King Saud University
College of Sciences
Biochemistry Department

الأيض (١)
Metabolism (1)
BCH 340

Lecture 6: Metabolism of Glycogen

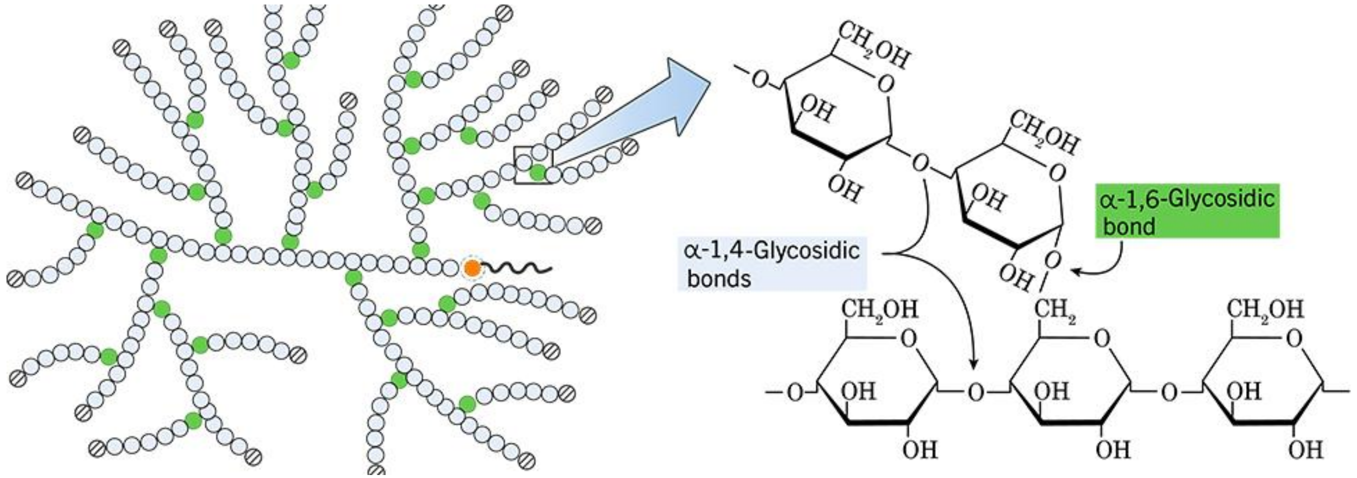
Intended learning outcomes (ILOs)

By the end of this lecture, students will be able to:

- Identify the structure and function of glycogen.
- Explain the process of glycogenesis, including the enzymes involved.
- Describe the process of glycogenolysis and the enzymes responsible for breaking down glycogen.
- Recognize the importance of glycogen metabolism in maintaining blood glucose levels and energy supply.
- Explain how hormonal and allosteric regulators influence glycogen synthesis and degradation.

Glycogen structure

- Glycogen is a complexed branched-chain homopolysaccharide made of α-D-glucose units linking together by glycosidic bonds:
  - The majority of the glucose residues in glycogen are connected by α-(1→4) glycosidic bonds, forming linear chains.
  - At regular intervals along the linear chains, there are branch points created by α-(1→6) glycosidic bonds. These branching points allow for the highly branched structure of glycogen.



Function of glycogen

- Glycogen serves as the primary storage form of glucose in animals (it is predominantly found in the liver and skeletal muscles).

Liver glycogen:

- It serves as a dynamic reservoir to maintain blood glucose levels.
  - During the well-fed state, excess glucose is taken up by the liver and converted into glycogen through glycogenesis.
  - During fasting, liver glycogen is broken down into glucose through glycogenolysis, contributing to the maintenance of blood glucose levels.

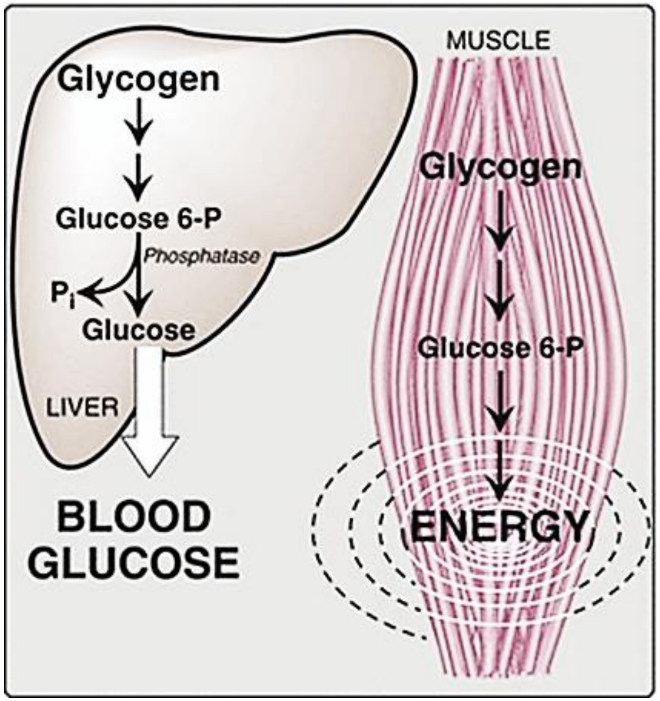
Function of glycogen (cont.)

Muscles glycogen:

- It provides a local source of energy for muscle contraction during physical activity.
  - Muscles utilize glycogen as an immediate energy source during high-intensity exercise.
  - Glycogenolysis in muscles supports the energy demands of working muscles.

Function of glycogen (cont.)

- Liver and muscle glycogen stores **are interconnected in the overall energy metabolism** of the body:
  - During prolonged exercise or fasting, liver glycogen contributes to maintaining blood glucose levels, while muscle glycogen supports muscle function.



Synthesis of glycogen (glycogenesis)

- Glycogenesis is an energy-consuming process by which α-D-glucose is converted into glycogen.
- This process occur in the cytosol of mainly liver and muscle cells.

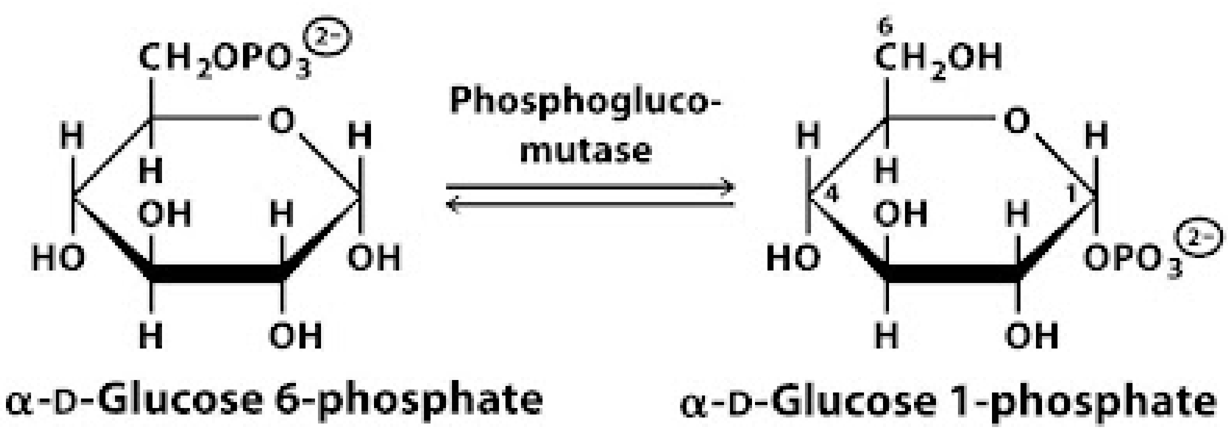
It plays a vital role in maintaining glucose homeostasis:

- Excess glucose is stored in the form of glycogen when blood glucose levels are high (such as after a meal).
- Glycogen provides a readily available source of energy for the body during fasting or increased energy demand.

Steps of glycogenesis

i. Formation of glucose 1-phosphate:

- First step in the synthesis of glycogen is the phosphorylation of glucose to glucose 6-phosphate by hexokinase/glucokinase (in muscles or liver, respectively).
- Glucose 6-phosphate is then converted to glucose 1-phosphate by phosphoglucomutase.

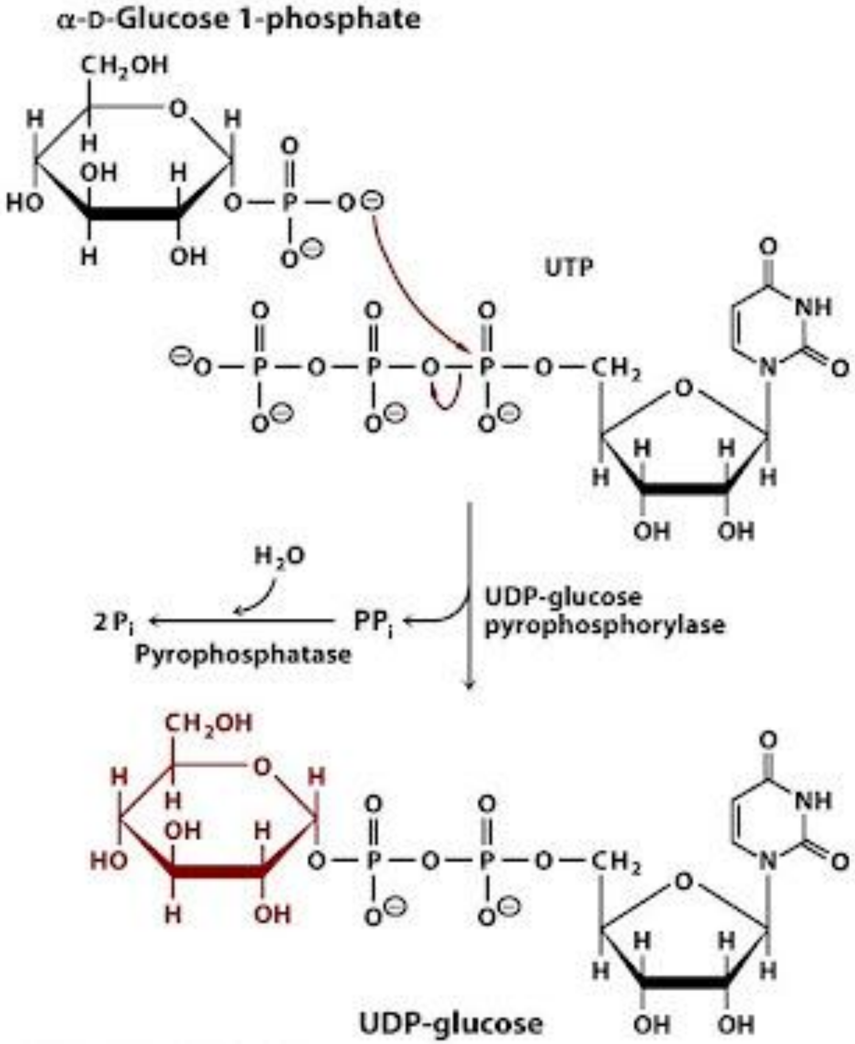


Steps of glycogenesis (cont.)

ii. Synthesis of UDP-glucose:

- Glucose 1-phosphate reacts with UTP (uridine triphosphate) to form active UDP-glucose, releasing pyrophosphate (PPi).

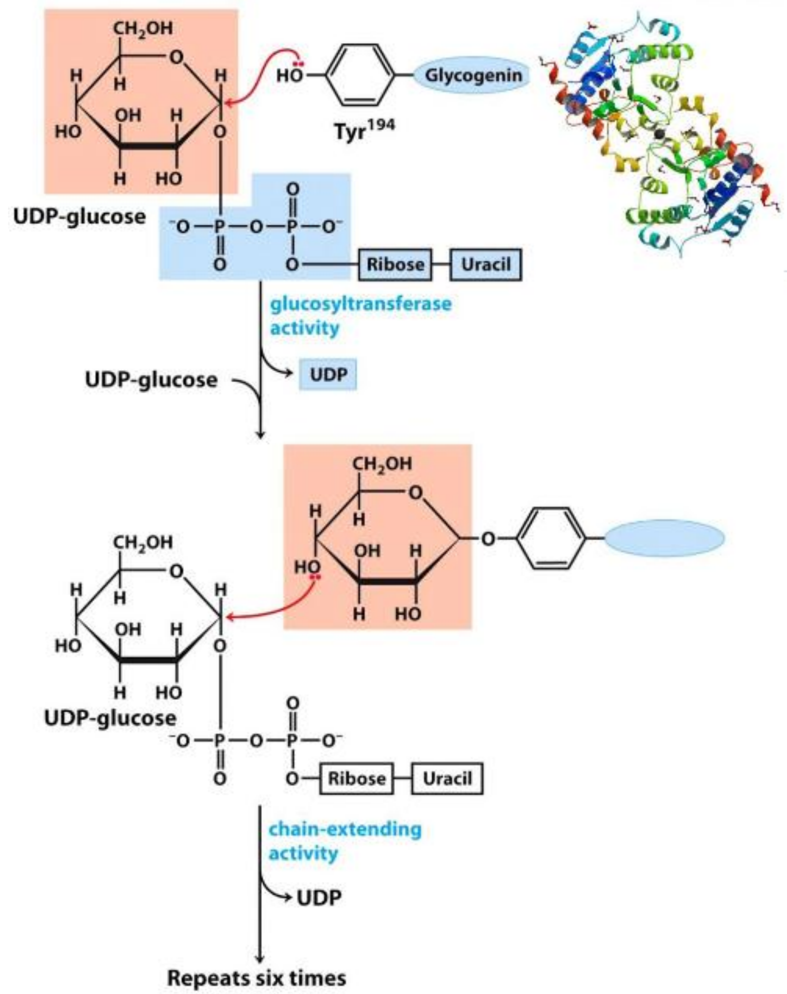
- This reaction is catalyzed by the enzyme UDP-glucose pyrophosphorylase.



Steps of glycogenesis (cont.)

iii. Attachment to glycogenin:

- The newly formed UDP-glucose is attached to a small protein primer called glycogenin, which initiate glycogen chain elongation.
- A glucose molecule is covalently attached to a tyrosine residue on glycogenin through a glycosidic bond, releasing UDP.
- The enzyme (glycogenin) catalyzes the addition of the first several glucose units, typically around 8-12, forming an oligosaccharide chain, linked by α-(1→4) glycosidic bonds.



Steps of glycogenesis (cont.)

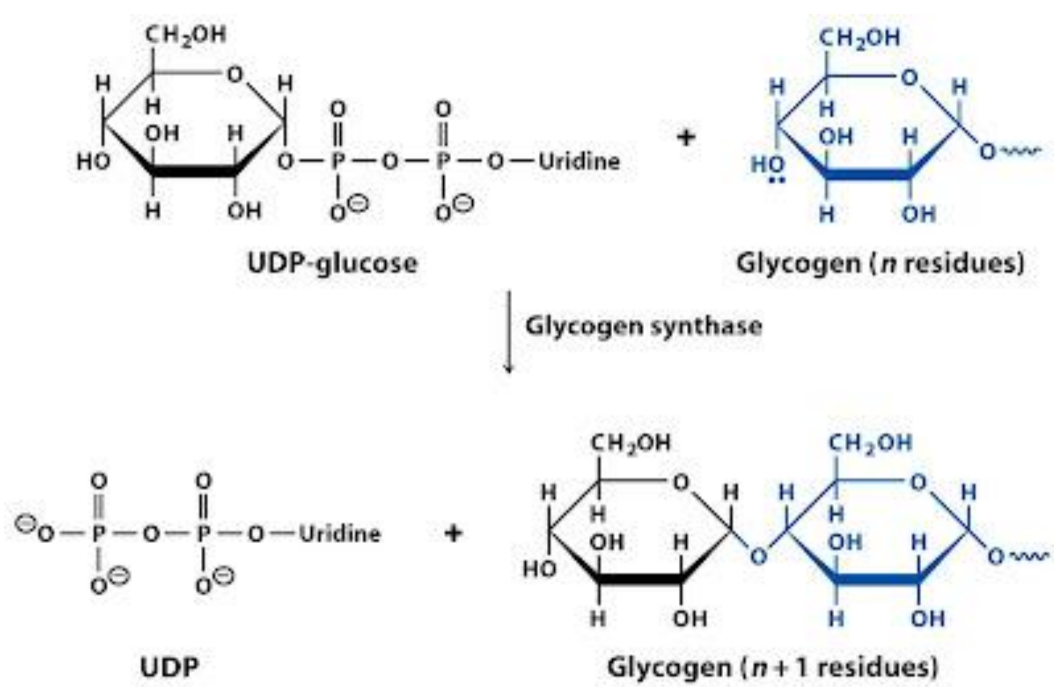
iv. Glycogen chain elongation:

- Once the oligosaccharide chain reaches a certain length, glycogen synthase takes over the elongation of the glycogen molecule.

- Glycogen synthase adds additional UDP-glucose units to the glycogen primer, extending the chain by creating α-(1→4) glycosidic linkages.

- UTP is regenerated from UDP in a reaction catalyzed by nucleoside diphosphokinase:

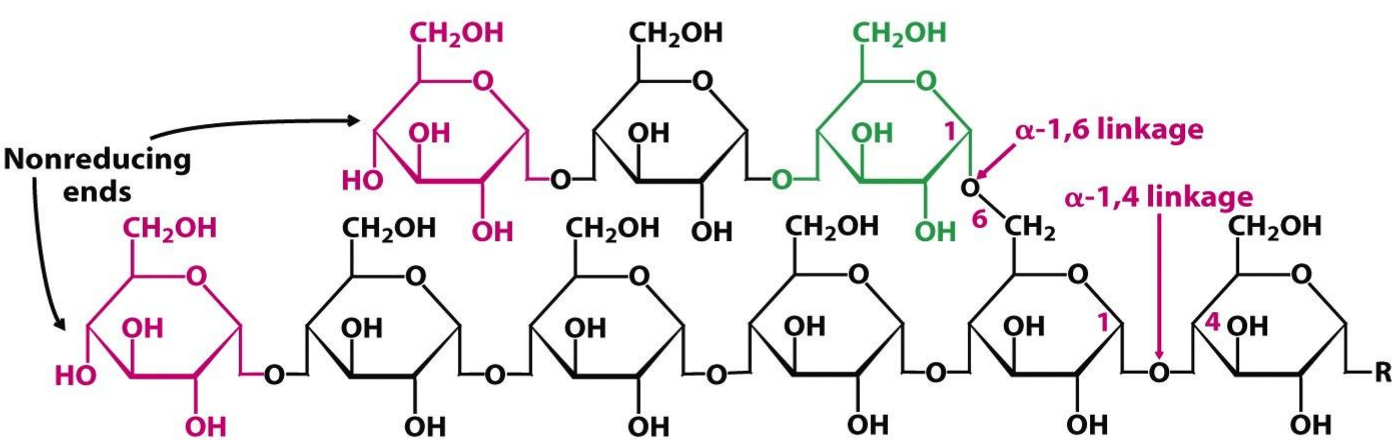
  UDP + ATP → UTP + ADP



Steps of glycogenesis (cont.)

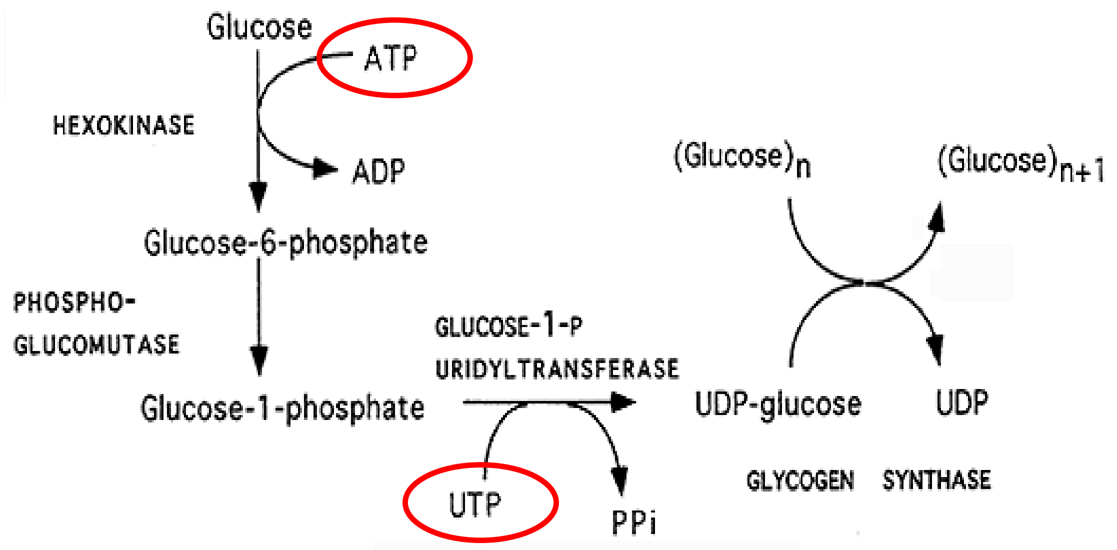
v. Branching of glycogen chains:

- The branching enzyme (amylo-(1,4→1,6)-transglycosylase) is responsible for creating branching points.
- It transfers a portion of the growing chain (six glucose residues) onto another position within the same or a neighboring chain, forming α-(1→6) glycosidic linkages.
- The new branches are elongated by glycogen synthase.
- The branching points are typically found every 8 to 12 glucose residues.



Energy cost of glycogenesis

- The incorporation of one glucose molecule to glycogen is an endergonic process that consumes energy supplied by ATP and UTP as following:
  - The first phosphorylation reaction by hexokinase/glucokinase (Step 1) consumes one molecule of ATP.
  - The glucose activation reaction catalyzed by UDP-glucose pyrophosphorylase (Step 3) requires one molecule of UTP.



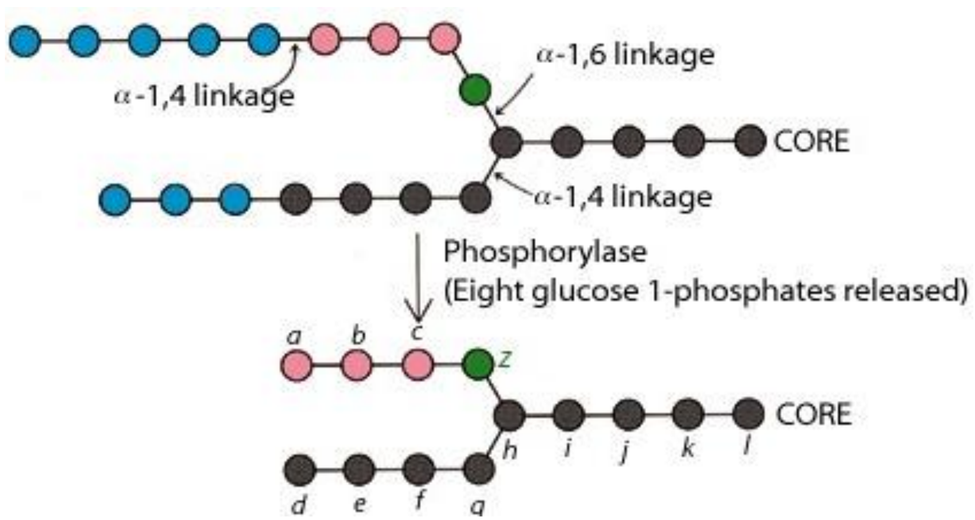
Degradation of Glycogen
(glycogenolysis)

- The degradation of glycogen (glycogenolysis) is the process by which glycogen is broken down into glucose molecules to provide a quick and accessible source of energy.
- Glycogen degradation is NOT a reversal of the glycogen synthesis pathway.
- This process occurs in response to energy demands, such as during fasting or intense physical activity.
- The enzymes involved in this process include:
  - Glycogen phosphorylase
  - Glycogen debranching enzyme

Steps of glycogenolysis

i. Shortening of chains:

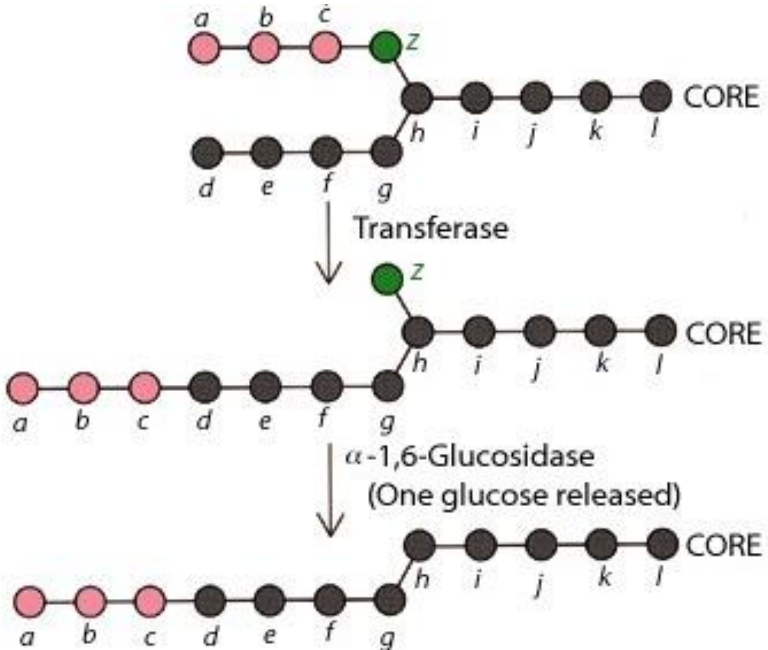
- Glycogenolysis is initiated by the activation of glycogen phosphorylase, an enzyme that catalyzes the sequential phosphorolytic cleavage of glucose from the non-reducing ends of glycogen chains.
- Glycogen phosphorylase acts on α-(1→4) glycosidic bonds, releasing glucose 1-phosphate.
- The enzyme works until it reaches the fourth glucose unit before a branching point.



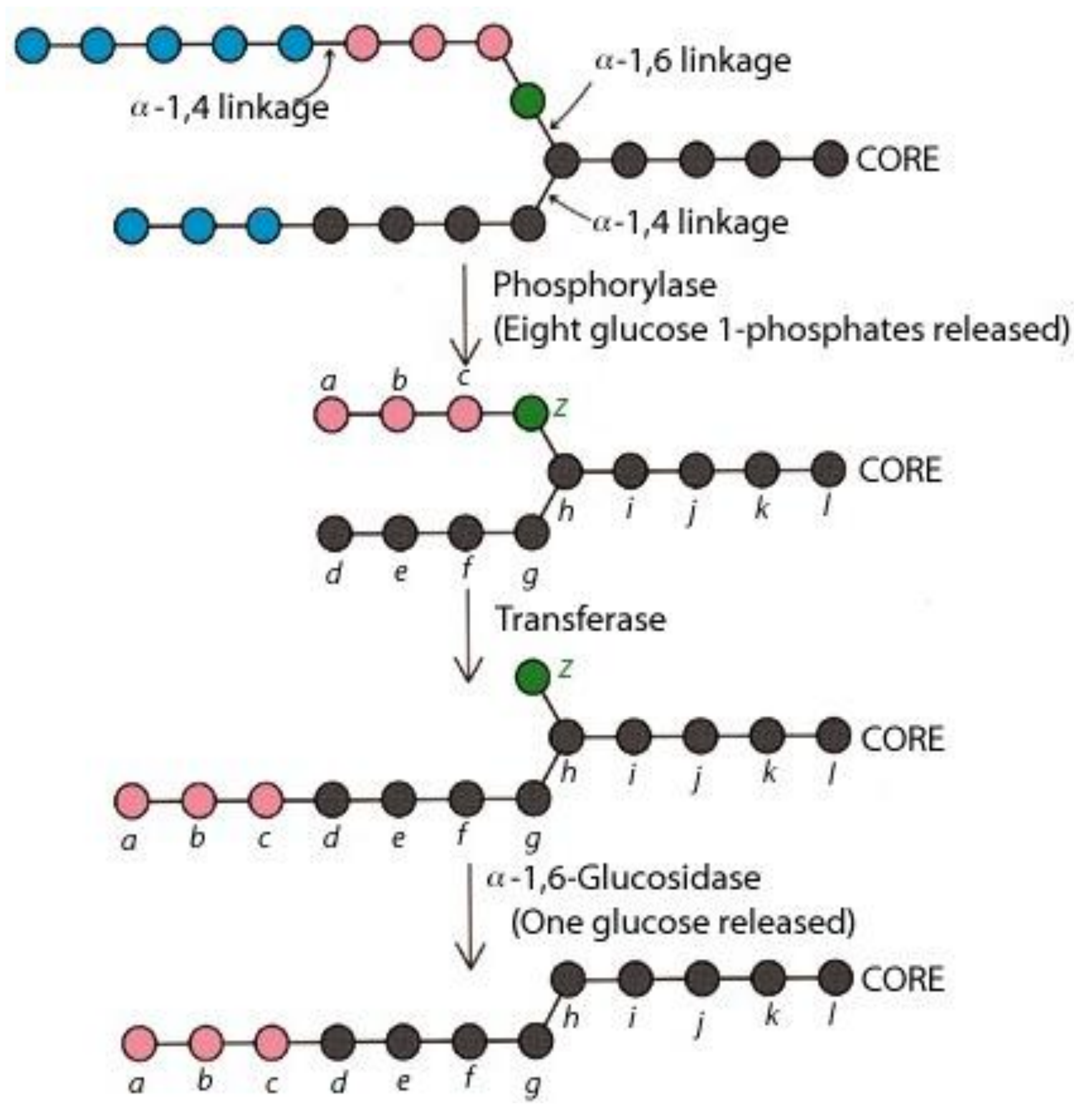
Steps of glycogenolysis (cont.)

ii. Removal of branches:

- The glycogen debranching enzyme has two activities; transferase activity and amylo-α-1,6-glucosidase activity:
  - By the transferase activity, the enzyme moves a block of three glucose residues from one branch to the main chain, leaving only one glucose residue at the branch point.
  - The glucosidase activity allows the enzyme to cleave the remaining glucose residue at the branch point (i.e. cleaves the α-(1→6) glycosidic bond), releasing a free glucose molecule.



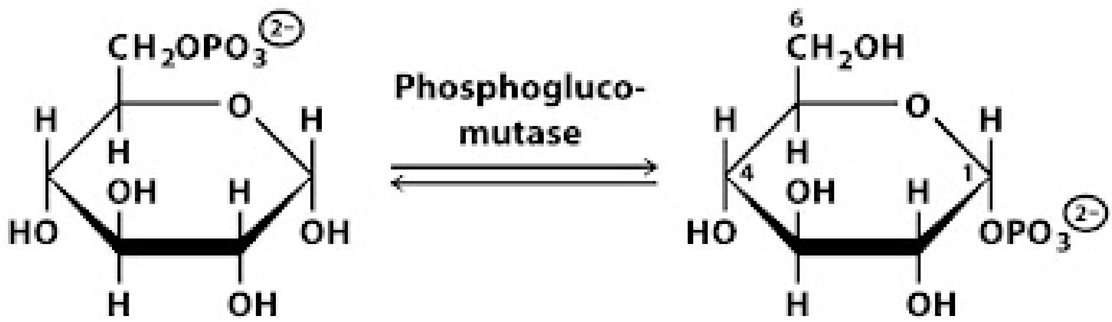
Overview of glycogenolysis



Steps of glycogenolysis (cont.)

iii. Formation of glucose 6-phosphate:

- The glucose 1-phosphate produced by the action of glycogen phosphorylase is converted to glucose 6-phosphate by the enzyme phosphoglucomutase.

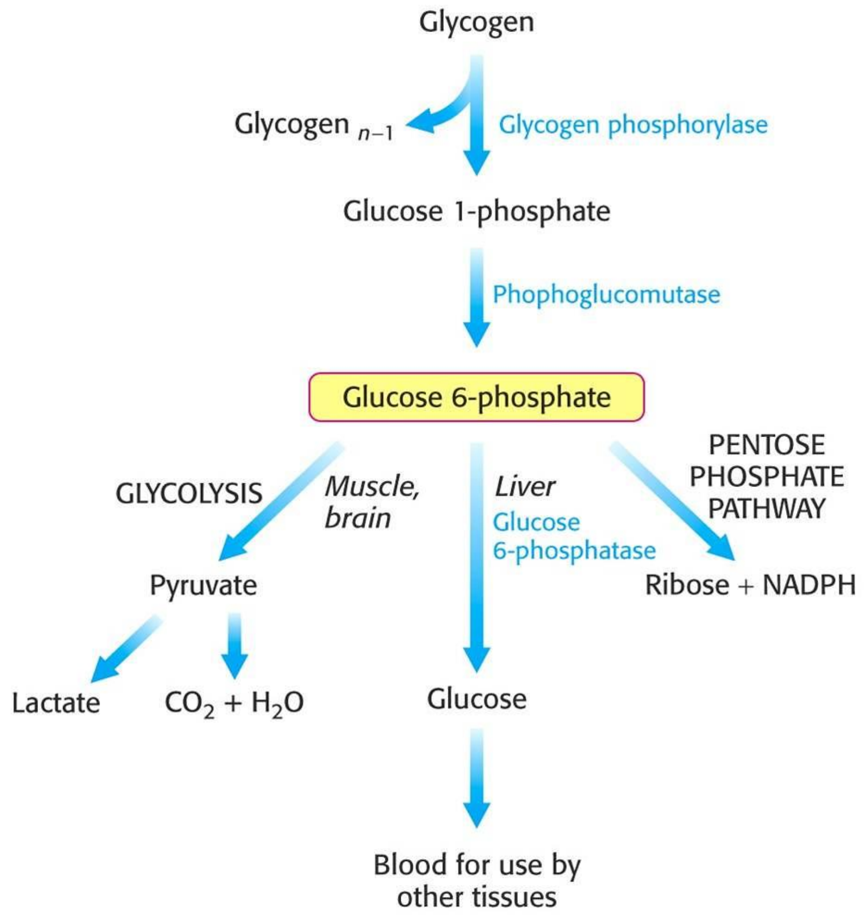


α-D-Glucose 6-phosphate   α-D-Glucose 1-phosphate

Fates of glucose 6-phosphate

Glucose 6-phosphate is a key intermediate in glucose metabolism:

- It can be further hydrolyzed to produce free glucose in the liver (by the action of glucose 6-phosphatase) and released into the blood to maintain a relatively level of blood glucose.
- It can enter glycolysis, where it is metabolized to produce energy in the form of ATP (in the muscles).
- It can be used in the pentose phosphate pathway, which generates NADPH and ribose-5-phosphate.



Regulation of glycogen metabolism

- Regulating glycogen metabolism is crucial for maintaining glucose homeostasis:
  - Ensuring a constant supply of glucose for energy production.
  - While preventing excessive glucose levels.

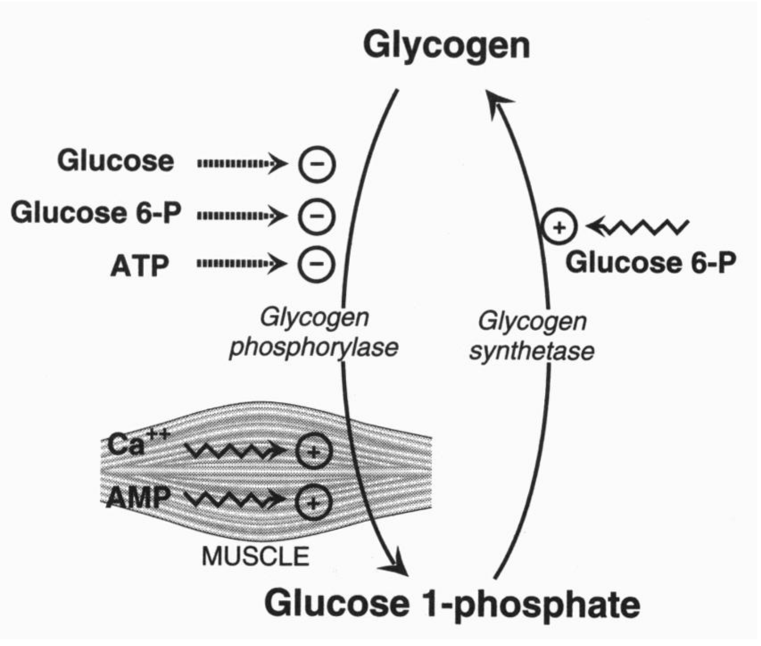
- The storage and utilization of glucose (in the form of glycogen) are complex processes that involve:
  - Allosteric regulation (regulating several enzymes involved in glycogen synthesis and degradation).
  - Hormonal regulation (through covalent modification; phosphorylation).

Allosteric regulation

- Glycogen synthase and glycogen phosphorylase respond to the levels of metabolites and energy needs of the cell.
  - Therefore, glycogen synthesis is activated when substrate availability and energy levels are high.
  - Whereas, glycogen degradation is stimulated when glucose supplies and energy levels are low.

Allosteric regulators for glycogen synthase:

-High levels of glucose 6-phosphate activate glycogen synthase, promoting glycogen synthesis.



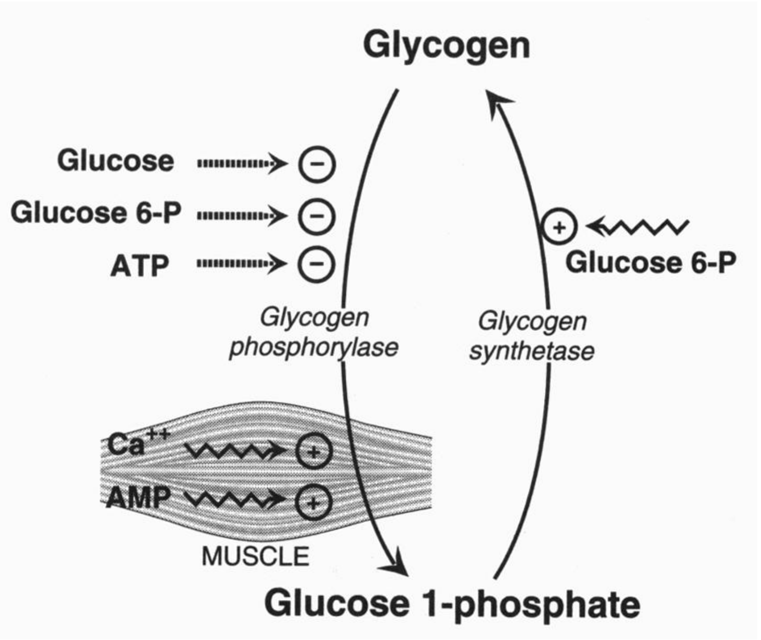
Allosteric regulation (cont.)

Allosteric regulators for glycogen phosphorylase:

- High levels of glucose, glucose 6-phosphate, and ATP inhibit glycogen phosphorylase, preventing unnecessary degradation of glycogen when glucose is abundant.
- Conversely, low ATP levels (or high AMP levels in muscles), signaling low energy status, activate glycogen phosphorylase, promoting glycogenolysis.

Note:

- Glycogen phosphorylase in muscle is subjected to allosteric regulation by AMP, ATP, and glucose 6-phosphate.
- A separate isozyme of glycogen phosphorylase expressed in liver is less sensitive to these allosteric regulators.



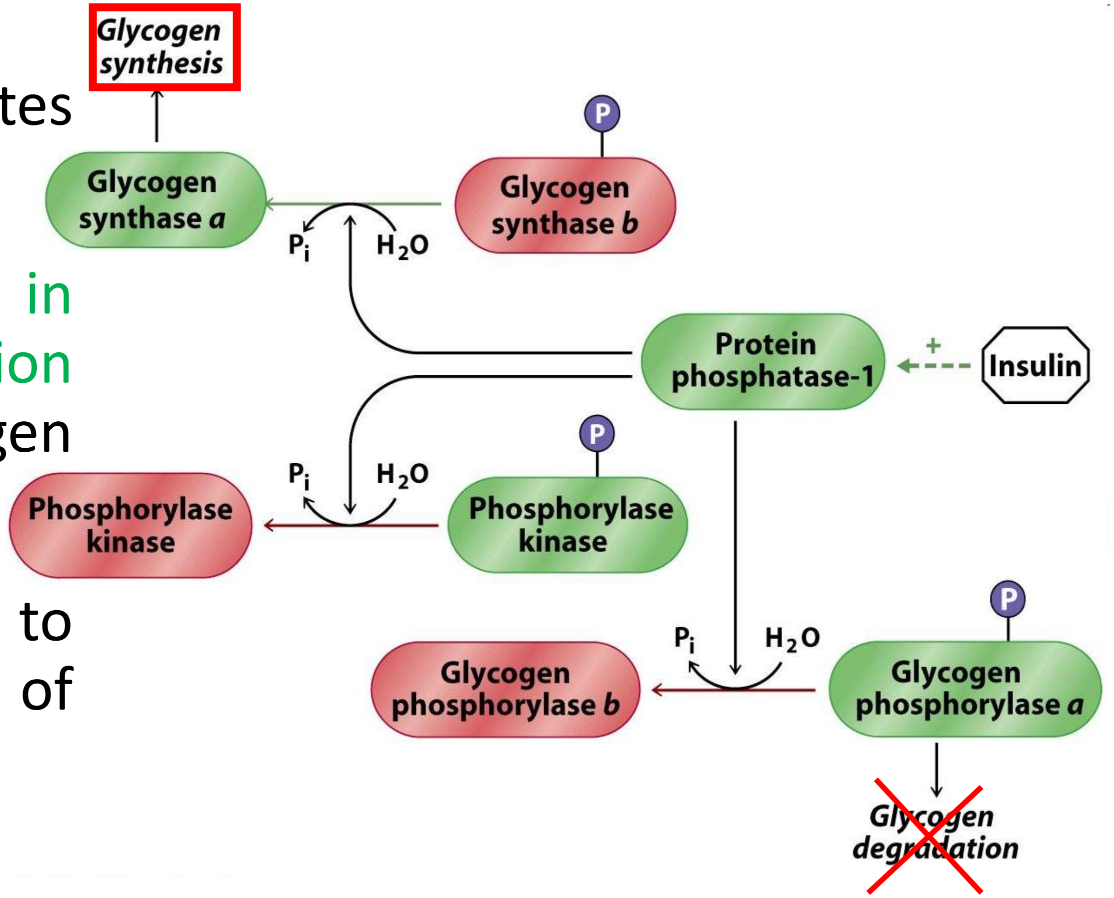
Hormonal regulation

Insulin:

- Insulin release from the β-cells of the pancreas is stimulated by elevated blood glucose levels (typically after a meal).
- Insulin binds to its receptor on the cell membrane of target cells (primarily liver and muscle cells).
- The insulin signaling pathway involves a series of (sequential phosphorylation and dephosphorylation) steps that lead to:
  - The activation of glycogen synthase, the enzyme responsible for glycogen formation.
  - The inhibition of glycogenolysis by suppressing the activity of glycogen phosphorylase.

Hormonal regulation (cont.)

- Insulin activates glycogenesis through a series of signaling events involving a several key enzymes including protein phosphatase-1.
- Insulin indirectly activates protein phosphatase-1.
- This activation results in the dephosphorylation (activation) of glycogen synthase.
- Thus, allowing it to catalyze the synthesis of glycogen.



Hormonal regulation (cont.)

Glucagon:

- Low blood glucose levels stimulate the secretion of glucagon from the α-cells of the pancreas (typically occur during fasting, signaling a need for glucose).

- Glucagon acts primarily on the liver to regulate glycogen metabolism as it binds to its receptor on the surface of cell membrane.

- Glucagon stimulates glycogenolysis by activating glycogen phosphorylase.

- It also promotes gluconeogenesis, ensuring the production of glucose from non-carbohydrate sources.

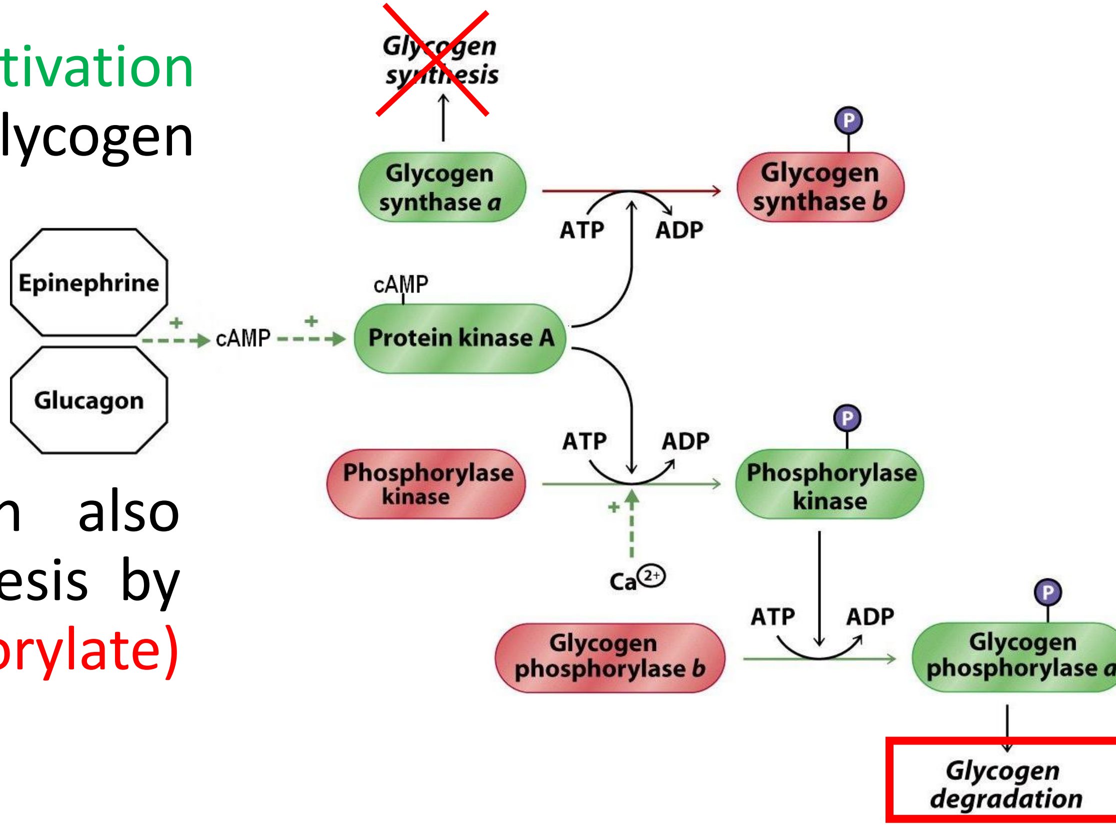
Hormonal regulation (cont.)

Epinephrine:

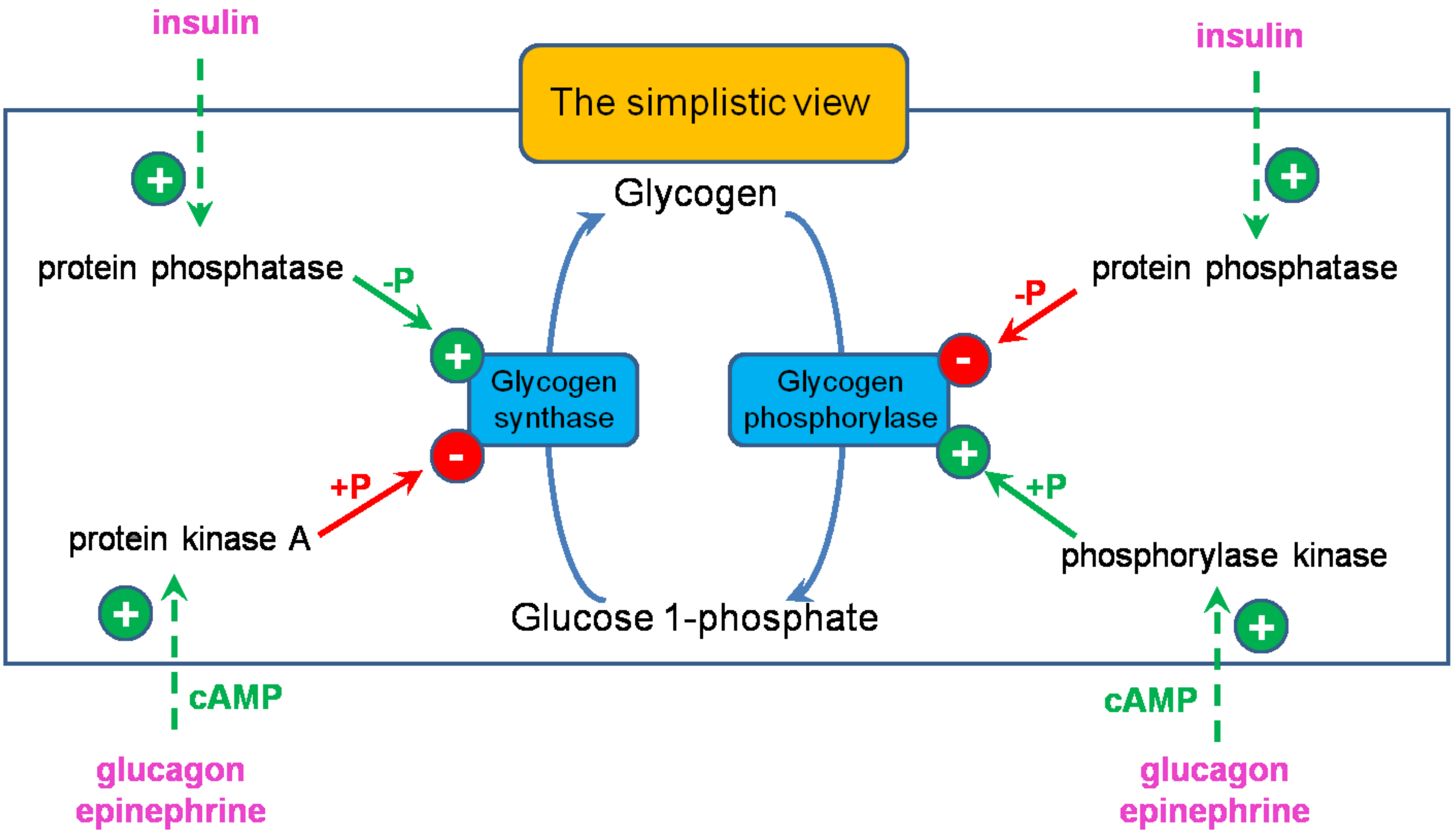
- Epinephrine plays a role in promoting the degradation of glycogen into glucose units.
- It is a hormone released from the adrenal glands in response to stress or physical activity.
- Epinephrine acts primarily on the skeletal muscles to provide a quick release of glucose to meet the increased energy demands during fight-or-flight responses.
- In skeletal muscle, epinephrine stimulates a cascade of signaling events that lead to the activation of glycogenolysis and inhibition of glycogenesis.

Hormonal regulation (cont.)

- Glucagon and epinephrine inhibit glycogenesis through the activation of the cAMP-dependent protein kinase A pathway.
- Both hormones indirectly activate protein kinase-A.
- This results in the activation (phosphorylation) of glycogen phosphorylase.
- Therefore, promoting glycogen degradation.
- Protein kinase-A, can also inhibit glycogen synthesis by inactivate (phosphorylate) glycogen synthase.



Hormonal regulation of glycogen metabolism



Difference between liver and muscle glycogen

	Liver glycogen	Muscles glycogen
Source of glycogen	Glucose, other hexoses, and non-carbohydrate sources	Glucose ONLY
Amount (max.)	100 grams	400 grams
Concentration (%)	10% of adult liver fresh weight	1-2% of resting muscles weight
Function	Maintain blood glucose level, ensuring steady supply of glucose for various tissues	Provide energy source for muscle during physical activity
Hormonal regulation	Insulin (+ synthesis) Glucagon (+ degradation)	Insulin (+ synthesis) Epinephrine (+ degradation)
Degradation	Gives glucose	Gives lactic acid (absence of *glucose 6-phosphatase*)

Summary

- Glycogen (a branched-chain polysaccharide composed of α-D-glucose units) is primarily stored in the liver and muscles.
- Glycogen metabolism is a crucial aspect of glucose homeostasis in the body, serving as a dynamic storage and release system for glucose.
- During periods of elevated blood glucose, insulin stimulates the conversion of excess glucose into glycogen through the activation of glycogen synthase, the enzyme responsible for glycogenesis.
- Conversely, when blood glucose levels drop, glucagon and epinephrine prompt the breakdown of glycogen into glucose, ensuring a steady supply of glucose for energy production.

Examples related to glycogen metabolism

Scenario No.1:

A person consumes a large meal rich in carbohydrates.

- Explain how glycogen metabolism contributes to the regulation of blood glucose levels during a well-fed state. Discuss the role of insulin in this process.

Examples related to glycogen metabolism (cont.)

Scenario No.2:

A deficiency in the enzyme responsible for glycogenolysis is discovered in a patient.

- Predict the physiological consequences of this deficiency and propose potential treatments or interventions.

Scenario No.3:

A teenage girl with a glycogen storage disorder wants to participate in a school sports competition.

- Assess the potential challenges and risks associated with engaging in physical activity with this condition.
- Propose strategies to ensure the individual's safety and performance.