HNS 103: BIOCHEMISTRY

LECTURE 5: Disaccharide metabolism

08/03/2022

Dr. MULINGE
Email: mmulinge@uonbi.ac.ke

Course Outline

WEEK	DATE	TOPIC
1	22.02	BIOENERGETICS: standard free energy in chemical reactions, exergonic and endergonic reactions; Standard free energy of hydrolysis of ATP, Enzymatic transfer of phosphate groups to ATP; Properties of. ATP and high energy phosphate compounds
2	01.03	**CARBOHYDRATE METABOLISM:** Carbohydrate digestion & mobilization; Glycolysis and Its regulations, Substrate Level Phosphorylation; pyruvate oxidation.
3	08.03	**KREBS CYCLE:** Krebs cycle and regulation; Anaploretic reactions; ~~phosphogluconate pathway.~~
4	15.03	**MITOCHODRIAL STRUCTURE & FUNCTION:** Electron Transfer Chain; Oxidative Phosphorylation; Mechanisms of ATP generation; Uncouplers; inhibitors of ATP generation
5	22.03	**DISACCHARIDE METABOLISM:** Phosphogluconate pathway; Glycogen metabolism; Glycogenolysis and gluconeogenesis; Regulation of glycogen metabolism; Covalent modification; cAMP and hormonal regulation; Glycogen storage disease
	29.03	• CAT I

Phosphogluconate pathway aka Pentose-phosphate pathway (PPP)

Aims: (i) formation of pentose-phosphates through the oxidation of glucose-6P AND (ii) generation of reducing power, i.e. NADPH for reductive biosynthetic processes

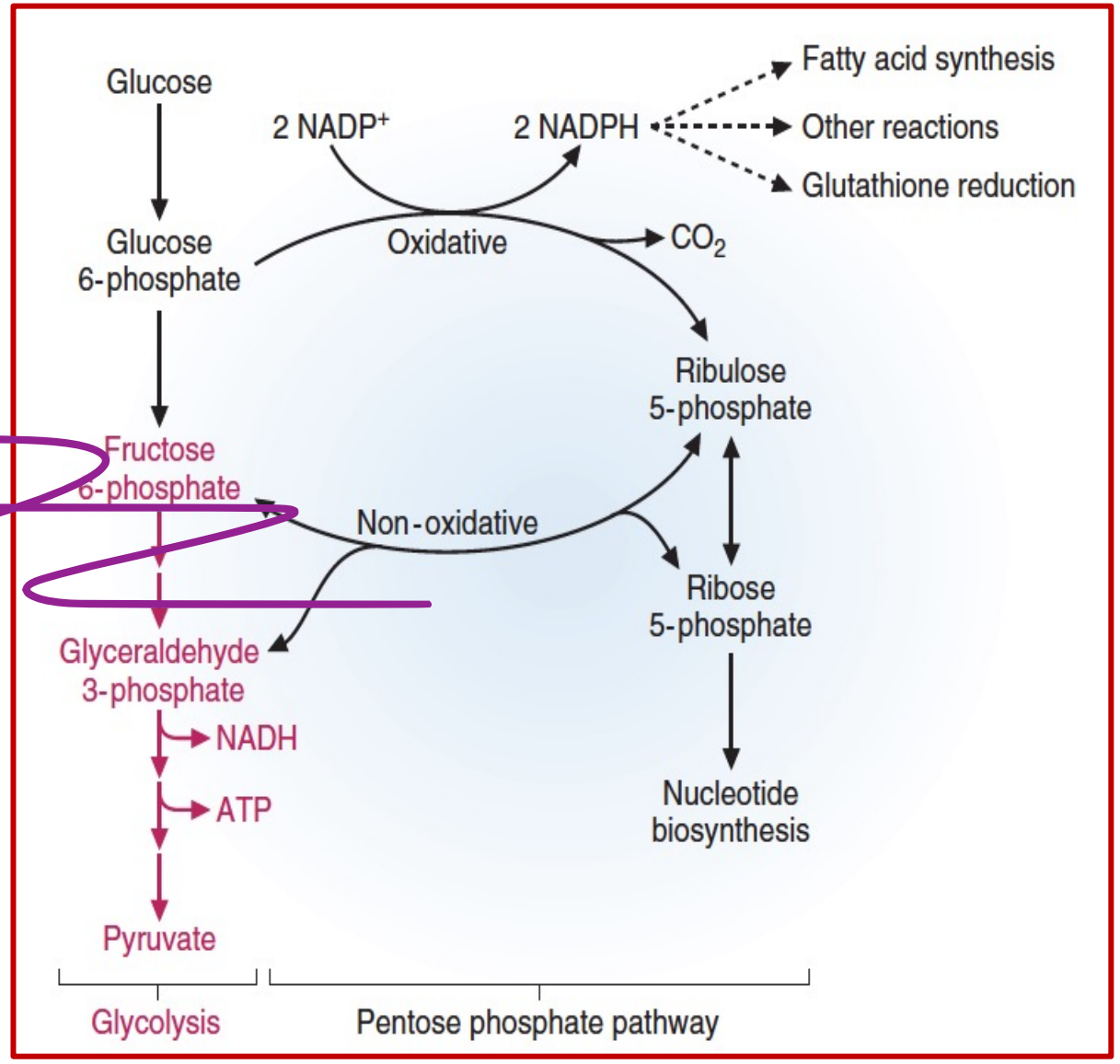
In the irreversible oxidative reactions of the pathway, one carbon of glucose-6-phosphate is released as CO_2; NADPH is generated and ribulose-5-phosphate is produced.

- NADPH is used for reductive biosynthesis (particularly of fatty acids) and for protection against oxidative damage (e.g., by reduction of glutathione).

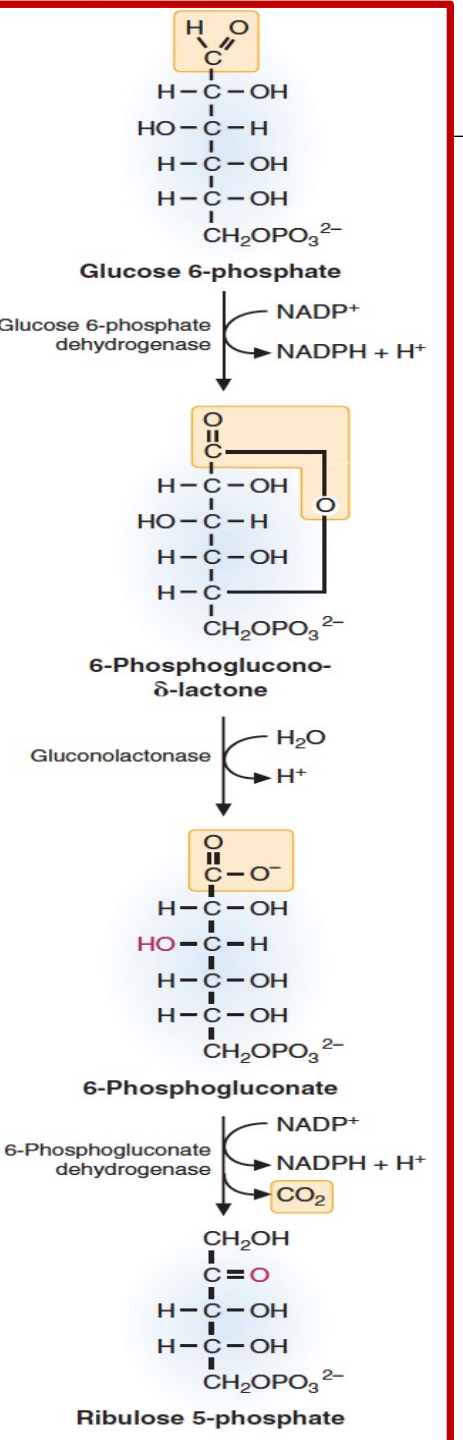
- Ribulose-5-phosphate provides ribose-5-phosphate for nucleotide biosynthesis or generates pentose phosphates, which enter the nonoxidative portion of the pathway.

- In the reversible nonoxidative reactions, pentose phosphates produced from ribulose- 5-phosphate are converted to the glycolytic intermediates fructose-6-phosphate and glyceraldehyde-3-phosphate.

***** Because the nonoxidative reactions are reversible, they can be used to generate ribose- 5-phosphate or nucleotide synthesis from intermediates of glycolysis.



OXIDATIVE REACTIONS OF PPP

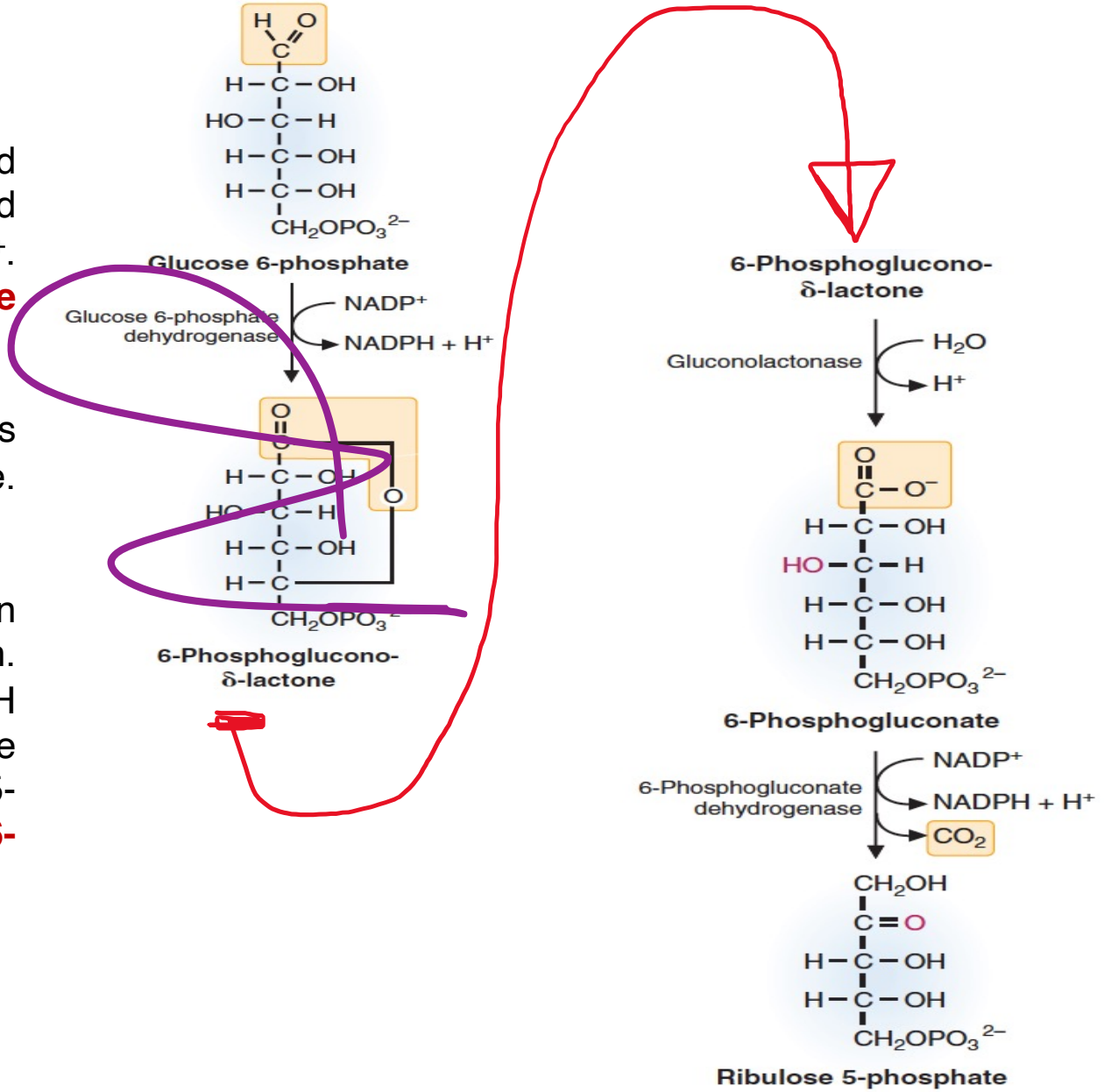


1. The oxidative reactions

a. Glucose-6-phosphate is converted to 6-phosphogluconolactone, and NADP1 is reduced to NADPH + H^+. **Enzyme: glucose-6-phosphate dehydrogenase**

b. 6-Phosphogluconolactone is hydrolyzed to 6-phosphogluconate. Enzyme: gluconolactonase

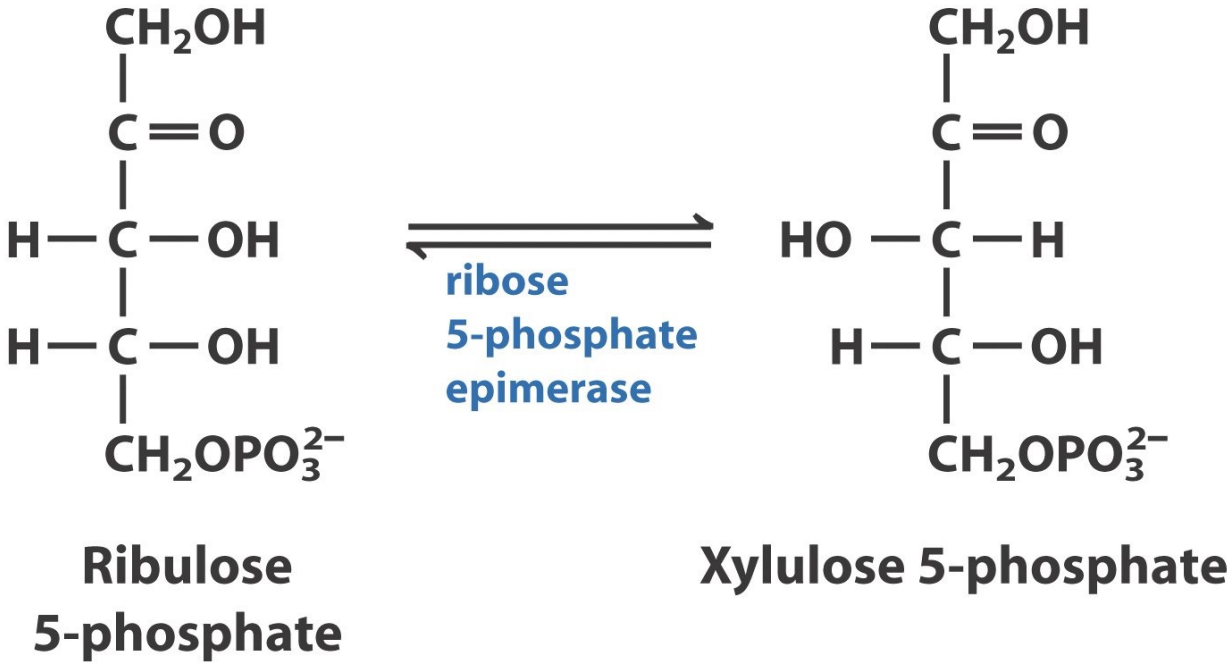
c. 6-Phosphogluconate undergoes an oxidation, followed by a decarboxylation. CO2 is released, and a second NADPH + H^+ is generated from $NADP^+$. The remaining carbons form ribulose-5-phosphate. **Enzyme: 6-phosphogluconate dehydrogenase**



NON-OXIDATIVE REACTIONS OF PPP

2. The NON-oxidative reactions

a. Ribulose-5-phosphate is isomerized to ribose-5-phosphate or epimerized to **xylulose-5-phosphate.**



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

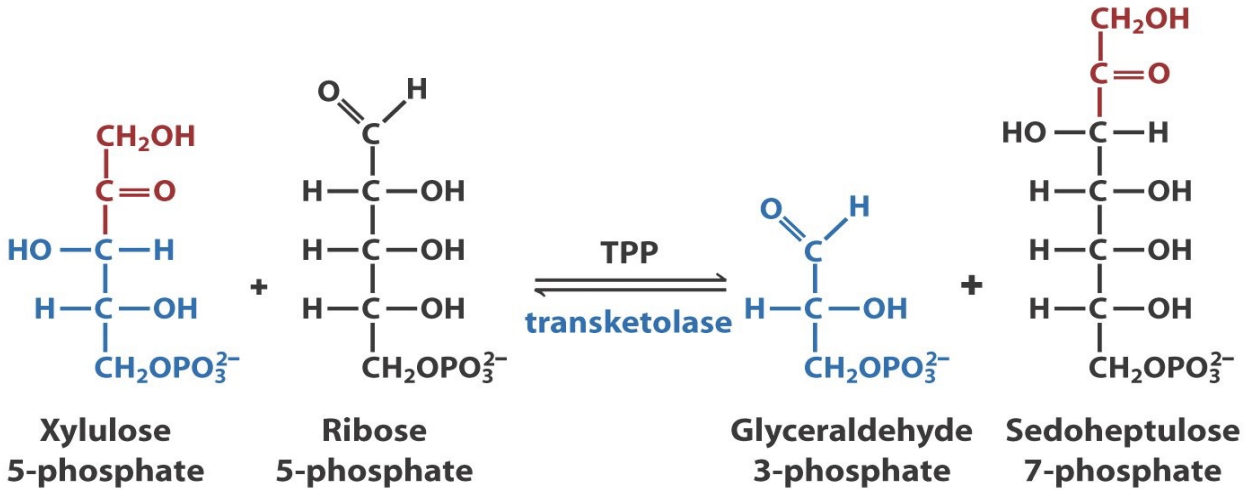
NON-OXIDATIVE REACTIONS OF PPP……. continued

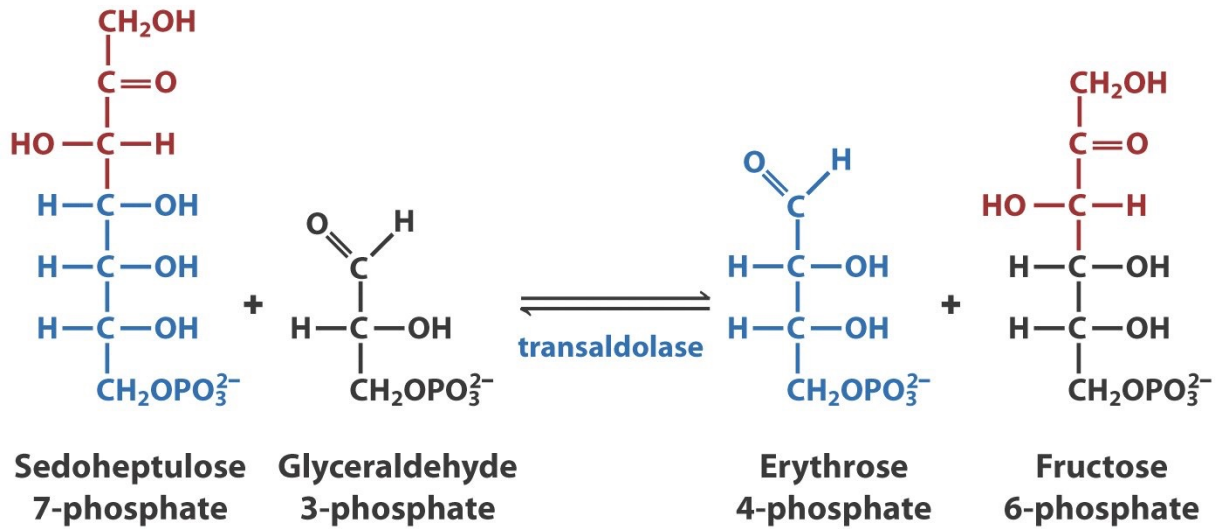
2. The NON-oxidative reactions

b. Ribose-5-phosphate and xylulose-5-phosphate undergo reactions, catalyzed by transketolase and transaldolase, that transfer carbon units, ultimately forming fructose 6-phosphate and glyceraldehyde-3-phosphate.

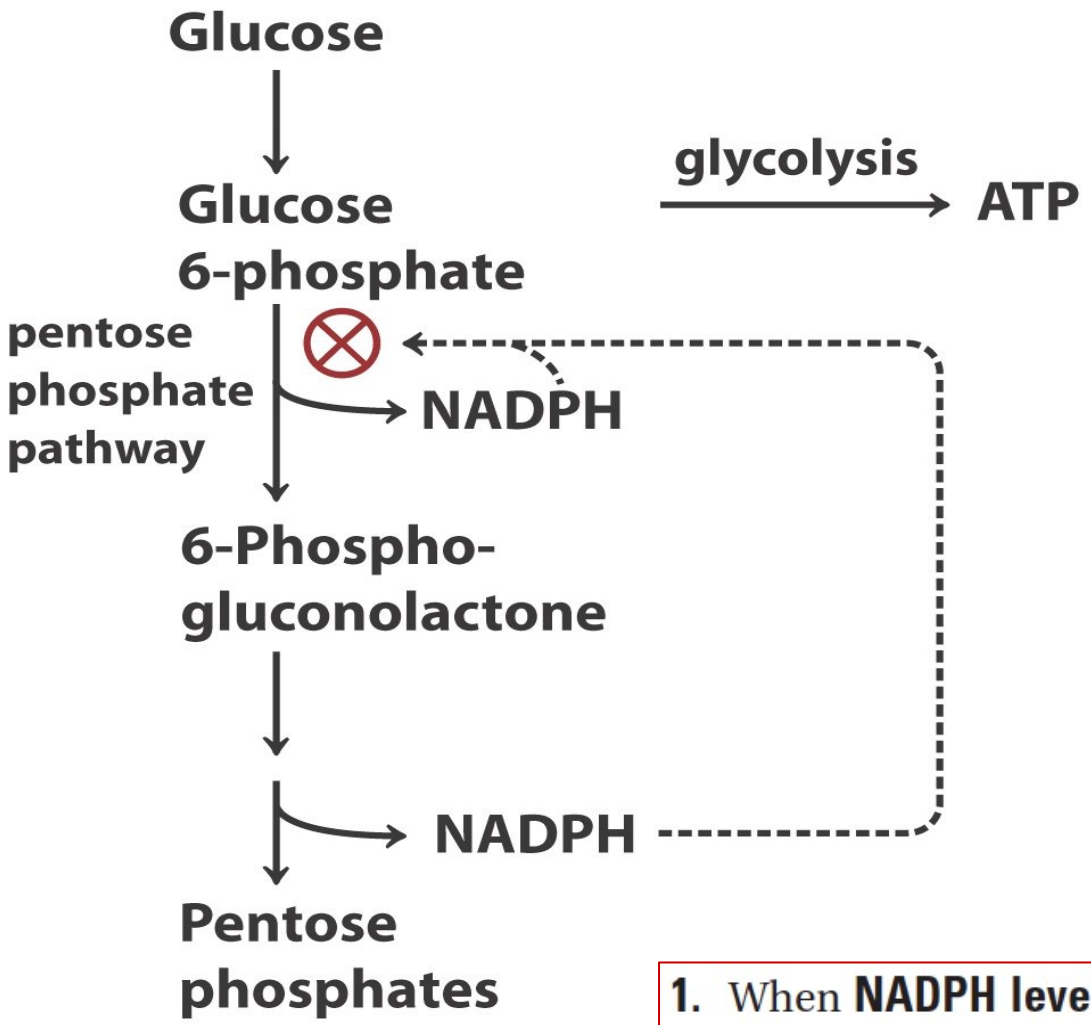
(1) Transketolase, which requires thiamine pyrophosphate, transfers two-carbon units.

(2) Transaldolase transfers three-carbon units.





Partititioning of glucose-6P between glycolysis and PPP



When NADPH is formed faster than being used in biosynthetic processes, the [NADPH] rises and inhibits the first enzyme of the pentose-phosphate pathway.

Glucose-6P is available for glycolysis

1. When **NADPH levels are low**, the oxidative reactions of the pathway can be used to generate ribose-5-phosphate for nucleotide biosynthesis.
2. When **NADPH levels are high**, the reversible nonoxidative portion of the pathway can be used to generate ribose-5-phosphate for nucleotide biosynthesis from fructose-6-phosphate and glyceraldehyde-3-phosphate.

FUNCTIONS OF NADPH

1. The pentose phosphate pathway produces NADPH for fatty acid synthesis. Under these conditions, the fructose-6-phosphate and glyceraldehyde-3-phosphate generated in the pathway
reenter glycolysis.

2. NADPH is also used to reduce glutathione (γ-glutamylcysteinylglycine).

- Glutathione helps to prevent oxidative damage to cells by reducing hydrogen peroxide (H2O2)
- Glutathione is also used to transport amino acids across the membranes of certain cells by the γ-glutamyl cycle.

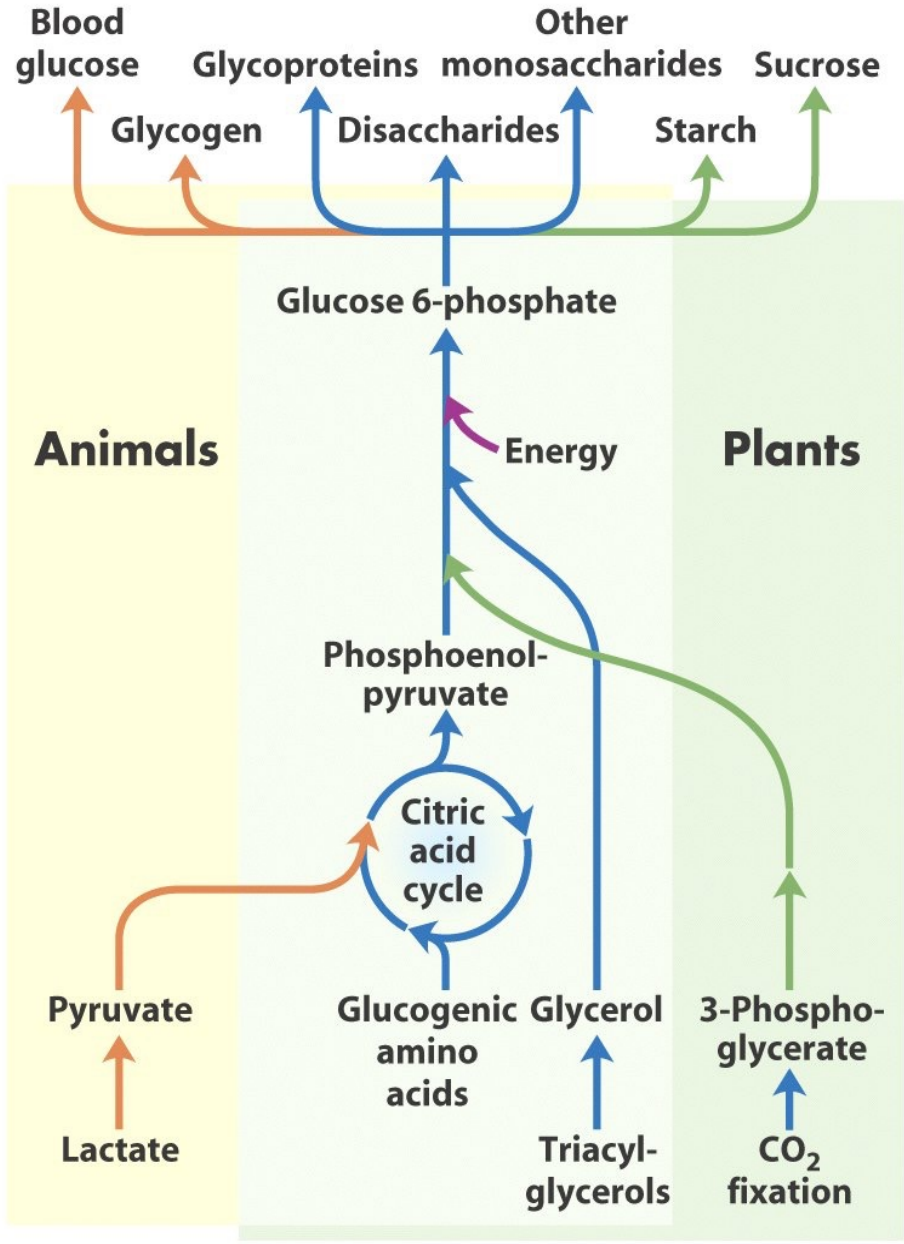
Gluconeogenesis

Gluconeogenesis

- Gluconeogenesis, which occurs mainly in the **liver**, is the synthesis of glucose from compounds that are not carbohydrates. Plants ** Equivalent of photosynthesis

- The major precursors for gluconeogenesis are:
  - **lactate,**
  - **amino acids** (which form pyruvate or TCA cycle intermediates), and
  - **glycerol** (which forms DHAP).

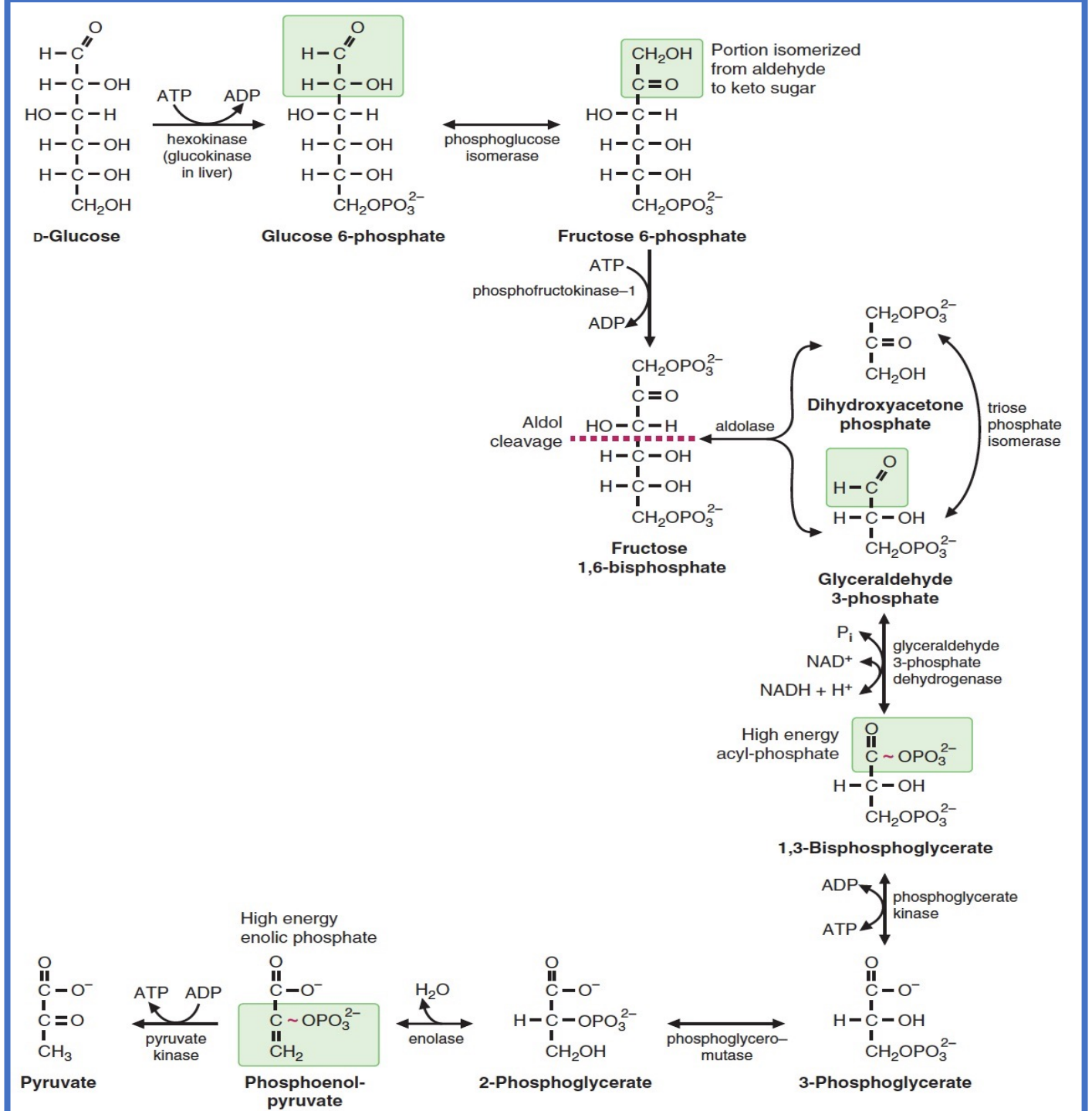
- * Even–chain length fatty acids do not produce any net glucose.



Remember: → GLYCOLYSIS

KEY CONCEPTS

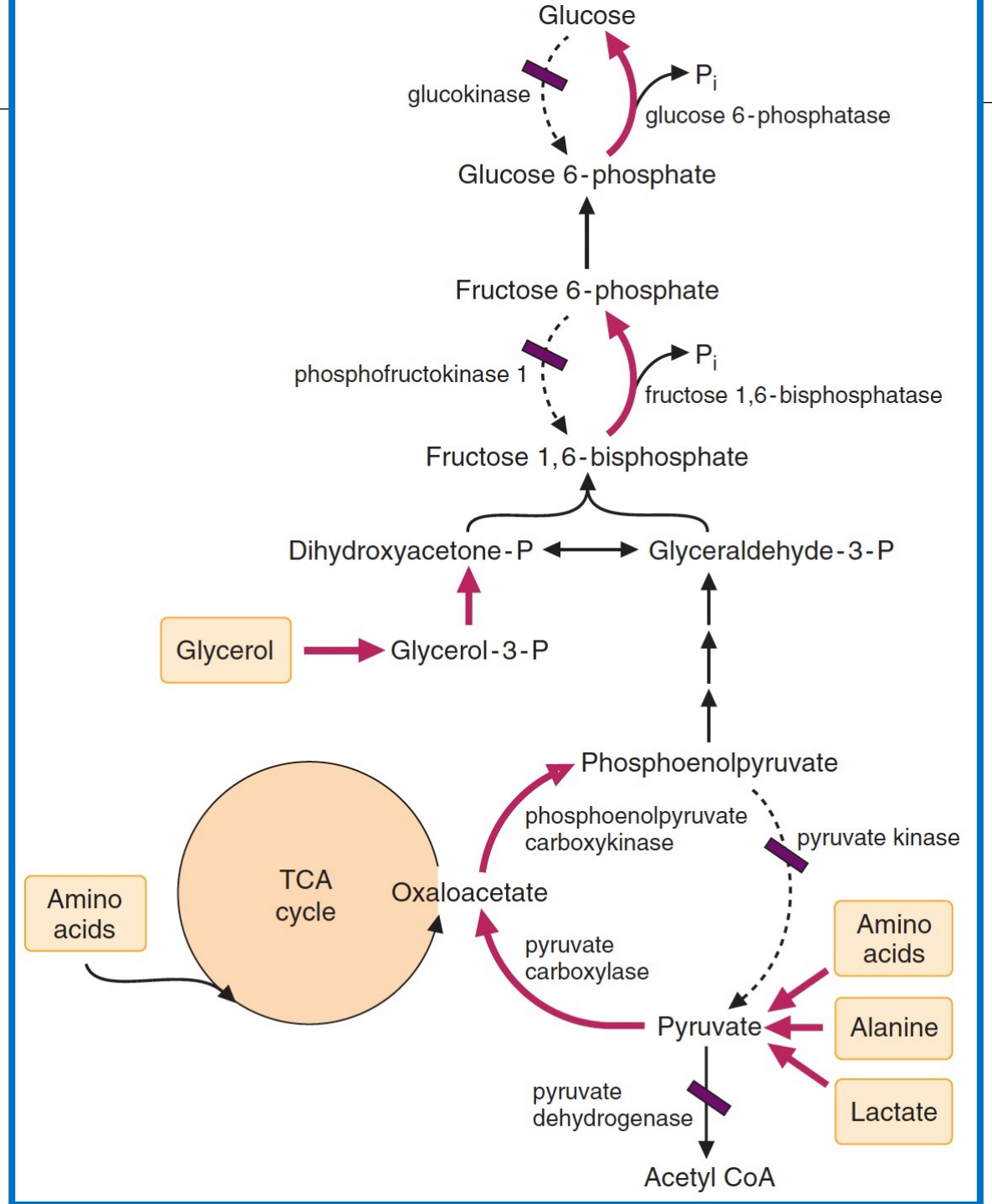
- Glycolysis is a 10-step pathway in which glucose is converted to two molecules of pyruvate.
- Energy is invested in the first half of the pathway, and the second half of the pathway generates 2 ATP and 2 NADH.
- Flux through the pathway is controlled primarily at the phosphofructokinase step.
- Pyruvate can be converted to lactate, acetyl-CoA, or oxaloacetate.



Gluconeogenesis

Glycolysis and gluconeogenesis share many steps

Remember: 3 steps in glycolysis are irreversible ➔ bypases using seperate sets of enzymes are required



The key reactions of gluconeogenesis from the precursors alanine, lactate, and glycerol. **Heavy arrows** indicate steps that differ from those of glycolysis. Broken arrows are glycolytic reactions that are inhibited (!) under conditions in which gluconeogenesis is occurring.

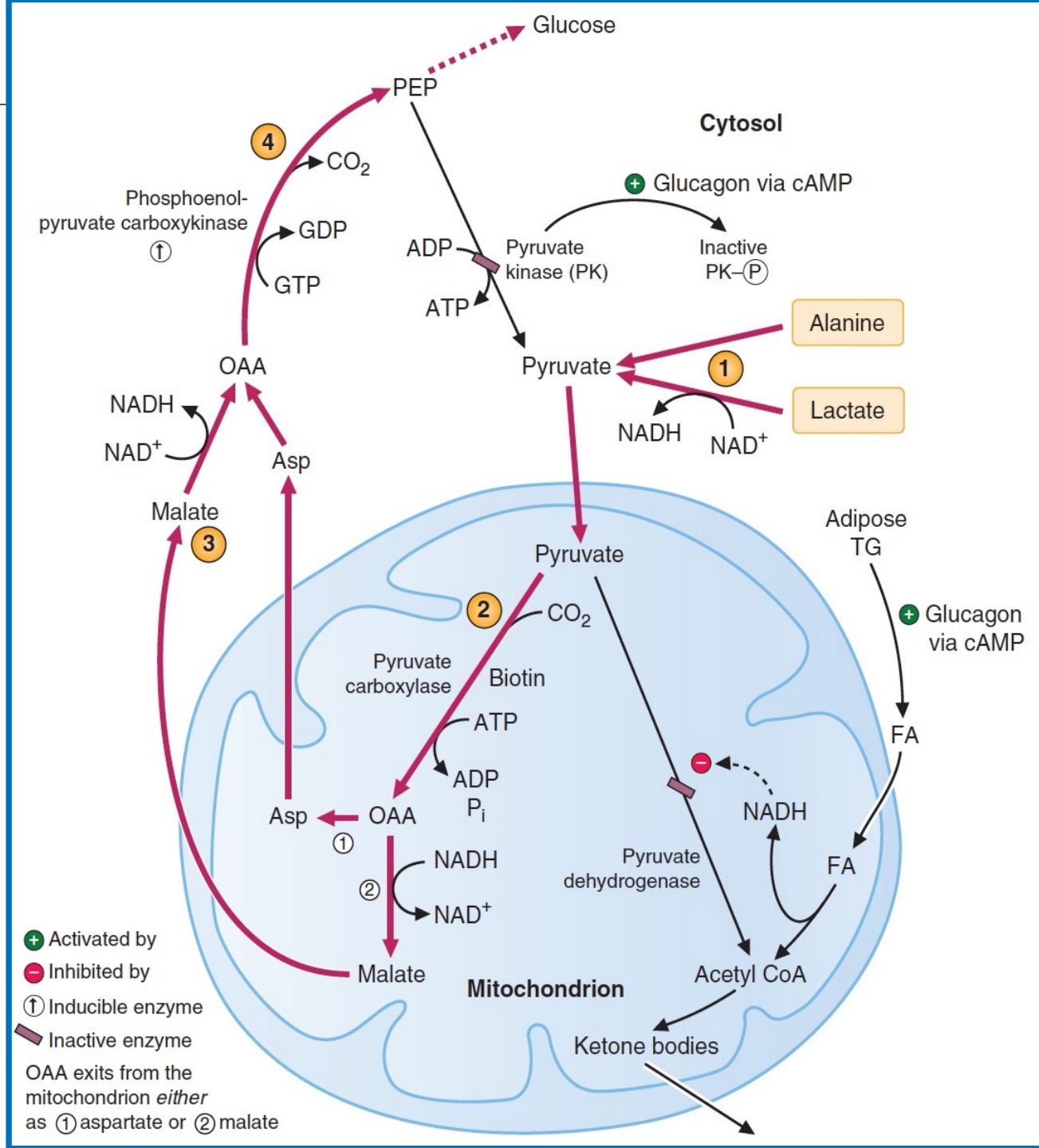
Reactions of gluconeogenesis

Conversion of pyruvate ➔ phosphoenolpyruvate occurs in the liver

1. **Pyruvate** (produced from lactate, alanine, and other amino acids) is first converted to **oxaloacetate** by **pyruvate carboxylase**, a mitochondrial enzyme that requires biotin and ATP. ** Oxaloacetate cannot directly cross the inner mitochondrial membrane. Therefore, it is converted to malate or to aspartate, which can cross the mitochondrial membrane and be reconverted to oxaloacetate in the cytosol.

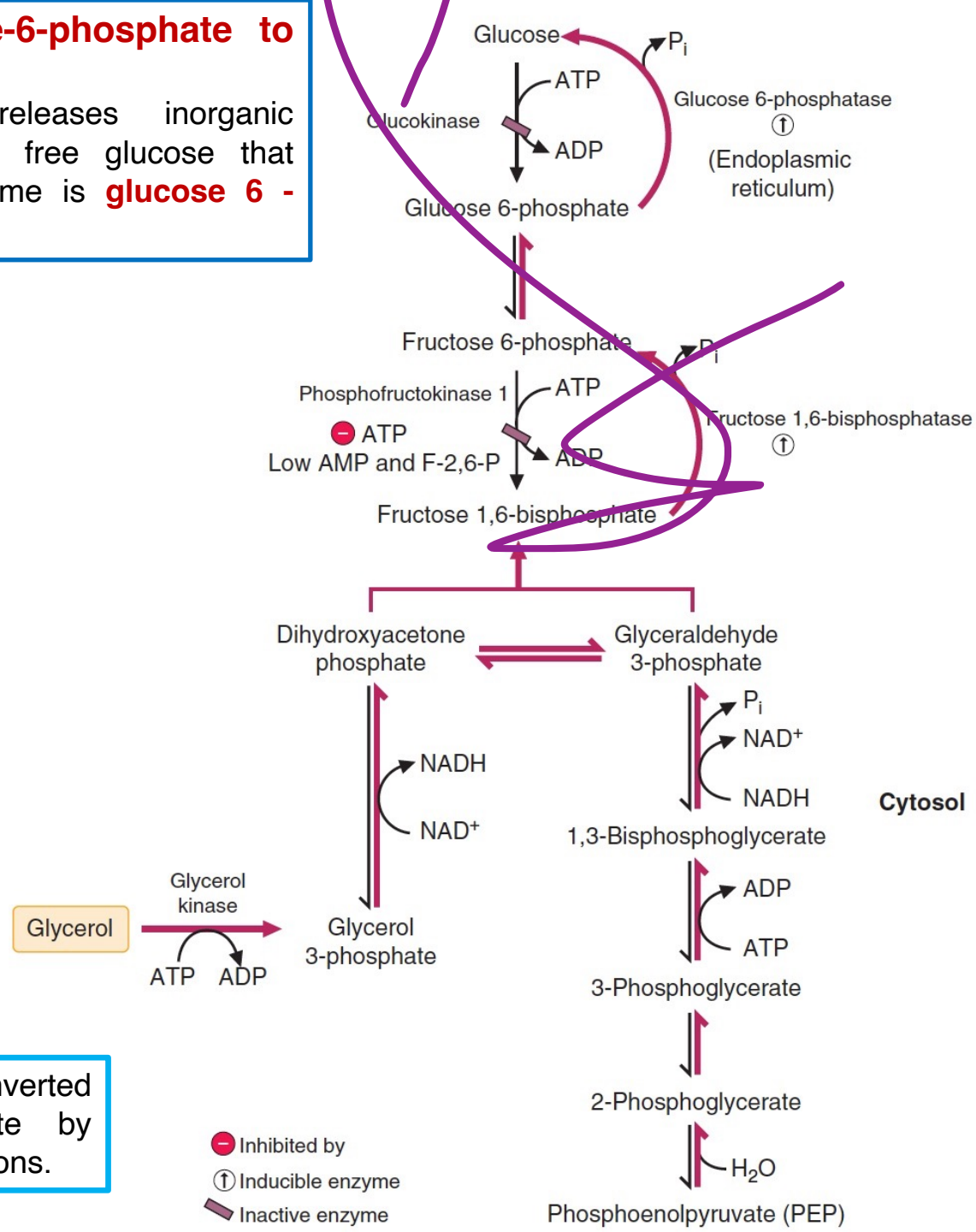
2. **Oxaloacetate** is decarboxylated by **phosphoenolpyruvate carboxykinase** to form phosphoenolpyruvate. This reaction requires GTP.

3. **Phosphoenolpyruvate** is converted to **fructose 1,6-bisphosphate** by reversal of the glycolytic reactions.



Conversion of glucose-6-phosphate to glucose

** Glucose-6-phosphate releases inorganic phosphate, which produces free glucose that enters the blood. The enzyme is **glucose 6 - phosphatase.**



Conversion of fructose 1,6-bisphosphate to fructose-6-phosphate

a. **Fructose-1,6-bisphosphate** is converted to fructose-6-phosphate in a reaction that releases inorganic phosphate and is catalyzed by **fructose-1,6-bisphosphatase.**

b. Fructose-6-phosphate is converted to glucose 6-phosphate by the same isomerase used in glycolysis.

Phosphoenolpyruvate is converted to fructose 1,6-bisphosphate by reversal of the glycolytic reactions.

Regulatory enzymes of gluconeogenesis

1. Under fasting conditions, **glucagon** is elevated and stimulates gluconeogenesis. Because of the changes in the activity of certain enzymes, futile cycles are prevented from occurring, and the overall flow of carbon is from pyruvate to glucose.
2. A futile cycle is the continuous recycling of substrates and products with the net consumption of energy and no significant change in substrate levels. This is also known as substrate cycling, as the same substrate is continuously synthesized and degraded (recycled).

a. Pyruvate dehydrogenase

i. Decreased insulin and increased glucagon stimulate the **release of fatty acids** from adipose tissue.
ii. **Fatty acids** travel to the liver and are **oxidized**, producing acetyl-CoA, NADH, and ATP, which cause inactivation of pyruvate dehydrogenase.
iii. Because **pyruvate dehydrogenase** is relatively inactive, pyruvate is converted to oxaloacetate, not to acetyl-CoA.

b. Pyruvate carboxylase

i. Pyruvate carboxylase, which converts pyruvate to oxaloacetate, is **activated by acetyl-CoA** (which is generated from fatty acid oxidation within the mitochondria).
ii. Note that pyruvate carboxylase is active in both the fed and fasting states.

Regulatory enzymes of gluconeogenesis

c. Phosphoenolpyruvate carboxykinase (PEPCK)

i. PEPCK is an inducible enzyme.

ii. Transcription of the gene encoding PEPCK is stimulated by binding of proteins (CREB, for cyclic AMP response element–binding protein) that are phosphorylated in response to cAMP and by binding of glucocorticoid–protein complexes to regulatory elements in the gene.

iii. Increased production of PEPCK mRNA leads to increased translation, resulting in higher PEPCK levels in the cell.

d. Pyruvate kinase

i. **Glucagon**, via cAMP and protein kinase A, causes pyruvate kinase to be phosphorylated and **inactivated**.

ii. Because pyruvate kinase is relatively inactive, phosphoenolpyruvate formed from oxaloacetate is not reconverted to pyruvate but, in a series of steps, forms fructose-1, 6- bisphosphate, which is converted to fructose-6-phosphate.

e. Phosphofructokinase 1

PFK1 is relatively **inactive** because the concentrations of its activators, AMP and F-2,6-P, are low and its inhibitor, ATP, is relatively high.

Regulatory enzymes of gluconeogenesis

f. Fructose 1,6-bisphosphatase

i. The level of F-2,6-P, an inhibitor of fructose 1,6-bisphosphatase, **is low during fasting**. Therefore, **fructose 1,6-bisphosphatase is more active.**

ii. Fructose1,6-bisphosphatase is also **induced** in the fasting state.

g. Glucokinase

Glucokinase is relatively **inactive** because it has a **high K_m** for glucose, and under conditions that favor gluconeogenesis, the glucose concentration is low. Therefore, free glucose is not reconverted to glucose-6-phosphate.

Precursors for gluconeogenesis

Lactate, amino acids, and glycerol are the major precursors for gluconeogenesis in humans.

1. Lactate is oxidized by NAD^+ in a reaction catalyzed by LDH to form pyruvate, which can be converted to glucose. The sources of lactate include red blood cells and exercising muscle.

2. Amino acids for gluconeogenesis come from degradation of muscle protein.

i. **Amino acids are released directly into the blood from muscle**
ii. Amino acids travel to the liver and provide carbon for gluconeogenesis. .
iii. **Alanine is also formed by transamination** of pyruvate that is derived by the oxidation of glucose Quantitatively, alanine is the major gluconeogenic amino acid.

3. Glycerol, which is derived from adipose triacylglycerols, reacts with ATP to form glycerol- 3-phosphate which is oxidized to DHAP and converted to glucose.

Role of fatty acids in gluconeogenesis

1. Even-chain fatty acids

a. Fatty acids are oxidized to acetyl-CoA, which enters the TCA cycle.

b. For every two carbons of acetyl-CoA that enter the TCA cycle, two carbons are released as CO2. Therefore, there is **no net synthesis of glucose from acetyl-CoA**.

c. The pyruvate dehydrogenase reaction is irreversible, thus acetyl-CoA cannot be converted to pyruvate.

d. Although even-chain fatty acids do not provide carbons for gluconeogenesis, β-oxidation of fatty acids provides ATP that drives gluconeogenesis.

2. Odd-chain fatty acids

a. The three carbons at the carbonyl-end of an odd-chain fatty acid are converted to propionate. **Propionate** enters the TCA cycle as succinyl-CoA, which forms malate, an intermediate in glucose formation.

Energy requirements for gluconeogenesis

1. From pyruvate

a. Conversion of pyruvate to oxaloacetate by **pyruvate carboxylase** requires one ATP.

b. Conversion of oxaloacetate to phosphoenolpyruvate by **phosphoenolpyruvate carboxykinase** requires one GTP (the equivalent of one ATP).

c. Conversion of 3-phosphoglycerate to 1,3-bisphosphoglycerate by **phosphoglycerate kinase** requires one ATP.

d. Since 2 moles of pyruvate are required to form 1 mole of glucose, 6 moles of high-energy phosphate are required for the synthesis of 1 mole of glucose.

2. From glycerol

a. Glycerol enters the gluconeogenic pathway at the DHAP level.

- Conversion of glycerol to glycerol-3-phosphate, which is oxidized to DHAP, requires one ATP.

- Since 2 moles of glycerol are required to form 1 mole of glucose, 2 moles of high-energy phosphate are required for the synthesis of 1 mole of glucose.

Hypoglycemia

CLINICAL CORRELATES

Hypoglycemia (low blood sugar) is caused by the inability of the liver to maintain blood glucose levels. It can result from excessive insulin, excessive cellular uptake of glucose, or an impairment of glycogenolysis or gluconeogenesis. Hypoglycemia is caused by liver disease, insulin-secreting tumors, and administration of inappropriately high doses of insulin or sulfonylureas. **Excessive alcohol ingestion** also can cause hypoglycemia. Metabolism of alcohol increases levels of NADH in the liver, which inhibit gluconeogenesis. Extremely rare mutations have been found in both phosphoenolpyruvate carboxykinase and fructose 1,6-bisphosphatase. Mutations in either enzyme will lead to hypoglycemia; inherited mutations in phosphoenolpyruvate carboxykinase will lead to an early death.

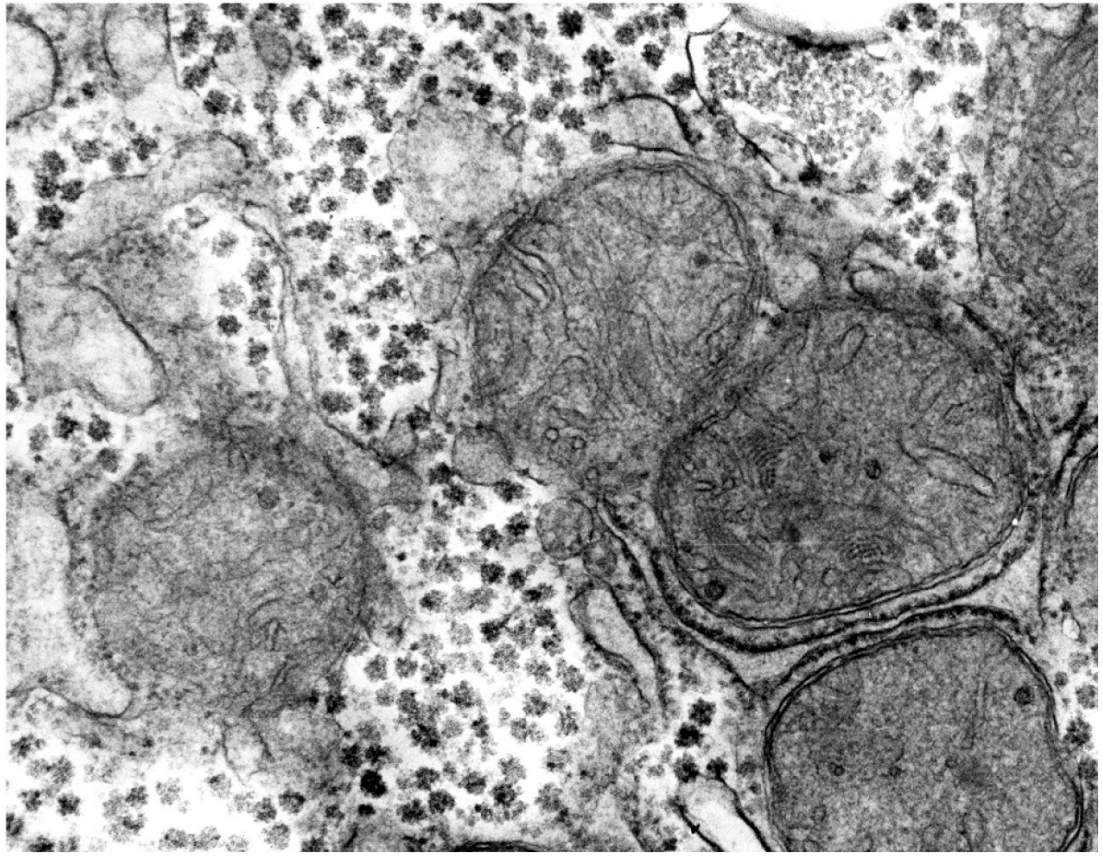
Glycogen metabolism

Glycogen metabolism

Excess glucose is stored as polymers such as starch in plants, and glycogen in vertebrates and many microorganisms.

Vertebrates store glycogen in liver (up to 10% of liver weight) and in muscles (up to 2% of muscle weight). In liver, the stored glycogen is of utmost importance to regulate the blood glucose levels.

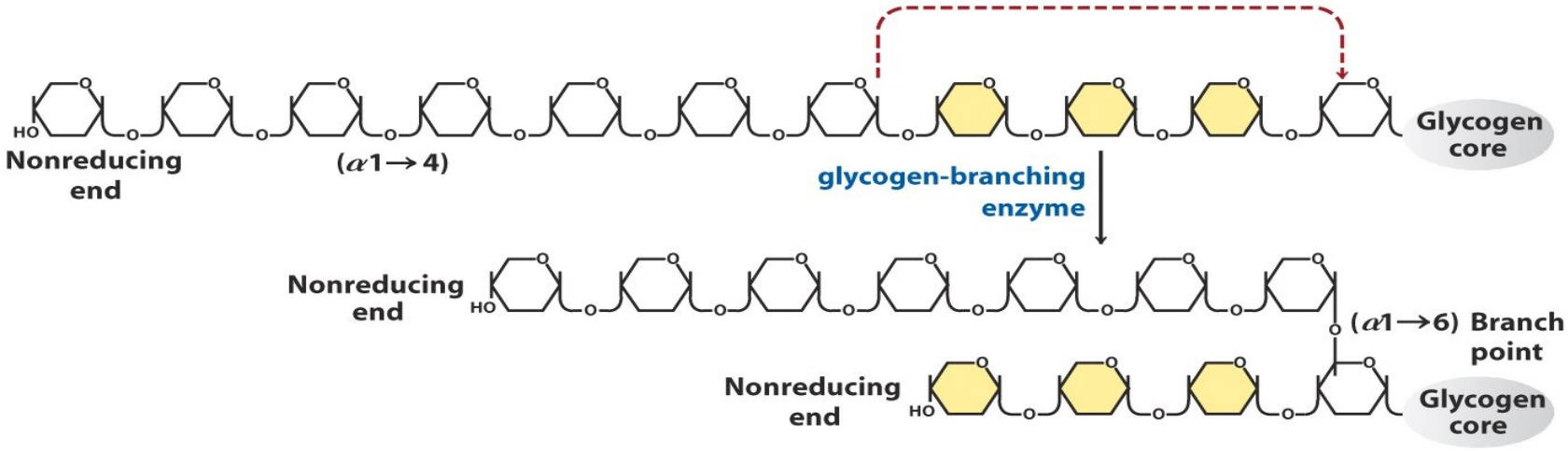
In muscle, glycogen is mainly a storage form to generate ATP.



Glycogen granules are complex aggregates of: glycogen, the enzymes involved in its biosynthesis and breakdown, the regulatory machinery of biosynthesis and breakdown

➔ ➔ need for meticulous regulation

Structure of glycogen



Glucose units are linked by (α1-4) and (α1-6) glycosidic bonds responsible for linear chains and branching respectively.

Glycogen is a large, branched polymer consisting of D-glucose residues

1. The linkages between glucose residues are α 1-4 except at branch points where the linkage is ` α 1-6 Branching is more frequent in the interior of the molecule and less frequent at the periphery, the average being an α-1,6 branch every 8 to 10 residues.
2. One glucose unit, located at the reducing end of each glycogen molecule, is attached to the protein glycogenin.
3. The glycogen molecule branches like a tree and has many nonreducing ends at which addition and release of glucose residues occur during synthesis and degradation, respectively.

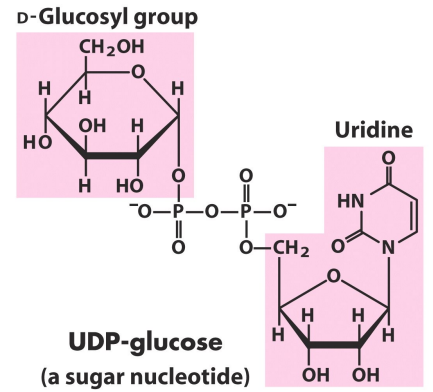
Anabolism (Synthesis) of glycogen

Remember: $Glycogen_n + P_i \longrightarrow glycogen_{(n-1)} + glucose\text{-}1P$

$Glycogen_n + UDP\text{-}glucose \longrightarrow glycogen_{(n+1)} + PP_i$

Glycogen breakdown and synthesis are not just the reverse of each other!

Anabolism of glycogen involves formation of (α1-4) glycosidic bonds to extend existing chains, and the formation of (α1-6) bonds to create branching in the molecule.



UDP-glucose is the precursor for glycogen synthesis.

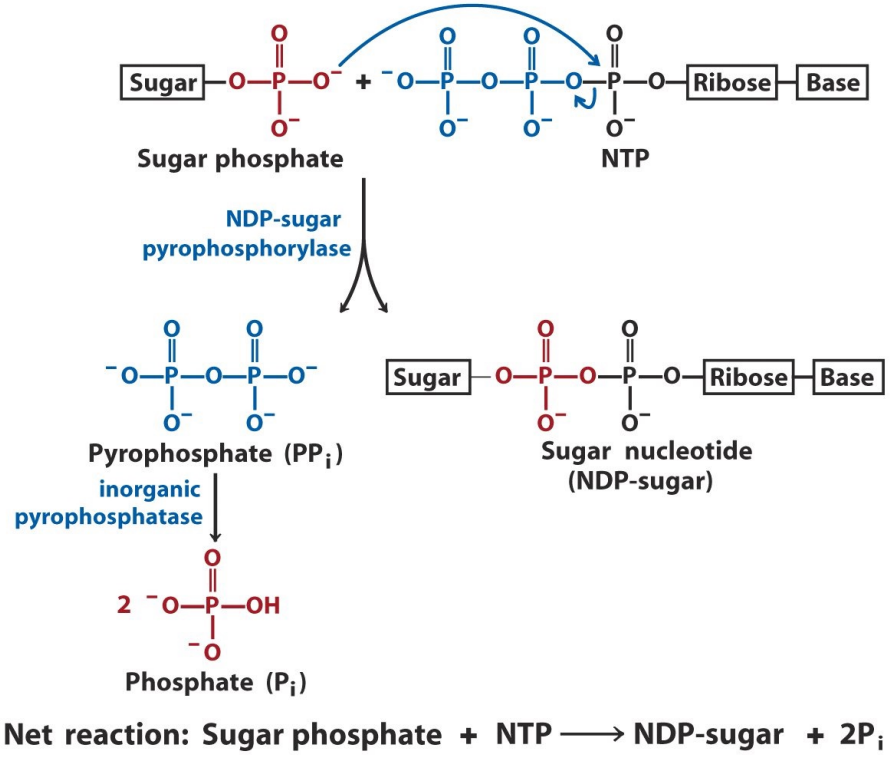
Step 1. Synthesis of UDP-glucose

a. Glucose enters cells and is phosphorylated to glucose-6-phosphate by hexokinase (or by glucokinase in the liver). ATP provides the phosphate group.

b. Phosphoglucomutase converts glucose-6-phosphate to glucose-1-phosphate.

c. Glucose-1-phosphate reacts with UTP, forming UDP-glucose in a reaction catalyzed by UDP-glucose pyrophosphorylase. Inorganic pyrophosphate (PPi) is released in this reaction.

   (i) PPi is cleaved by a pyrophosphatase to 2 Pi. This removal of product help to drive the process in the direction of glycogen synthesis.



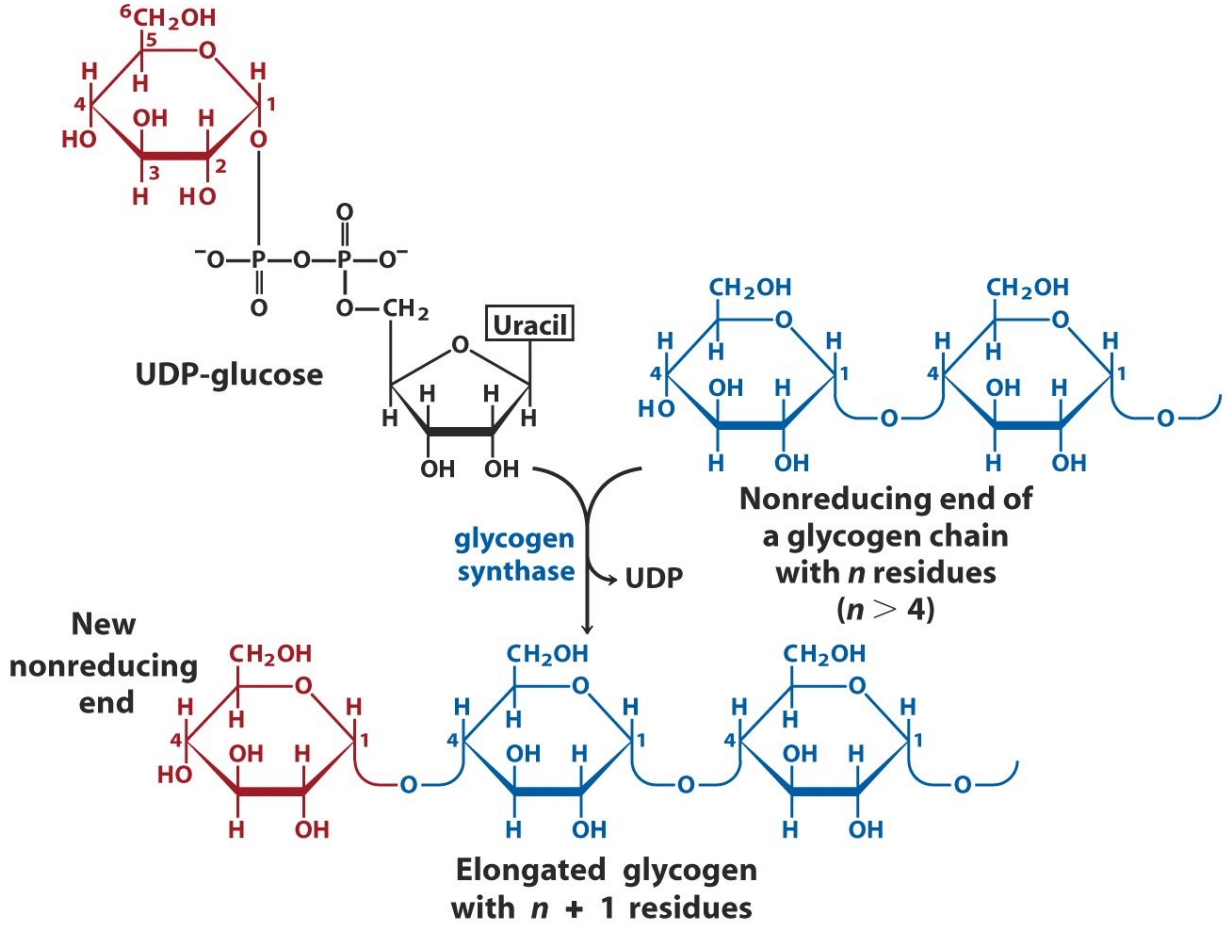
Glycogen synthase elongates glycogen chains

Step 2. Action of glycogen synthase

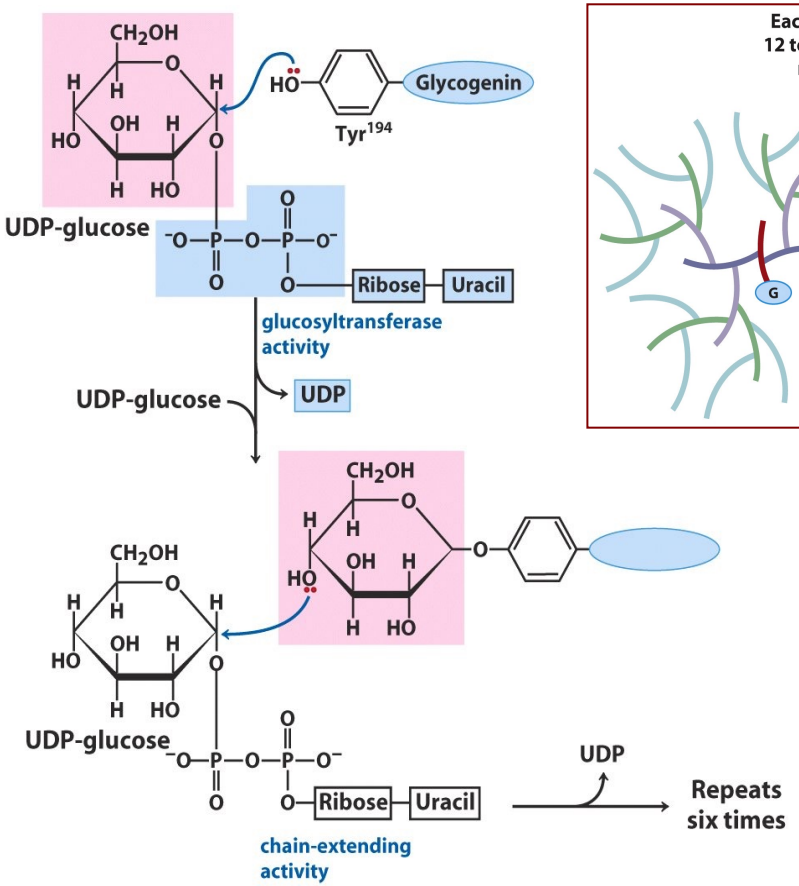
a. Glycogen synthase is the key regulatory enzyme for glycogen synthesis. It transfers glucose residues from UDP-glucose to the nonreducing ends of a glycogen primer.

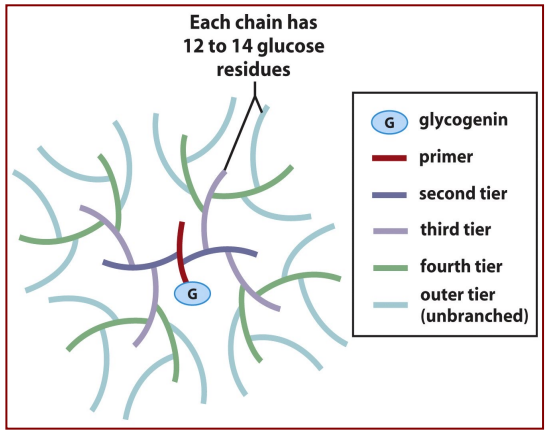
(i) UDP is released and reconverted to UTP by reaction with ATP.

b. The primers, which are attached to glycogenin, are glycogen molecules that were partially degraded in liver during fasting or in muscle and liver during exercise.

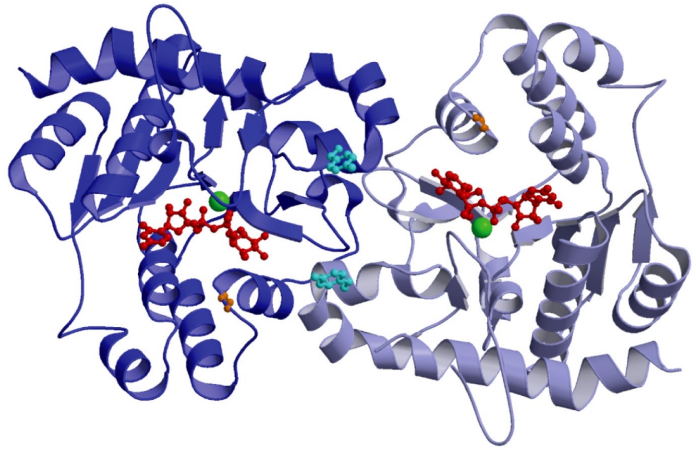


How is a new glycogen molecule initiated?





Muscle glycogenin, MM=37 kDa



Glycogen synthase can not initiate new glycogen chains.

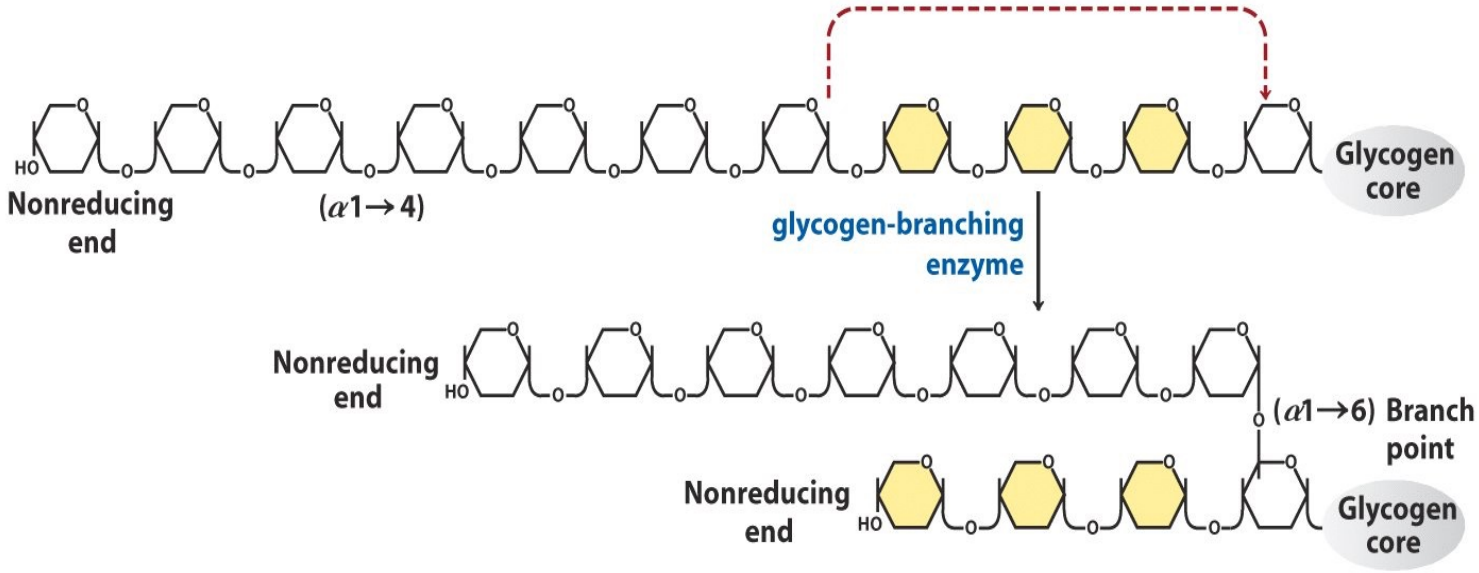
Glycogenin is both the primer on which new chains are assembled and the enzyme that catalyzes their assembly. Glycogenin displays 2 activities:

- glucosyltransferase activity
- chain extending activity

Glycogen branching enzyme creates new branching points

Step 3. Formation of branches

a. When a chain contains 11 or more glucose residues, an oligomer, six to eight residues in length, is removed from the nonreducing end of the chain. It is reattached via an α1,6 linkage to a glucose residue within an α-1,4-linked chain.
b. These branches are formed by the branching enzyme, a glucosyl 4:6 transferase, that breaks an α-1,4 bond and forms an α-1,6 bond.
c. The new branch points are at least four residues and an average of 7 to 11 residues from previously existing branch points.

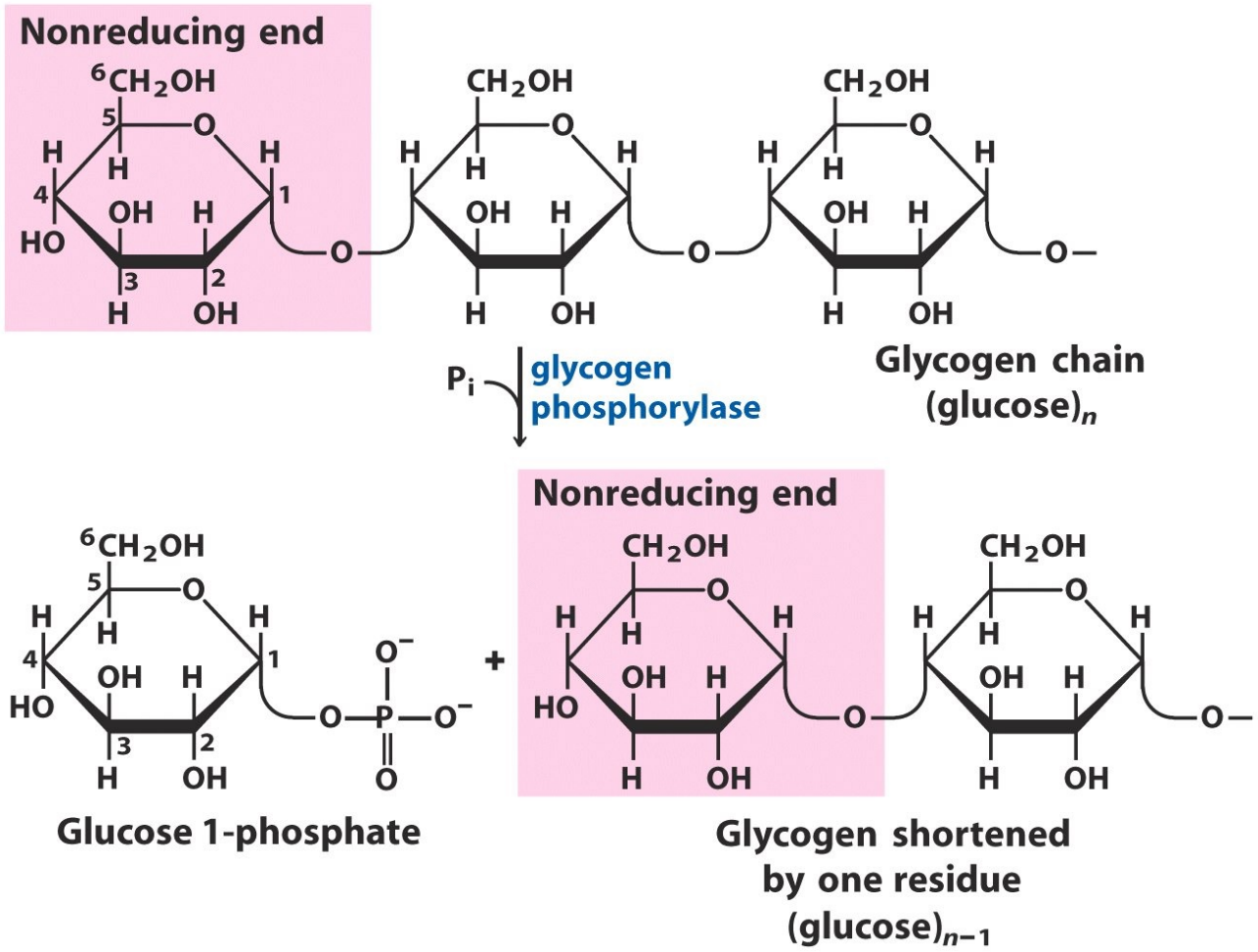


Efects of branching: makes glycogen more soluble, and creates new non-reducing ends.

Step 4. Growth of glycogen chains

a. Glycogen synthase continues to add glucose residues to the nonreducing ends of the newly formed branches as well as to the ends of the original chains.
b. As the chains continue to grow, additional branches are produced by the branching enzyme.

Catabolism (Breakdown) of glycogen



Glycogen phosphorylase releases glucose units from the non-reducing end of glycogen.

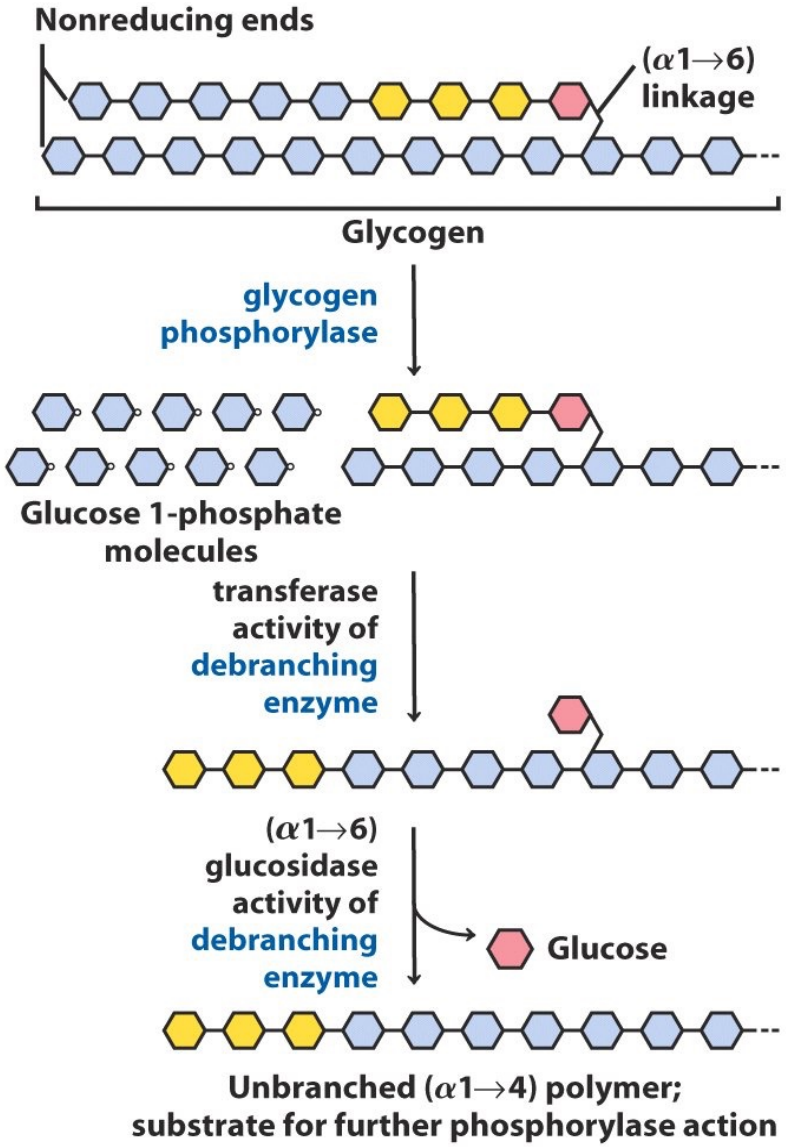
$Glycogen_n + P_i$

↓ Glycogen phosphorylase

$Glycogen_{(n-1)} + glucose\text{-}1P$

Notice that for cleaving (α1-4) bonds by phosphorylase P_i rather than water is used. This process is called **phosphorolysis**. **Advantage:** phosphorylated glucose is formed that can enter other pathways without first being phosphorylated at the expense of ATP.

Catabolism (Breakdown) of glycogen



Step 1. Action of glycogen phosphorylase

a. Glycogen phosphorylase, the key regulatory enzyme for glycogen degradation, removes glucose residues, one at a time, from the nonreducing ends of glycogen molecules.

b. Phosphorylase uses inorganic phosphate (Pi) to cleave α-1,4 bonds, producing glucose-1-phosphate.

c. Phosphorylase can act only until it is four glucose units from a branch point.

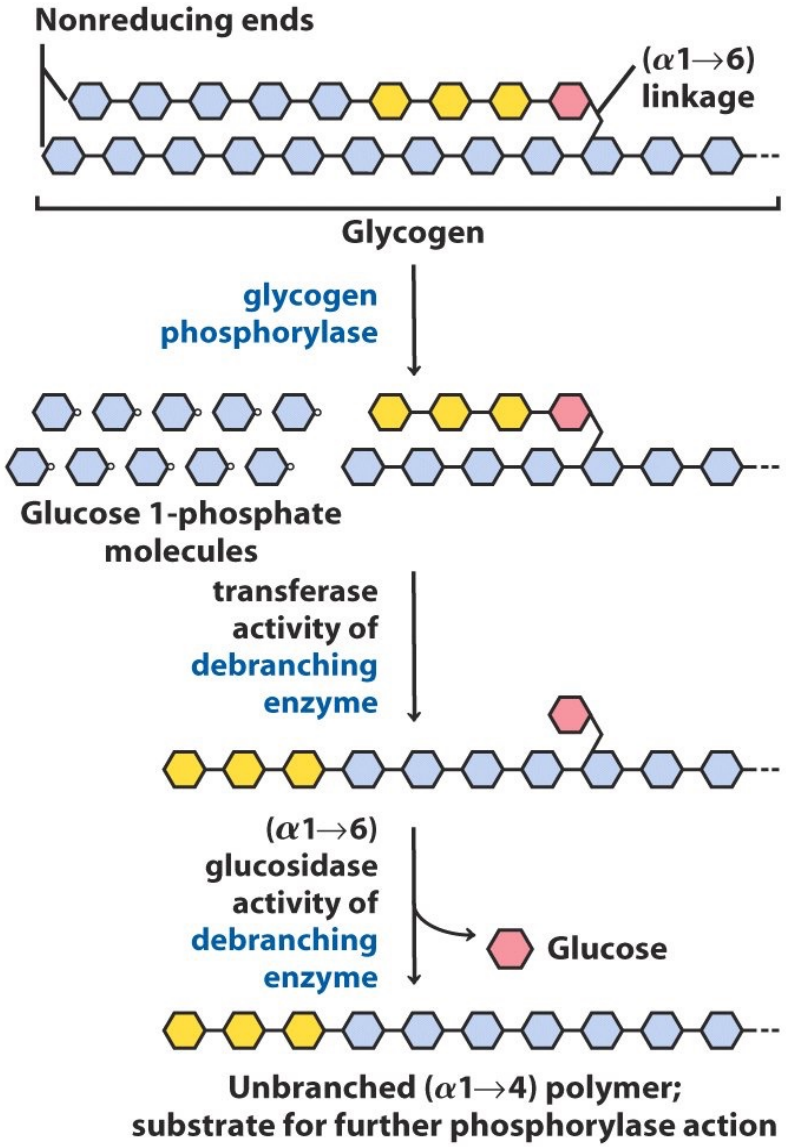
Step 2. Removal of branches

a. The four units remaining at a branch are removed by the debranching enzyme, which has both glucosyl 4:4 transferase and α-1,6-glucosidase activity.

(i) Three of the four glucose residues that remain at the branch point are removed as a trisaccharide and attached to the nonreducing end of another chain by a 4:4 transferase, which cleaves an α-1,4 bond and forms a new α-1,4 bond.

(ii) The last glucose unit at the branch point, which is linked α-1,6, is hydrolyzed by α1,6-glucosidase, forming free glucose.

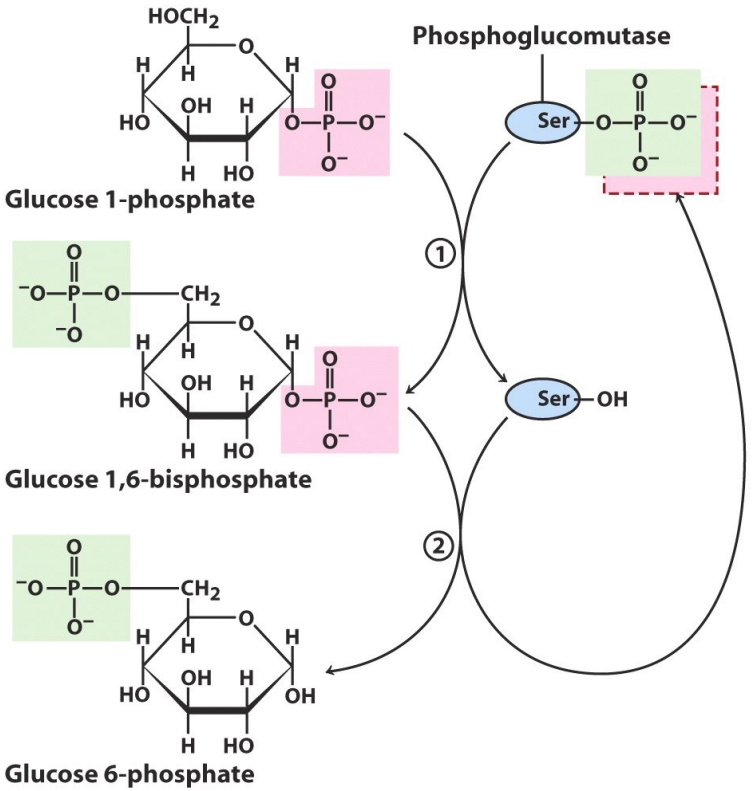
Catabolism (Breakdown) of glycogen…continued



Step 3. Degradation of glycogen chains

a. The phosphorylase/debranching process is repeated, generating glucose-1-phosphate and. free glucose in about a 10:1 ratio that reflects the length of the chains in the outer region of the glycogen molecule.

Catabolism (Breakdown) of glycogen…continued



4. Fate of glucosyl units released from glycogen

a. In the liver, glycogen is degraded to maintain blood glucose levels.

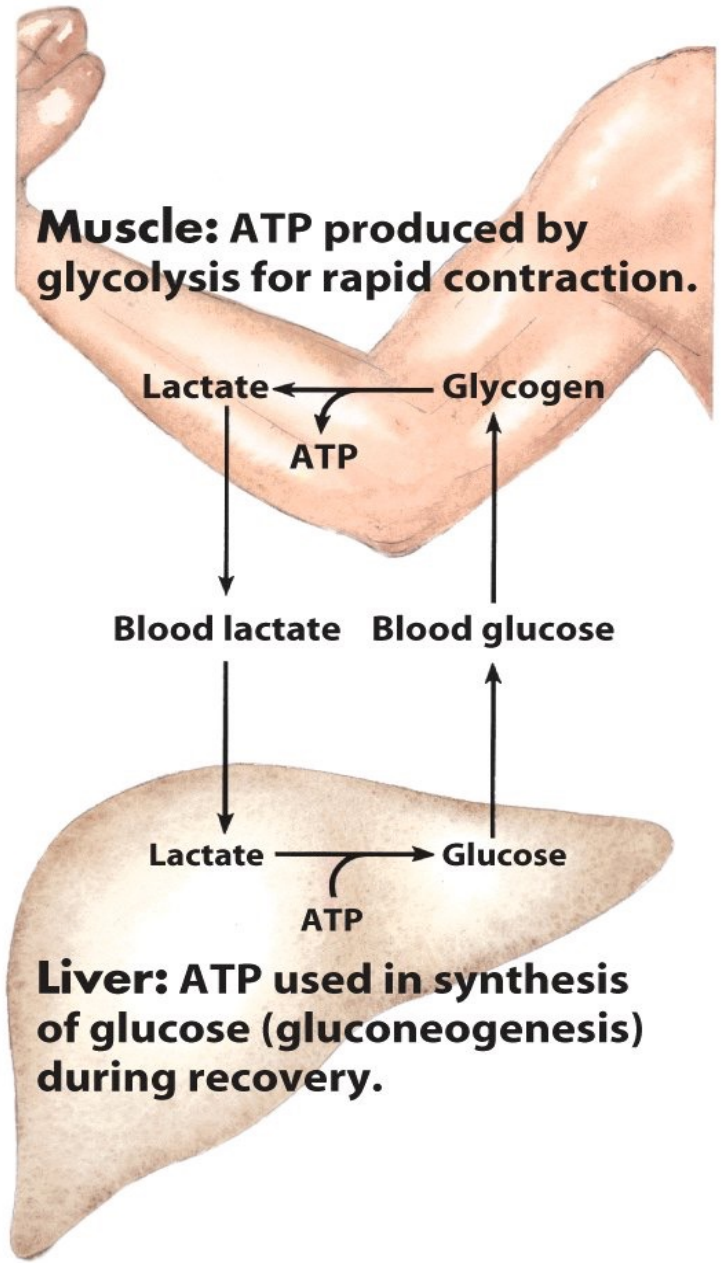
(i) Glucose-1-phosphate is converted by phosphoglucomutase to glucose-6-phosphate.

(ii) Inorganic phosphate is released by glucose 6-phosphatase, and free glucose enters the blood. This enzyme also acts in gluconeogenesis

b. In muscle, glycogen is degraded to provide energy for contraction.

(i) Phosphoglucomutase converts glucose-1-phosphate to glucose-6-phosphate, which enters the pathway of glycolysis and is converted either to lactate or to CO_2 and H_2O, generating ATP.

(ii) Muscle does not contain glucose-6-phosphatase and, therefore, does not contribute to the maintenance of blood glucose levels.



Metabolic cooperation between skeletal muscle and the liver: the Cori cycle

Lysosomal degradation of glycogen

- Glycogen is also degraded by an α-glucosidase located in lysosomes.
- Lysosomal degradation is not necessary for maintaining normal blood glucose levels.
- A lack of this enzyme activity leads to a fatal glycogen storage disease, Pompe disease.

Glycogen storage Diseases

Type	Enzyme Affected	Primary Organ Involved	Manifestations[a]
0	Glycogen synthase	Liver	Hypoglycemia, hyperketonemia, failure to thrive, early death.
I[b]	Glucose 6-phosphatase (Von Gierkes disease)	Liver	Enlarged liver and kidney, growth failure, severe fasting hypoglycemia, acidosis, lipemia, gout, thrombocyte dysfunction.
II	Lysosomal α-glucosidase (Pompe disease): may see clinical symptoms in childhood, juvenile, or adult life stages, depending on the nature of the mutation.	All organs with lysosomes	Infantile form: early-onset progressive muscle hypotonia, cardiac failure, death before age 2 y. Juvenile form: later-onset myopathy with variable cardiac involvement. Adult form: limb-girdle muscular dystrophy-like features. Glycogen deposits accumulate in lysosomes.
III	Amylo-1,6-glucosidase (debrancher): form IIIa is the liver and muscle enzymes, form IIIb is a liver-specific form, and IIIc a muscle-specific form	Liver, skeletal muscle, heart	Fasting hypoglycemia; hepatomegaly in infancy in some myopathic features. Glycogen deposits have short outer branches.
IV	Amylo-4,6-glucosidase (branching enzyme) (Andersen disease)	Liver	Hepatosplenomegaly; symptoms may arise from a hepatic reaction to the presence of a foreign body (glycogen with long outer branches). Usually fatal.
V	Muscle glycogen phosphorylase (McArdle's disease) (expressed as either adult or infantile form)	Skeletal muscle	Exercise-induced muscular pain, cramps, and progressive weakness, sometimes with myoglobinuria.
VI[c]	Liver glycogen phosphorylase (Her's disease) and its activating system (includes mutations in liver phosphorylase kinase and liver PKA)	Liver	Hepatomegaly, mild hypoglycemia; good prognosis.
VII	Phosphofructokinase 1 (Tarui syndrome)	Muscle, red blood cells	As in type V; in addition, enzymopathic hemolysis.
XI	GLUT2 (glucose/galactose transporter); Fanconi–Bickel syndrome	Intestine, pancreas, kidney, liver	Glycogen accumulation in liver and kidney; rickets, growth retardation, glucosuria.

The coordinated regulation of glycogen synthesis and breakdown

Cells are able to receive signals form beyond the plasma membrane and to react on them:

Signal → Receptor → Response

Bacteria: receptors that sample information on pH of the medium, osmotic strength, availability of food, oxygen, light, toxic chemicals, predators

→ response: movement towards food, move away from toxic substances, formation of spores in response to nutrient depletion from the medium, etc.

Plant cells: respond to growth hormones, and to variations in sun light.

Animal cells: exchange information about the concentrations of ions and glucose in extracellular fluids, the interdependent metabolic activities taking place in different tissues, etc.

Signal (information) —signal transduction→ Chemical change (respose)

Regulation of glycogen breakdown

1. Hormones that use 3',5'-cyclic AMP (cAMP) as a second messenger stimulate a mechanism, resulting in the phosphorylation of enzymes.

2. Glycogen degradation is stimulated, and synthesis is inhibited when the enzymes of glycogen metabolism are phosphorylated.

a. Glucagon acts on liver cells and epinephrine (adrenaline) acts on both liver and muscle cells to stimulate glycogen degradation.

- ❑ These hormones via G-proteins activate adenylate cyclase in the cell membrane, which converts ATP to cAMP
- ❑ Adenylate cyclase is also called adenyl or adenylyl cyclase.

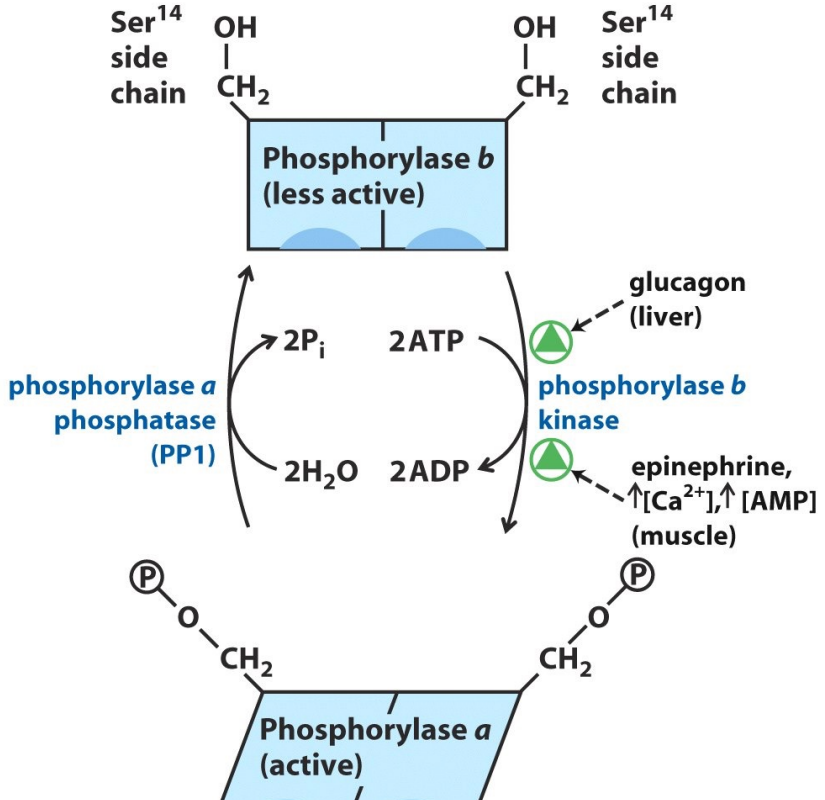
b. cAMP activates protein kinase A, which consists of two regulatory and two catalytic subunits. cAMP binds to the regulatory (inhibitory) subunits, releasing the catalytic subunits in an active form.

c. Protein kinase A phosphorylates glycogen synthase, causing it to be less active, thus decreasing the glycogen synthesis.

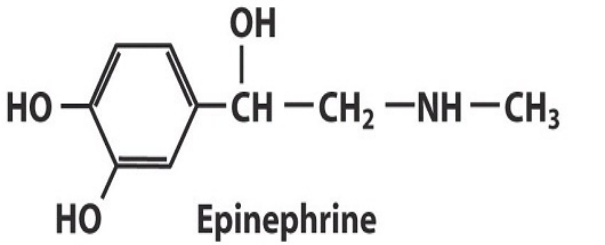
d. Protein kinase A phosphorylates phosphorylase kinase.

e. Phosphorylase kinase phosphorylates phosphorylase b, converting it to its active form, phosphorylase a.

f. Phosphorylase a cleaves glucose residues from the nonreducing ends of glycogen chains, producing glucose-1-phosphate, which is oxidized or, in the liver, converted to blood glucose.



Transduction of the epinephrine signal: the β-adrenergic pathway

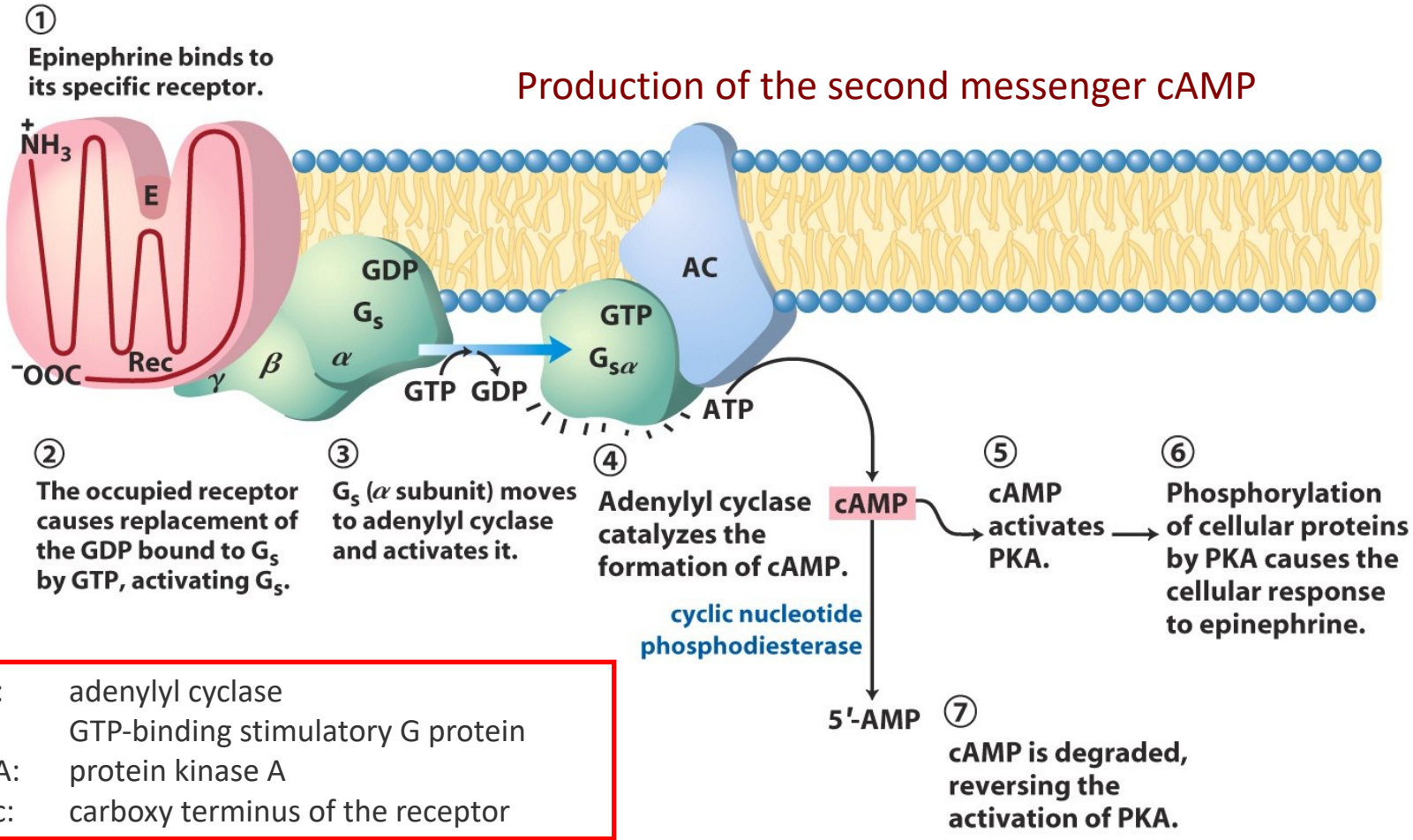


k_d (μM)

5

Epinephrine (adrenaline) is released from the adrenal gland and regulates energy yielding metabolism in muscle, liver and adipose tissue.

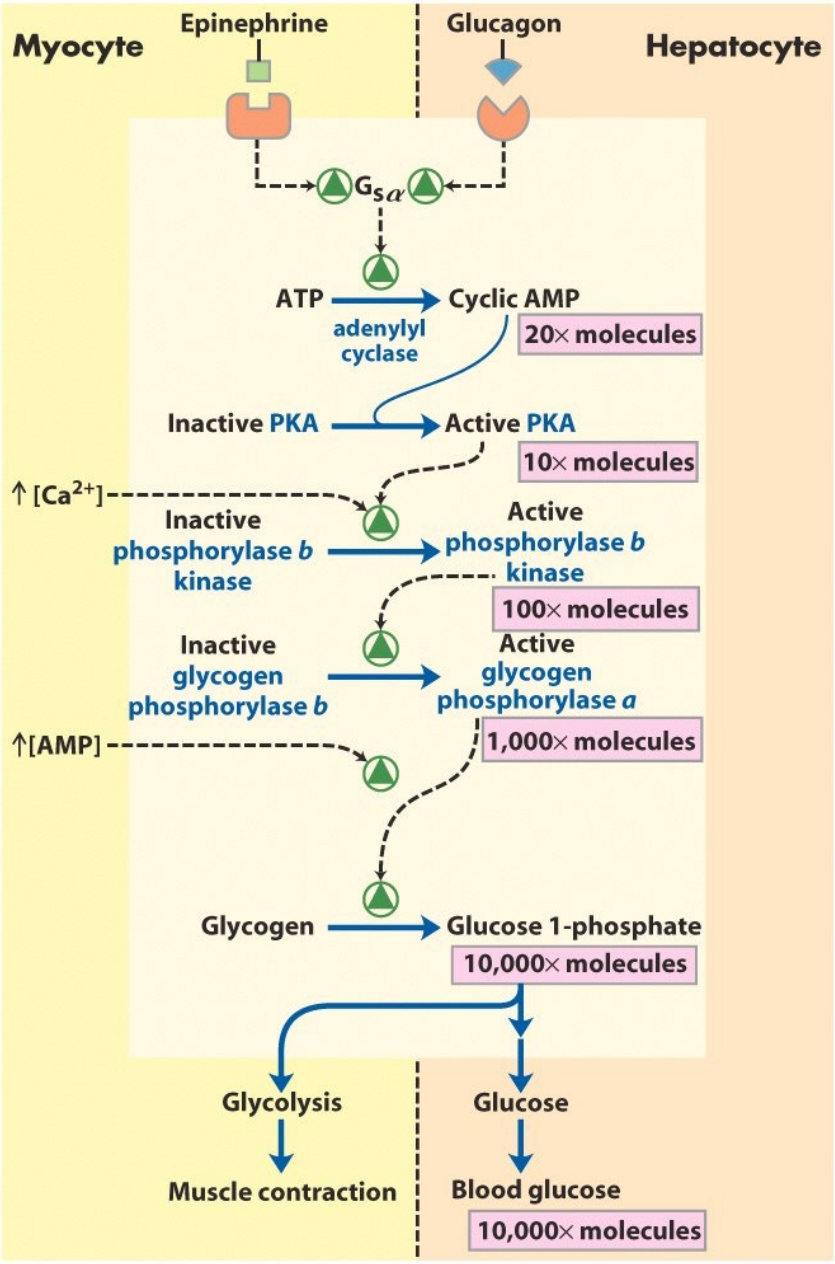
Production of the second messenger cAMP

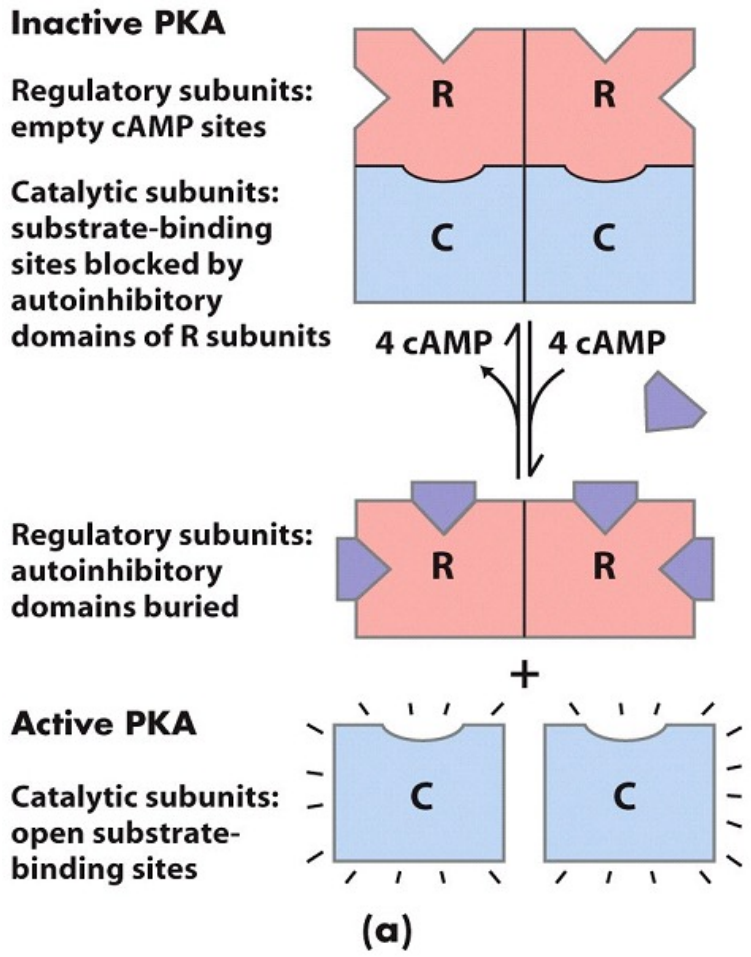


AC:	adenylyl cyclase
G_s:	GTP-binding stimulatory G protein
PKA:	protein kinase A
Rec:	carboxy terminus of the receptor

Cascade mechanism of epinephrine and glucagon action

How does cAMP activate protein kinase?





Regulation of glycogen synthesis

Insulin, which is elevated after a meal, stimulates the synthesis of glycogen in liver and muscle.

1. Factors that promote glycogen synthesis in the liver

a. In the fed state, glycogen degradation decreases because glucagon is low, and the cAMP cascade is not activated.

- ❖ cAMP is converted to AMP by a cell membrane phosphodiesterase.
- ❖ As cAMP decreases, the regulatory subunits rejoin the catalytic subunits of protein kinase A, and the enzyme is inactivated.
- ❖ Dephosphorylation of phosphorylase kinase and phosphorylase a causes these enzymes to be inactivated.

➔ Insulin causes the activation of the phosphatases that dephosphorylate these enzymes.

(i) A key phosphatase is protein phosphatase I (PP-1).

(ii) PP-1 is regulated by a protein inhibitor, which is activated by phosphorylation by protein kinase A. The inhibitor, when phosphorylated, binds to and inhibits PP-1 activity.

(iii) The PP-1:inhibitor complex allows for slow hydrolysis of the phosphorylated inhibiton by PP-1. When the inhibitor is dephosphorylated, it no longer has affinity for PP-1 and falls out of the complex, leading to a fully active PP-1.

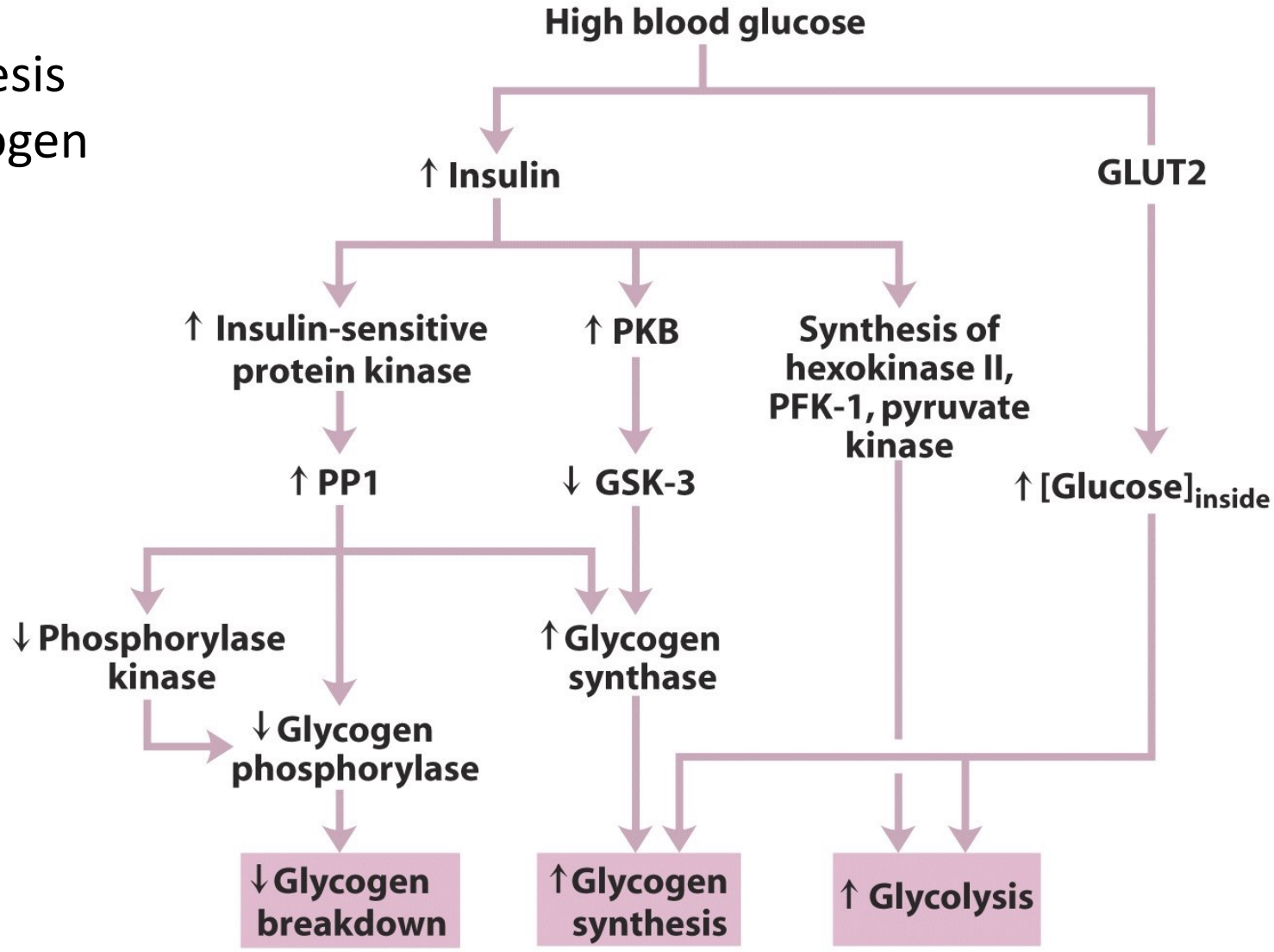
b. **Glycogen synthesis is promoted by the activation of glycogen synthase** and by the increased concentration of glucose, which enters liver cells from the hepatic portal vein.

- ❖ The inactive, phosphorylated form of glycogen synthase is dephosphorylated, causing the enzyme to become active Insulin causes the activation of the phosphatase that catalyzes this reaction.

Regulation of carbohydrate metabolism in the hepatocyte

High blood glucose levels

➡ stimulation of glycogen synthesis and glycolysis, and inhibition of glycogen breakdown



Regulation of glycogen synthesis….continued

2. Factors that promote glycogen synthesis in the Muscle

a) After a meal, muscle will have low levels of cAMP, AMP, and Ca^{2+} if it is not contracting and epinephrine is low. Consequently, muscle glycogen degradation will not occur.

b) Insulin stimulates glycogen synthesis by mechanisms similar to those in the liver.

c) In addition, insulin stimulates the transport of glucose into muscle cells, providing increased substrate for glycogen synthesis.

Clinical correlates

CLINICAL CORRELATES

Insulinomas and glucagonomas are rare neuroendocrine tumors of the pancreas that can episodically release large amounts of either insulin or glucagon, respectively. Insulinomas will lead to **hypoglycemia**, due to the stimulation of glucose transport into the muscle and fat cells, particularly if the insulin is released under fasting conditions. Glucagonomas will lead to **hyperglycemia**, as the liver is instructed to release glucose via glycogenolysis and gluconeogenesis in the presence of glucagon.

Q & A