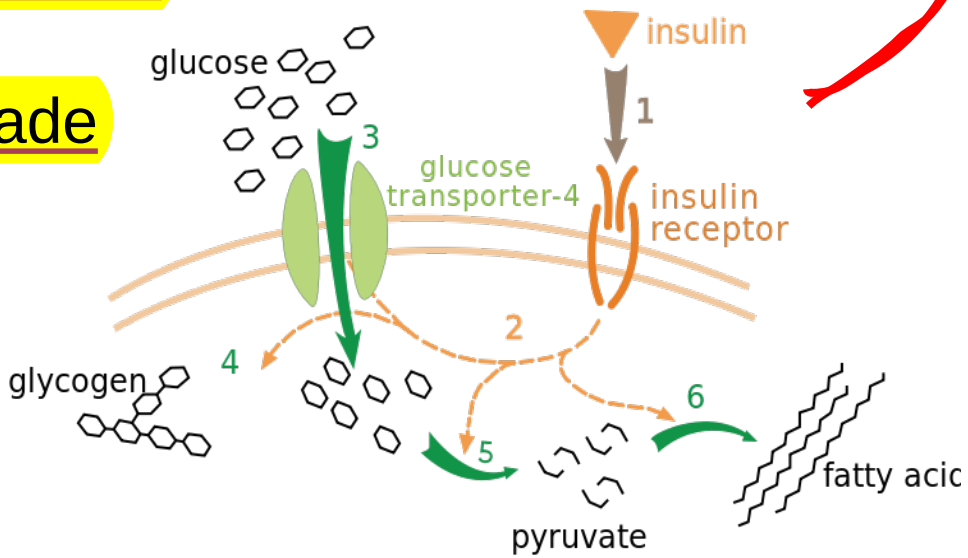
- Mainly found in skeletal muscle (up to 1-2% of muscle mass) and liver cells (up to 10% of liver mass). It is found in the cytosol as granules ranging in diameter from 10-40 nm
- Other tissues particularly the brain require a constant supply of blood glucose for survival
- Glycogen in synthesized (glycogenesis) 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 and striated muscles (skeletal and cardiac muscles). It is regulated by insulin: insulin binds its receptor and initiates downstream signaling cascade which allows the influx of glucose and consequently stimulates glycogenesis in muscles and fatty acids synthesis in adipose tissue

IN ADPIOSE TISSUE
GLUCOSE →glycolysis → pyruvate →ACETYL-COA →FATTY ACID

insulin dependent

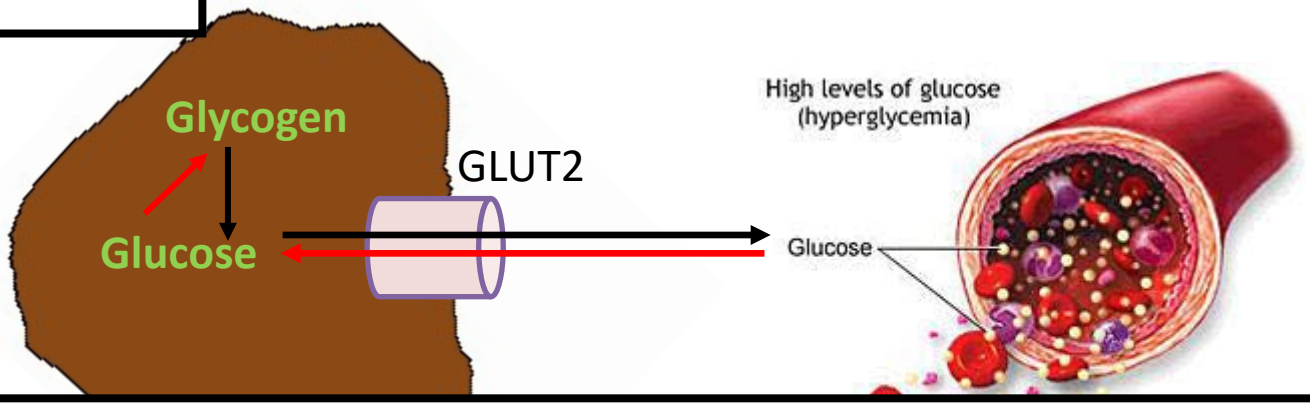


Glucose Transporter Protein

- 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)

insulin independent / facilitated diffusion

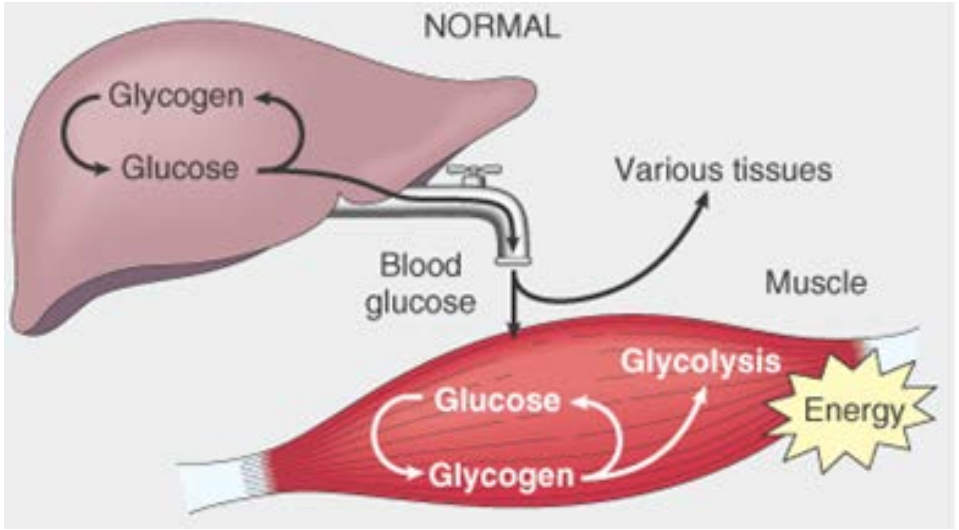
BLOOD VESEELS



1- only in liver G-6-PHOSHATASE
2- THE LIVER IS RESPOSIBLE FOR MANTAIN THE LEVEL OF BLOOD GLUCOSE NORMAL SO ↓ IN BLOOD GLUCOSE →GLYCOGENLYSIS OF GLYCOGEN TO G-6-P THEN TO GLUCOSE BY **G-6-PHOSHATASE**(PREVENT TRAP OF GLUCOSE BY REMOVE PHOSOAHTE GROUP FORM G-6-P) WHICH GET OUTSIDE BY GLUT-2
3- IN MUSCLE AND BRAIN NO G-6-PHOSHATASE SO THE GLUCOSE WILL REMAN PHOSPHOLRATED AND TRAP IT IN THER CELL FOR ITS OWN USE
4- INSULIN WILL ↑ glycogenesis and ↓ glycogenlysis in liver cell

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



waht is UDP?
1- uridine→one P →UMP
2- URIDINE → 2 P→UDP
3- URIDINE →3P→UTP

Glycogenesis

KEY ENZYME FOR GLYCOGEN SYNTESIS WHICH CALLED (GLYCOGEN SANTHASE ENZYME) ACT ONLY ON UDP-GLUCOSE
NOT ACT ON GLUCOSE

- 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

A-INSULIN ACT BY TO WAY :
1-ACT ON GLUT4 OPEN THE GATE FOR ENTERY OF GLUCOSE
2- INDUCE EXPRESSION AND ACTIVATE ENZYME RESPOSIBLE FOR GLYCOGENESIS
B→panceras WHICH HAVE GLLYT act as glucose sensor

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

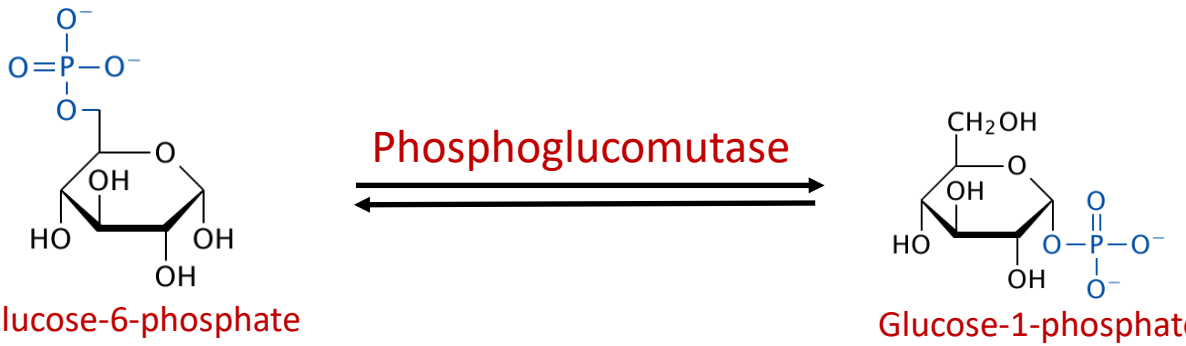
Glucose

Glucose-6-phosphate

HECOKINASE HAVE FOUR isomer different in
 expressing tissue AND other properties
- isomer 4(glucokinase) in liver+ pancreas →
1- specific for glucose not LIKE other ISOMER WHICH ARE NON-SPECIFIC
2- not inhibited by G-6-P SO IT ALLOW accumulate the G-6-P FOR GLYCOGEN IN LIVER SYNTHESIS
3- LOW AFFINTY FOR GLUCOSE →ACT ONLY WHEN HIGH LEVEL OF GLUCOSE
4- IN PANCERAS WHEN HIGH GLOCUSE LEVEL IT WILL ACT AND START TO PHOSPHOLYRATE GLUCOSE →SO IT ACT AS SENSOR FOR GLUCOSE LEVEL →B-CELL START TO SECRET INSULIN BY ITS ACTION

Glycogenesis

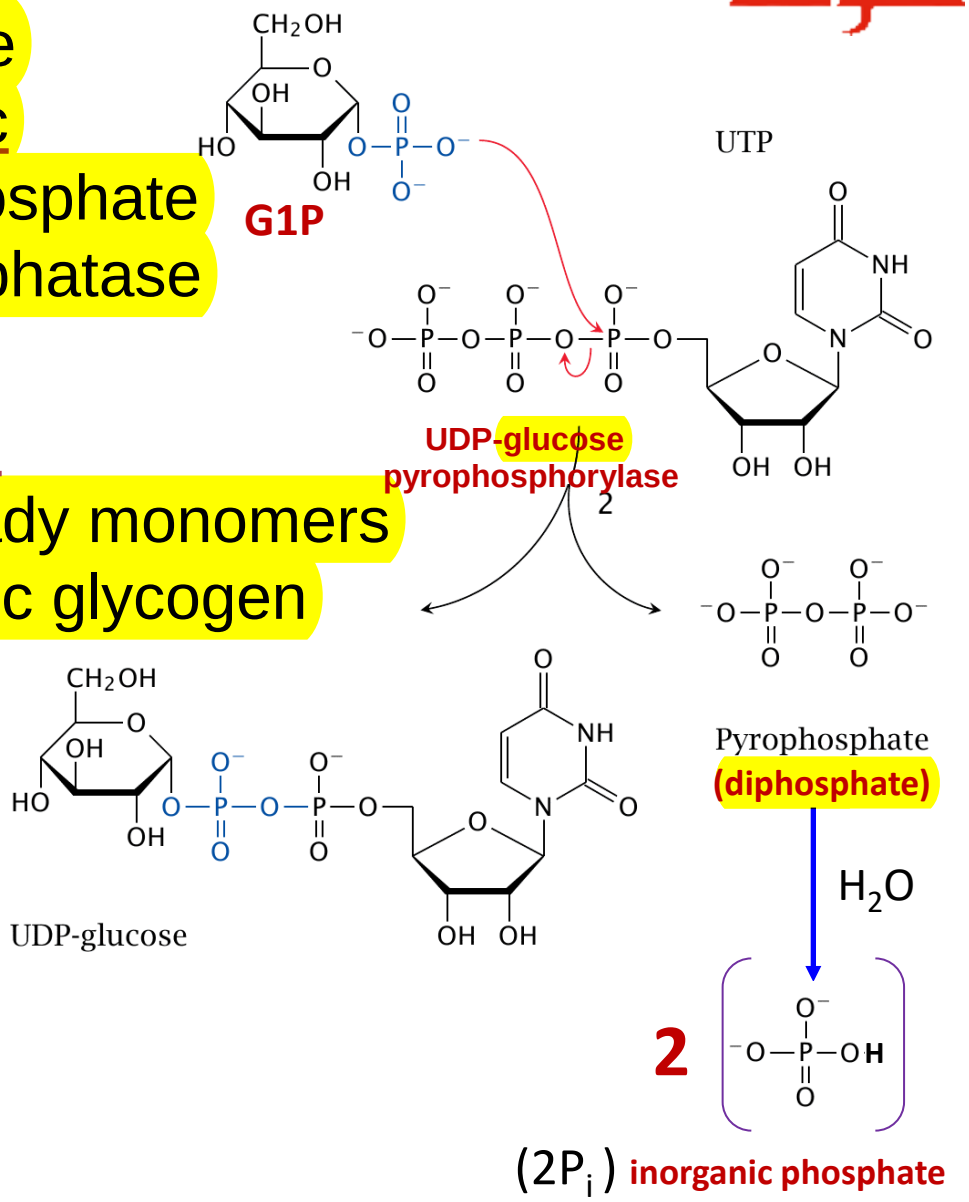
- **Step 2:** G6P is isomerized to G1P by phosphoglucomutase in a reversible reaction



- **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

ELONGATION STEP
BUT IT NEED BACKBONE TO WORK AND IT CAN ELONGATE THE PRIMER

طونله

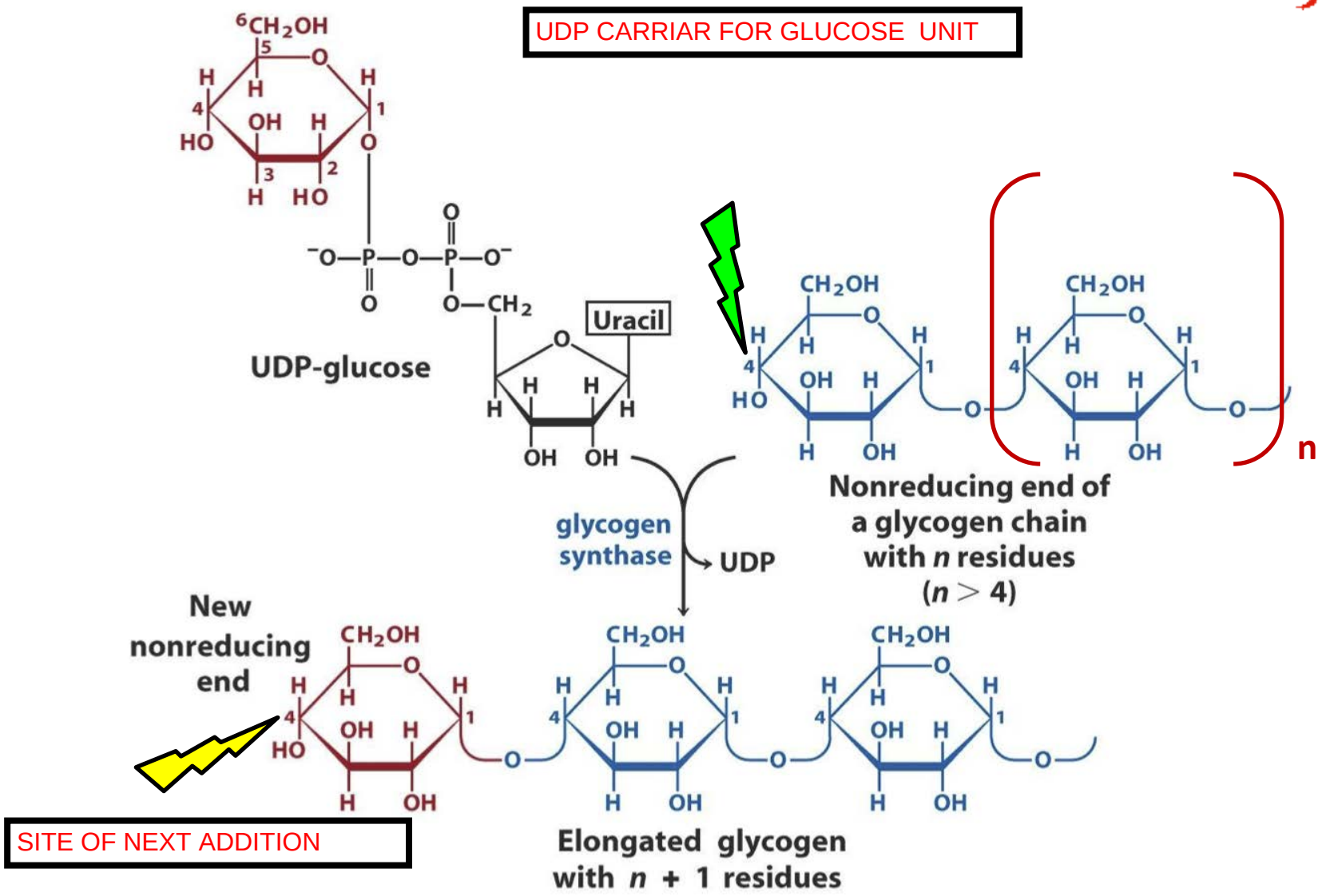
❖ The Glycogen Synthase reaction (the second phase)

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

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

- 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

Glycogenesis



Glycogen

because add glucosyl unit to non-reducing end it called

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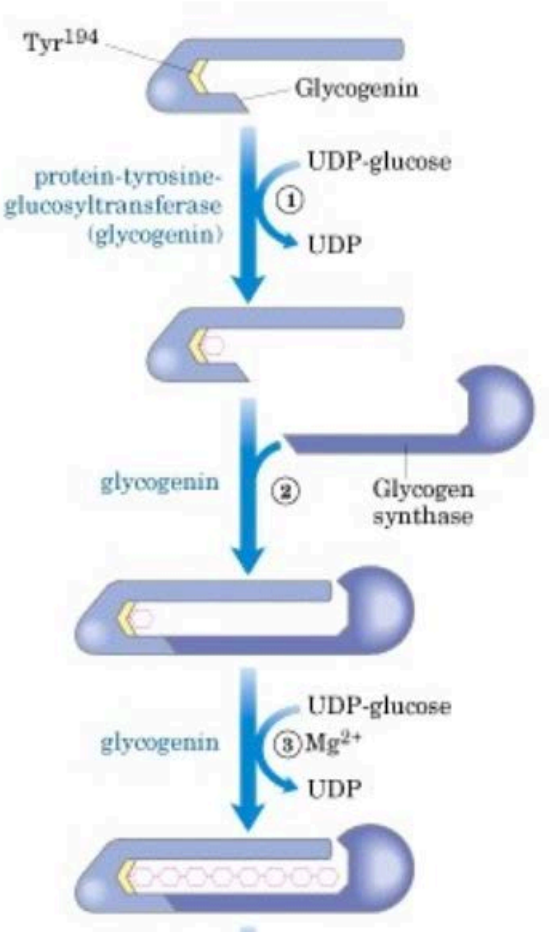
- α-1,4-glycosidic bond is formed between C1 of the transferred glucosyl moiety and C4 of the terminal glucose residue of the elongated chain
- This process is catalyzed by glycogen synthase (a glycosyltransferase enzyme)
- How is a new/nascent glycogen molecule initiated?

Glycogen Synthesis Initiation

TRANSFERASE ENZYME SO TI HAVE CATALYTIC ACTIVITY

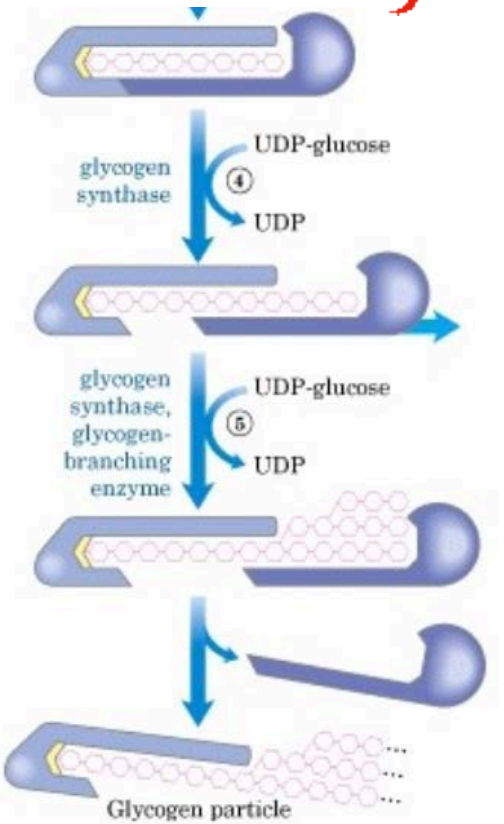
COME FROM UDP-GLUCOSE

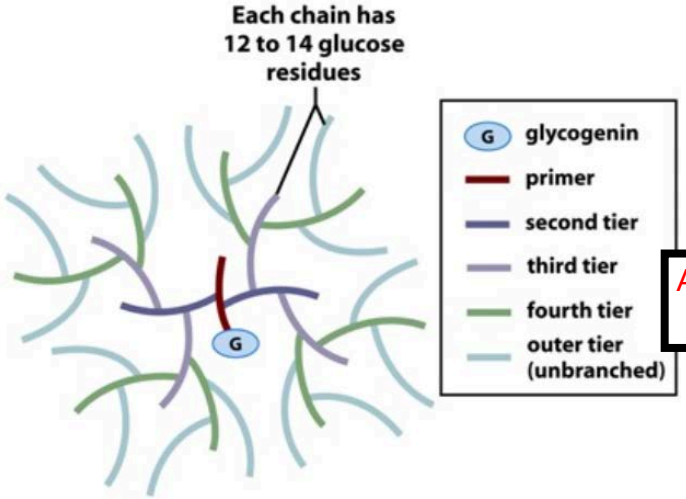
- Step 1: the first glucose is attached to tyrosine residue of a protein called glycogenin
- Step 2: glycogenin forms a tight complex with glycogen synthase
- Step 3: the chain is extended by sequential addition of up to 7 glucose residues autocatalyzed by glycogenin itself (α-1,4-glycosidic bond)
-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





ACT AS ANCHOR FOR REDUCING END OF GLYCOGEN

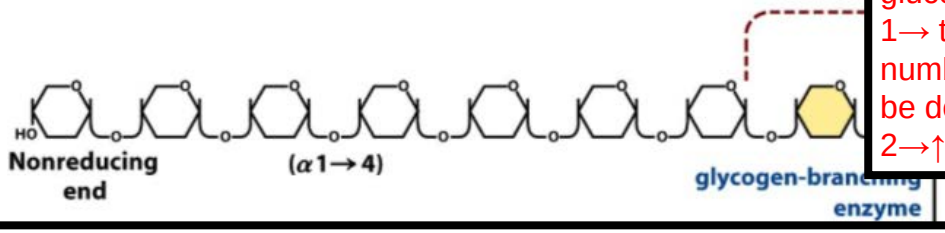
Glycogen Bran

DEBRANCHING ADD TO THE SAME CHAIN OR OTHER CAHIN
TRANSFER THEM TO MORE ANTERTIOR POINT

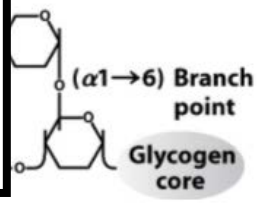
❖ Formation of branches (the third phase)

- 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

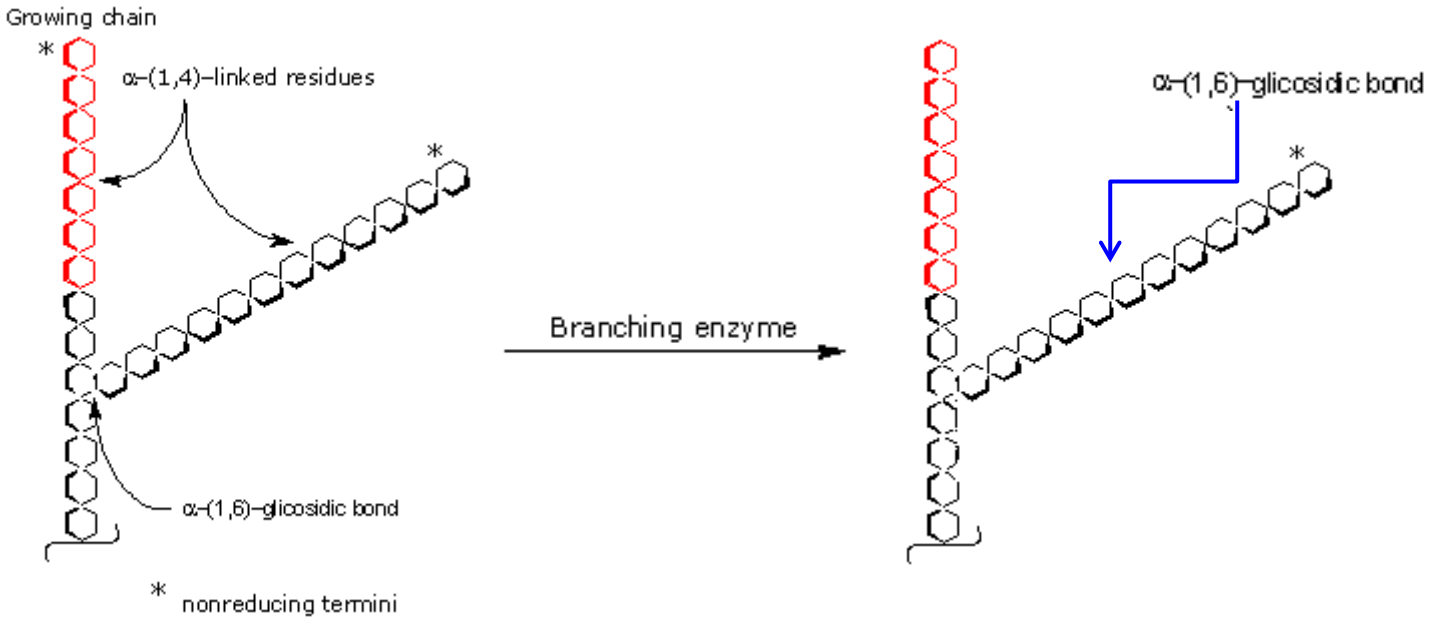
GLYOGEN: rapidly and easily mobilized form OF glucose /why it is highly branch?
1→ to be fast degradable so we have to increase number of non-reducing from which the G-1-P can be derived
2→↑ solubility



ELEVEN =7+4
SO IT WILL TAKE 7 TO MAKE NEW BRANCH SO THE FOUR WILL REMAIN IN ORIGINAL CAHIN THEY ARE ELONGATE BY ACTION OF GLYCOGEN SYNTHASE ENZYME
THE NEW BRACH ELONGATE BY ACTON OF GLYCOGEN SYNTHASE ENZYME



Glycogenesis

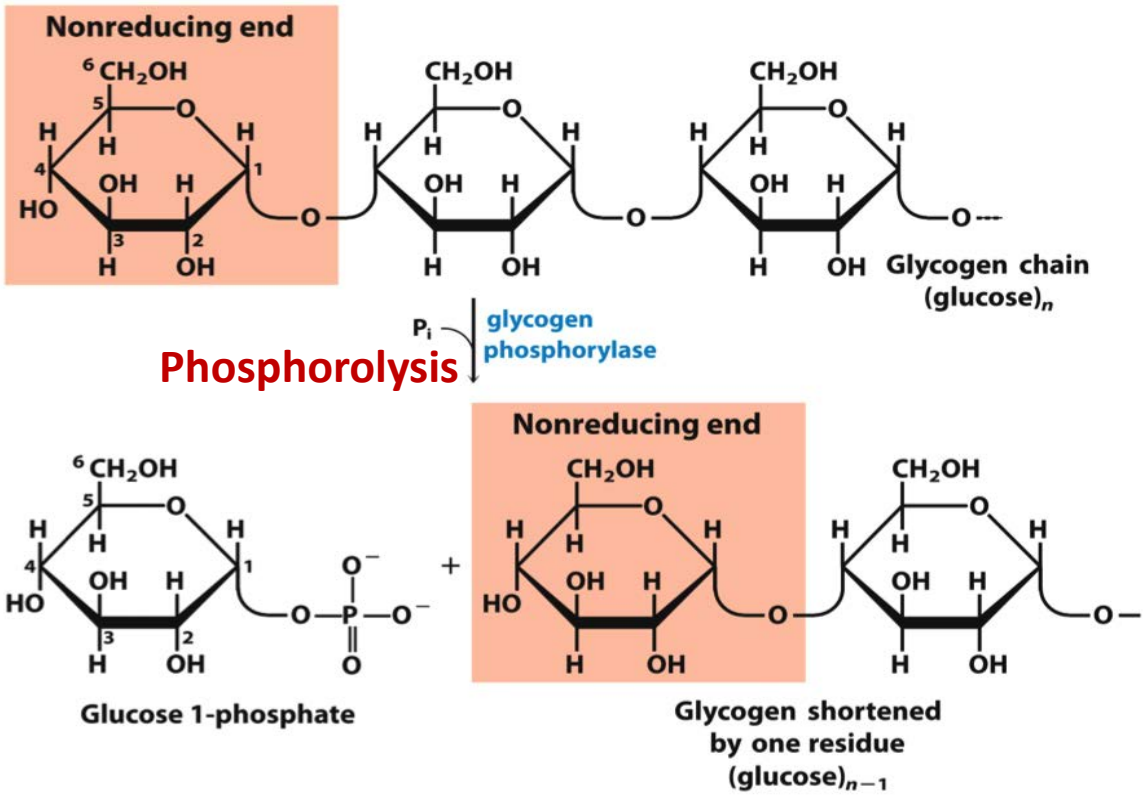


Glycogenolysis

- 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)



FRUCTOSE I.V AND HIF →↓ GLYCOGENLYSIS WHICH DEPEND ON PHOSPHROLYSIS (ADDITION OF PHOSPHATE GROUP TO CASE CLEAVAG)

Glycogenolysis

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

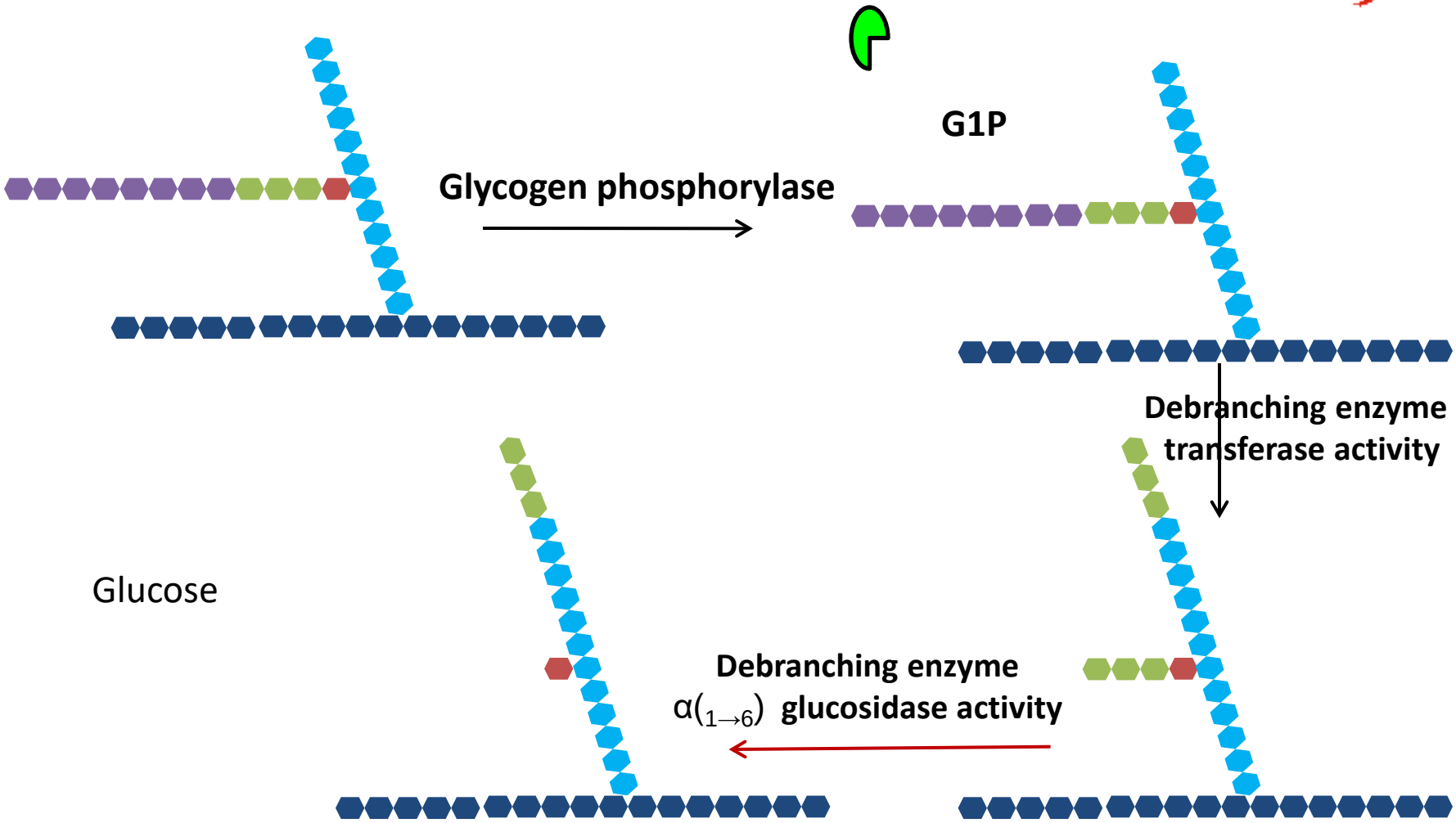
1. First "the transferase activity": the enzyme removes intact trisaccharide moiety (3 glucose units) and transfers it to the end of some other outer branch
2. Second " the ($\alpha_{1\rightarrow6}$) glucosidase activity": the enzyme removes the last glucose unit attached to the chain by ($\alpha_{1\rightarrow6}$)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

- 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

glycogen phosphorylase act on the branch until it reach last 4 glocuse molecule
it can not break them but another enzyme will come and break it we call it
debranching enzyme WHICH separate the first 3 glucose and attached them to the core of the branch and the remaining GLUCOSE ATTACHD TO THE MAIN CHAIN BY ($\alpha_{1\rightarrow6}$) SO IT CLEAVE IT AND release IT AS free glucose

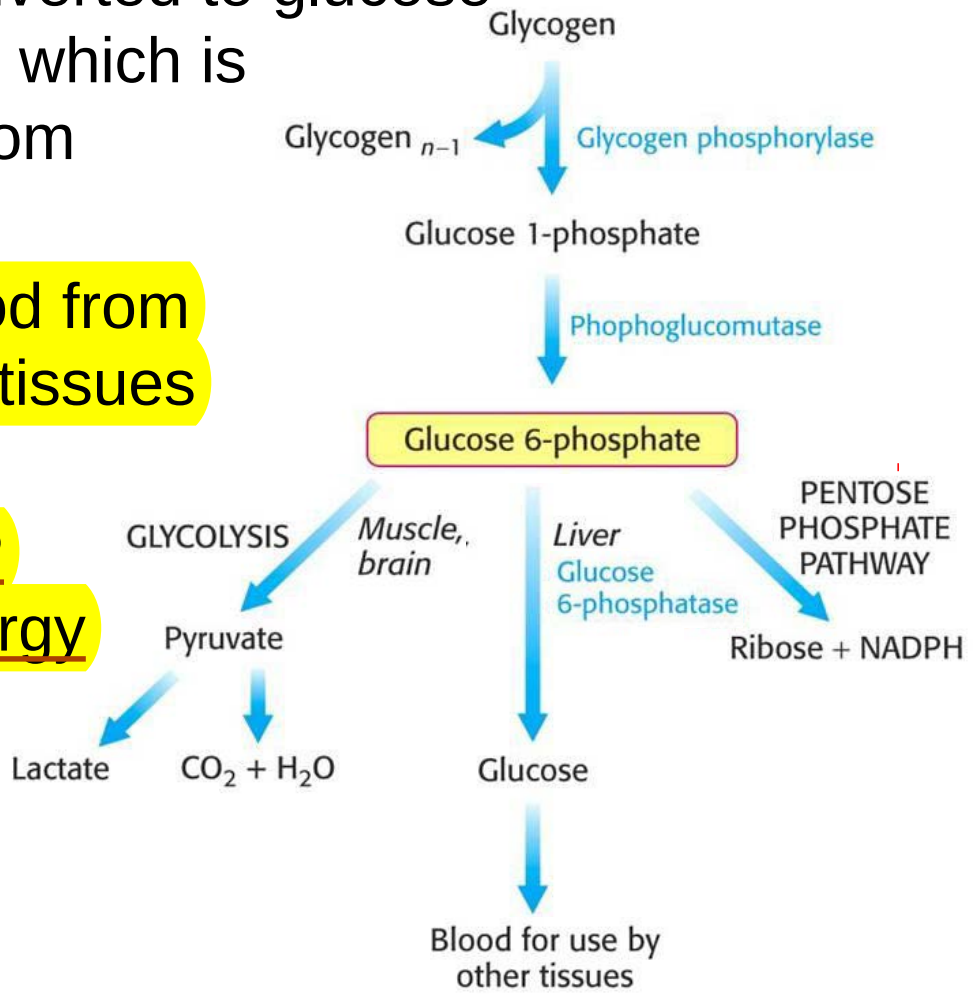
so the result of glycogenlysis is
1- glycogen phosphorylase→release G-1-P
2-debranching enzyme→release free glucose FROM EACH BRANCHING POINT

Glycogenolysis



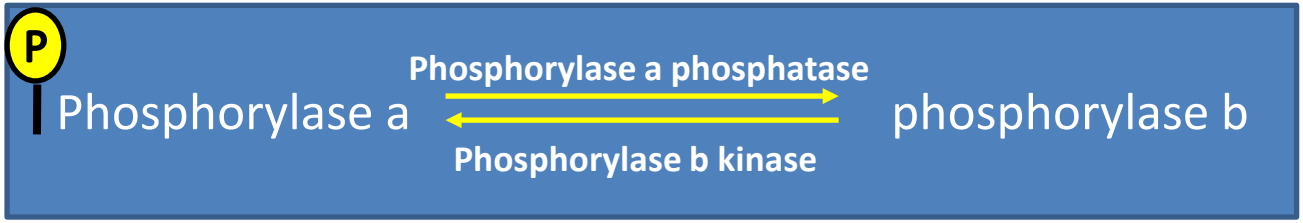
Glycogenolysis

- 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



Regulation of Glycogenolysis

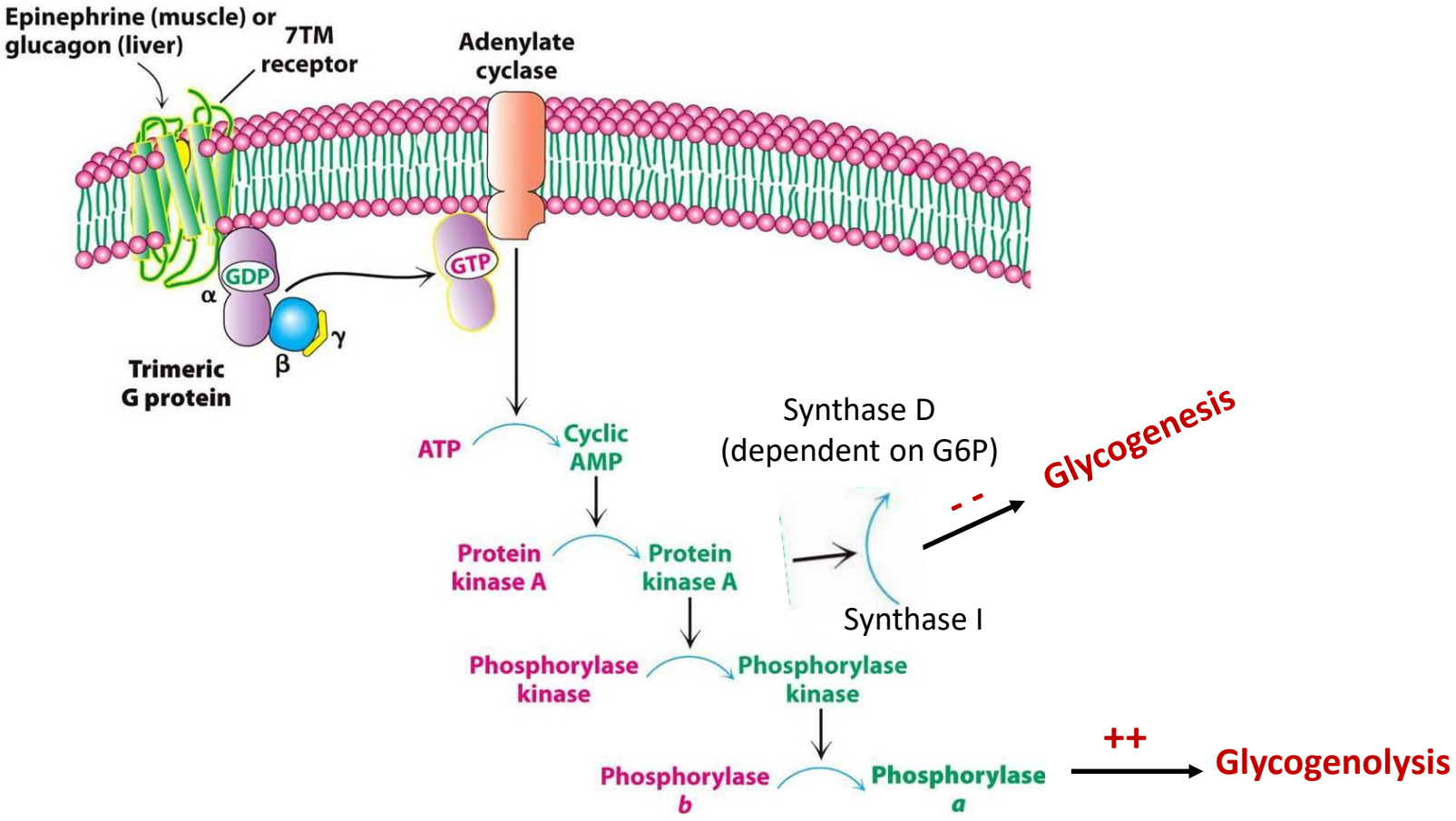
- Glycogen breakdown is under non-hormonal (allosteric) as well as hormonal regulation. Glycogen phosphorylase is the target enzyme for regulation of glycogenolysis
- Glycogen phosphorylase exists in two interconvertible forms: phosphorylase a (active) and phosphorylase b (inactive)



- Glycogenolysis is stimulated in muscle primarily by epinephrine (adrenaline) hormone secreted from the adrenal gland and in liver primarily by the pancreatic hormone glucagon

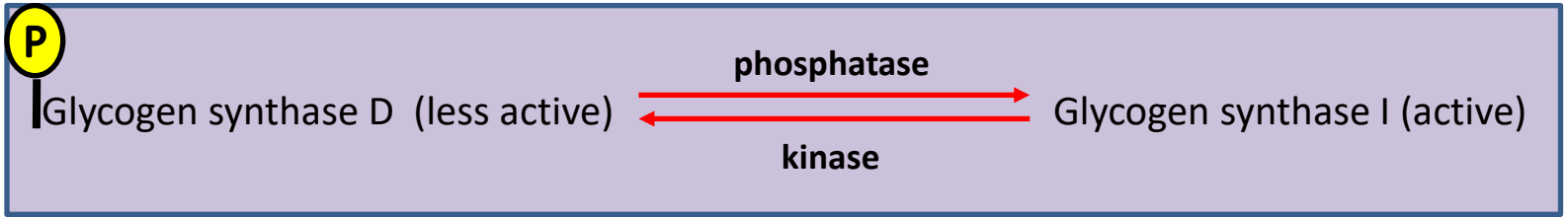
Regulation of Glycogenolysis

- The effect of these hormones is mediated by the second messenger pathways (cAMP) which is under the control of adenylate cyclase . Actually, this effect is amplified



Reciprocal Relationship between Glycogenolysis & glycogenesis

- Conditions that activate glycogenolysis inhibit glycogenesis and vice versa. Therefore, epinephrine and glucagon secretion inhibit glycogen synthesis. This happens due to cAMP-mediated inhibition of glycogen synthase



- So phosphorylation of glycogen synthase inhibits its activity only in the absence of G6P (which is an allosteric activator of glycogen synthase)
- Epi/glucagon inhibit glycogenesis only in the absence of G6P

Reciprocal Relationship between Glycogenolysis & glycogenesis

- Allosteric regulation: G6P is an allosteric activator of glycogen synthase (glycogenesis)
- Hormonal regulation: epinephrine (in muscle) and glucagon (in liver) stimulate glycogenolysis and inhibit glycogenesis through the cAMP. In contrast, insulin (secreted from the beta cells of pancreas) activates glycogenesis and inhibit glycogenolysis both in muscle and liver by inducing dephosphorylation of glycogen phosphorylase (inactive b form) and glycogen synthase (active I form)
- Unlike allosteric regulation, hormonal regulation is mediated through covalent modification of key enzymes by phosphorylation/dephosphorylation mechanism

Reciprocal Relationship between Glycogenolysis & glycogenesis