15 The Metabolism of Glycogen in Animals

P1 Principle 1 (1 of 2)

Glycogen provides vertebrate animals with a ready source of glucose to supply the brain and skeletal muscles with energy. Although animals store about 100 times more energy as fat than as glycogen, they cannot metabolize fat into glucose. The highly branched polymeric structure of glycogen granules allows cells in the liver and muscle to make large numbers of glucose and glucose phosphate monomers available quickly without raising the osmolarity of the cytosol by storing them in monomeric form.

P2 Principle 2 (1 of 3)

Monomers are released from glycogen granules by a phosphorolysis reaction that creates phosphorylated glucose molecules that can enter glycolysis to supply energy to the cell. Skeletal muscle cells especially require stores of glycogen to supply energy for bursts of activity. In the liver, the phosphate can be removed, allowing free glucose to be transported out of the cell to the blood for use in the brain and other tissues when dietary glucose is not sufficient.

P3 Principle 3 (1 of 4)

Glycogen synthesis requires a protein primer and an activated glucose precursor. Individual glucose molecules activated as sugar nucleotides are added to the nonreducing end of the growing linear chains in the outer tiers of the glycogen *β*-granules, and a branching enzyme adds branches periodically.

P4 Principle 4 (1 of 7)

Regulation of the balance between the formation of glycogen from excess glucose and the release of glucose from glycogen polymers when it is needed in metabolism is a critical function of cellular and organismal homeostasis. This balance, ultimately controlled by the hormones epinephrine, glucagon, and insulin, is achieved through allosteric regulation and phosphorylation of the synthetic and degradative enzymes. These enzymes and the regulatory proteins that act on them are integral parts of the glycogen granule.

15.1 The Structure and Function of Glycogen

P1 Principle 1 (2 of 2)

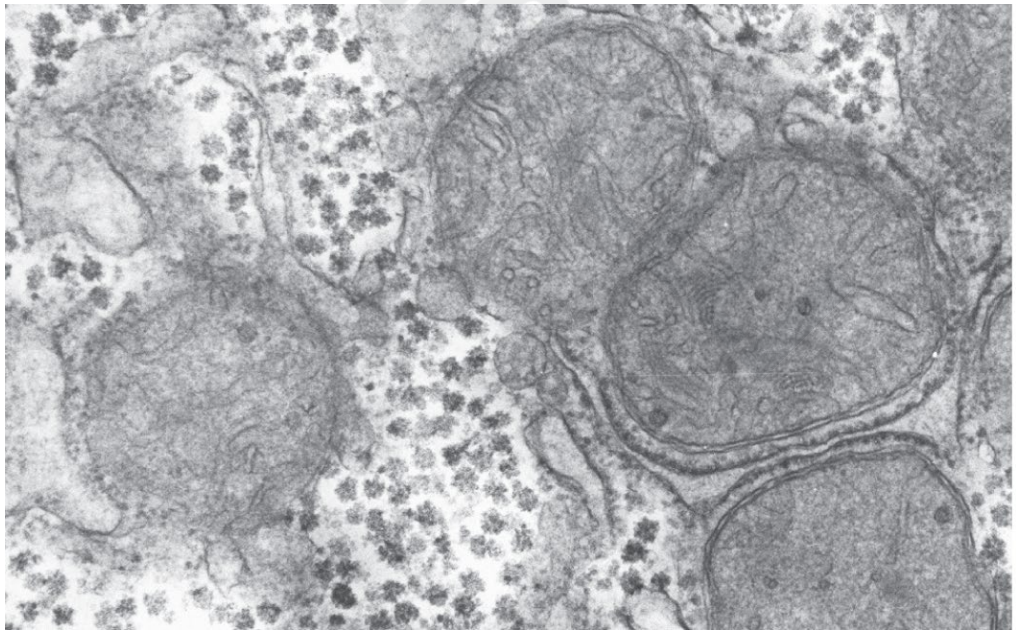
Glycogen provides vertebrate animals with a ready source of glucose to supply the brain and skeletal muscles with energy. Although animals store about 100 times more energy as fat than as glycogen, they cannot metabolize fat into glucose. The highly branched polymeric structure of glycogen granules allows cells in the liver and muscle to make large numbers of glucose and glucose phosphate monomers available quickly without raising the osmolarity of the cytosol by storing them in monomeric form.

Vertebrate Animals Require a Ready Fuel Source for Brain and Muscle

- glycogen = a polymeric storage form of glucose in animals that is found primarily in muscle and liver
- glycogen breakdown in muscle delivers glucose needed for muscle contraction within seconds
- glycogen stored in the liver provides a reservoir that maintains homeostasis of blood glucose

Glycogen Granules Have Many Tiers of Branched Chains of D-Glucose

- glycogen β-granules = cytosolic granules that vary in size, structure, and subcellular location
  - appear as electron-dense particles



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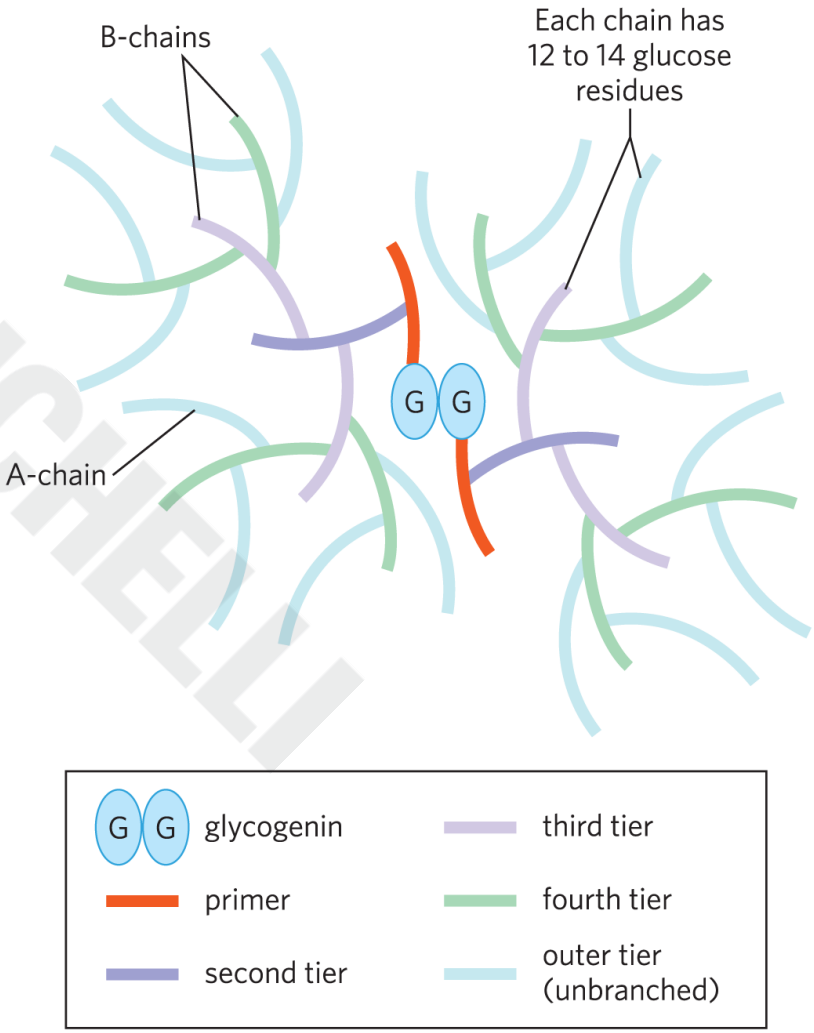
β-Granules Cluster to Form α-Granules in the Liver

- α-granules = protein-rich granules composed of 20-40 clustered β-granules
  - release glucose slower than β-granules
  - visible in well-fed animals, but absent after a 24-hour fast
  - often associate with tubules of the smooth ER

Structure of a Glycogen β-Granule

- glycogenin dimer = serves as a primer
- tiers of glucose residues are in (α1⟶4) linkage, with (α1⟶6)-linked branches
  - provides many free nonreducing ends



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15.2 Breakdown and Synthesis of Glycogen

Glycogenolysis and Glycogenesis

- **glycogenolysis** = the breakdown of cellular glycogen to glucose 1-phosphate

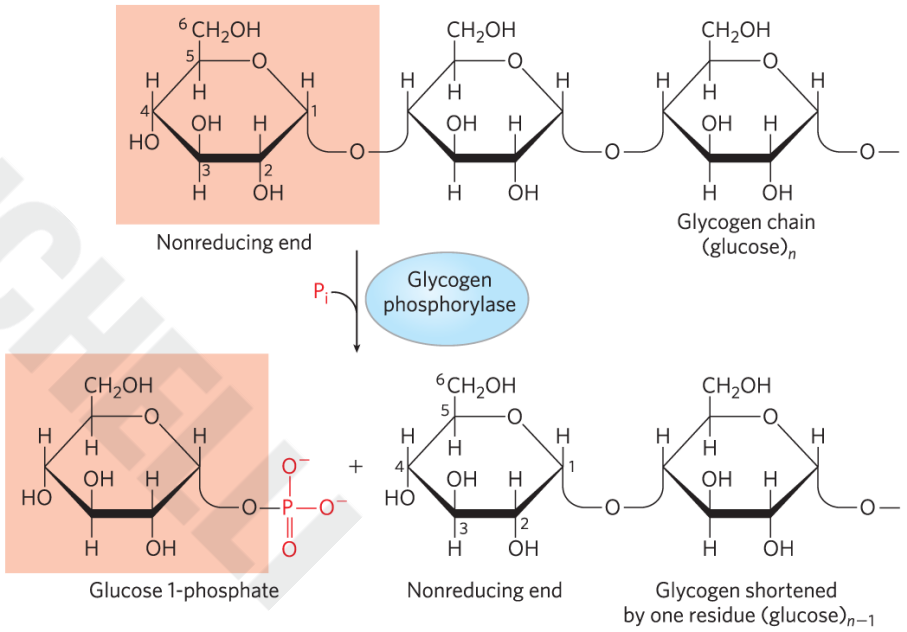
- **glycogenesis** = the synthesis of glycogen

P2 Principle 2 (2 of 3)

Monomers are released from glycogen granules by a phosphorolysis reaction that creates phosphorylated glucose molecules that can enter glycolysis to supply energy to the cell. Skeletal muscle cells especially require stores of glycogen to supply energy for bursts of activity. In the liver, the phosphate can be removed, allowing free glucose to be transported out of the cell to the blood for use in the brain and other tissues when dietary glucose is not sufficient.

Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase

- glycogen phosphorylase = catalyzes phosphorolytic cleavage at the nonreducing ends of glycogen chains
  - requires pyridoxal phosphate
  - acts repetitively until it reaches a point four residues away from a (α1⟶6) branch point



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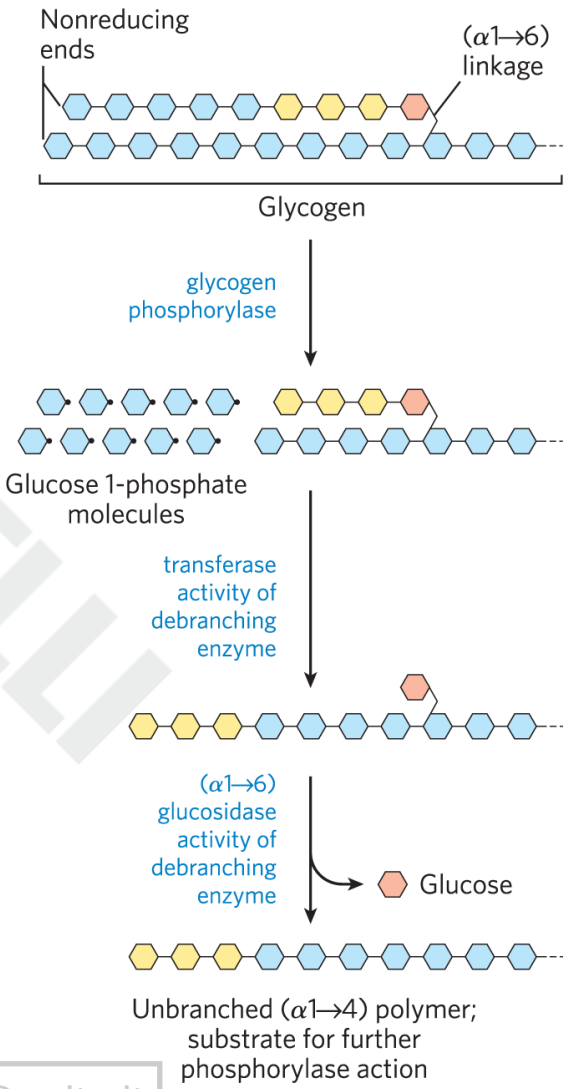
Debranching Enzyme

- **debranching enzyme** = transfers branches onto main chains and releases the residue at the (α1⟶6) branch as free glucose



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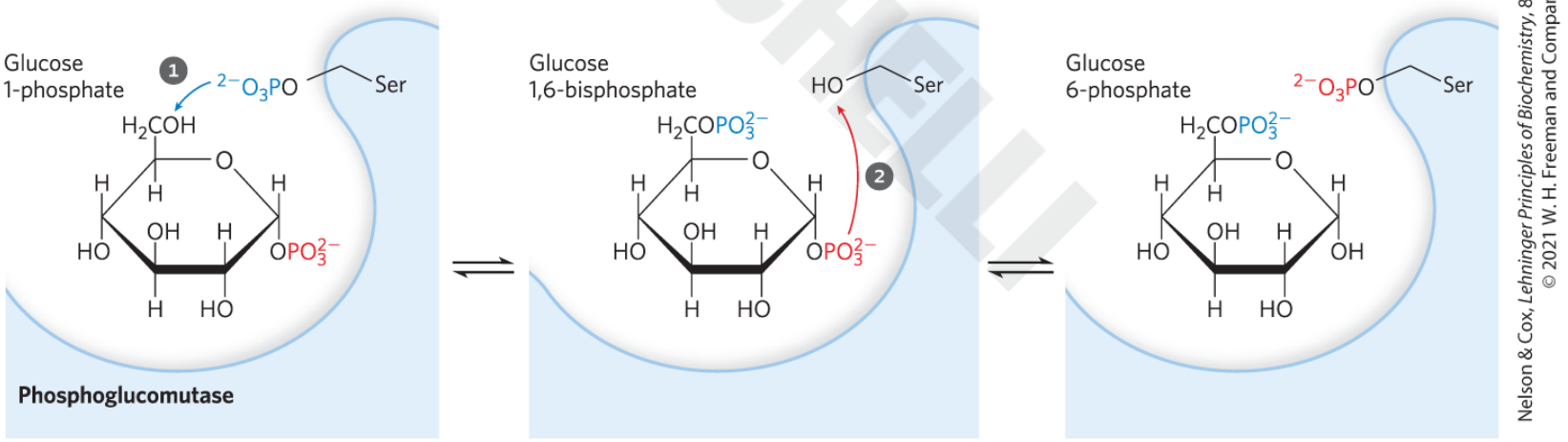
Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose

- **phosphoglucomutase** = catalyzes the reversible conversion of glucose 1-phosphate to glucose 6-phosphate



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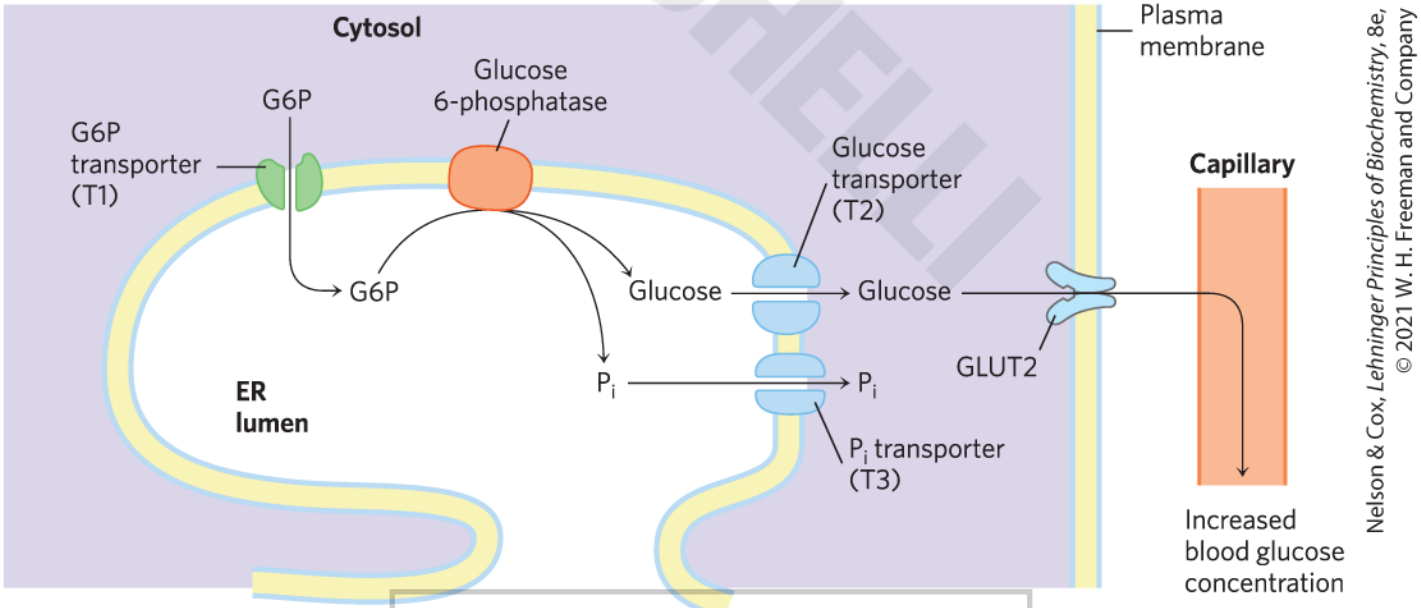
P2 Principle 2 (3 of 3)

Monomers are released from glycogen granules by a phosphorolysis reaction that creates phosphorylated glucose molecules that can enter glycolysis to supply energy to the cell. Skeletal muscle cells especially require stores of glycogen to supply energy for bursts of activity. In the liver, the phosphate can be removed, allowing free glucose to be transported out of the cell to the blood for use in the brain and other tissues when dietary glucose is not sufficient.

Fates of Glucose 6-Phosphate

- in skeletal muscle, glucose 6-phosphate enters glycolysis

- in liver, glucose 6-phosphatase converts glucose 6-phosphate to glucose in the ER for export to replenish blood glucose



Glycogen Storage Diseases

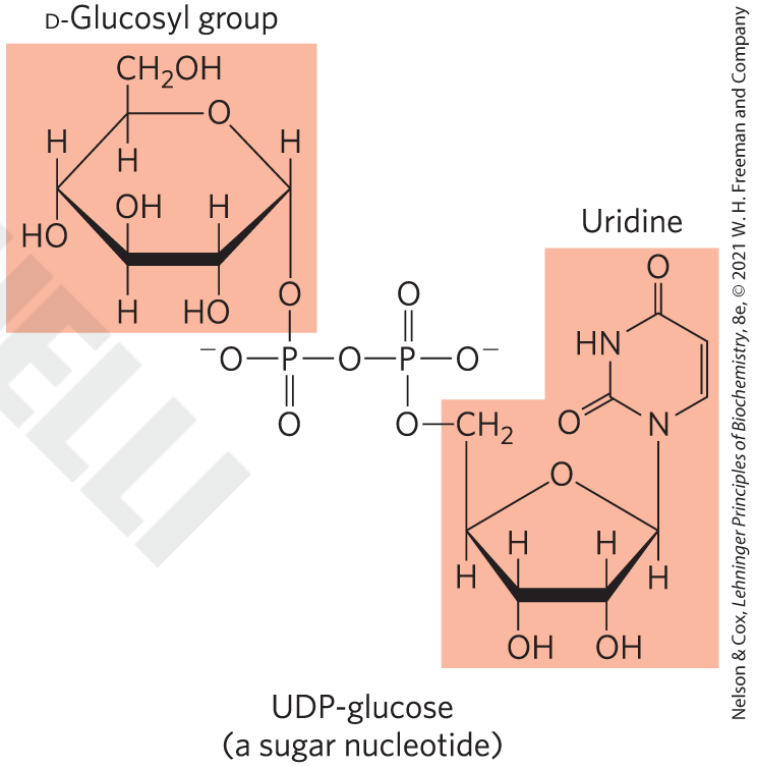
- genetic defects in either glucose 6-phosphatase or the glucose 6-phosphate transporter T1 cause type Ia glycogen storage disease

Table 1 Glycogen Storage Diseases of Humans

Type (name)	Enzyme affected	Primary organ/ cells affected	Symptoms
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone, bodies, early death
Type Ia (von Gierke)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in type Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P, transporter	Liver	As in type Ia
Type II (Pompe)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori or Forbes)	Debranching enzyme	Liver, skeletal, and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui)	Muscle PFK-1	Muscle, erythrocytes	As in type V; also hemolytic anemia
Type VIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction

The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis

- **sugar nucleotides** = compounds in which the anomeric carbon of a sugar is activated by attachment to a nucleotide through a phosphate ester linkage
  - involved in reactions where hexoses are transformed or polymerized



P3 Principle 3 (2 of 4)

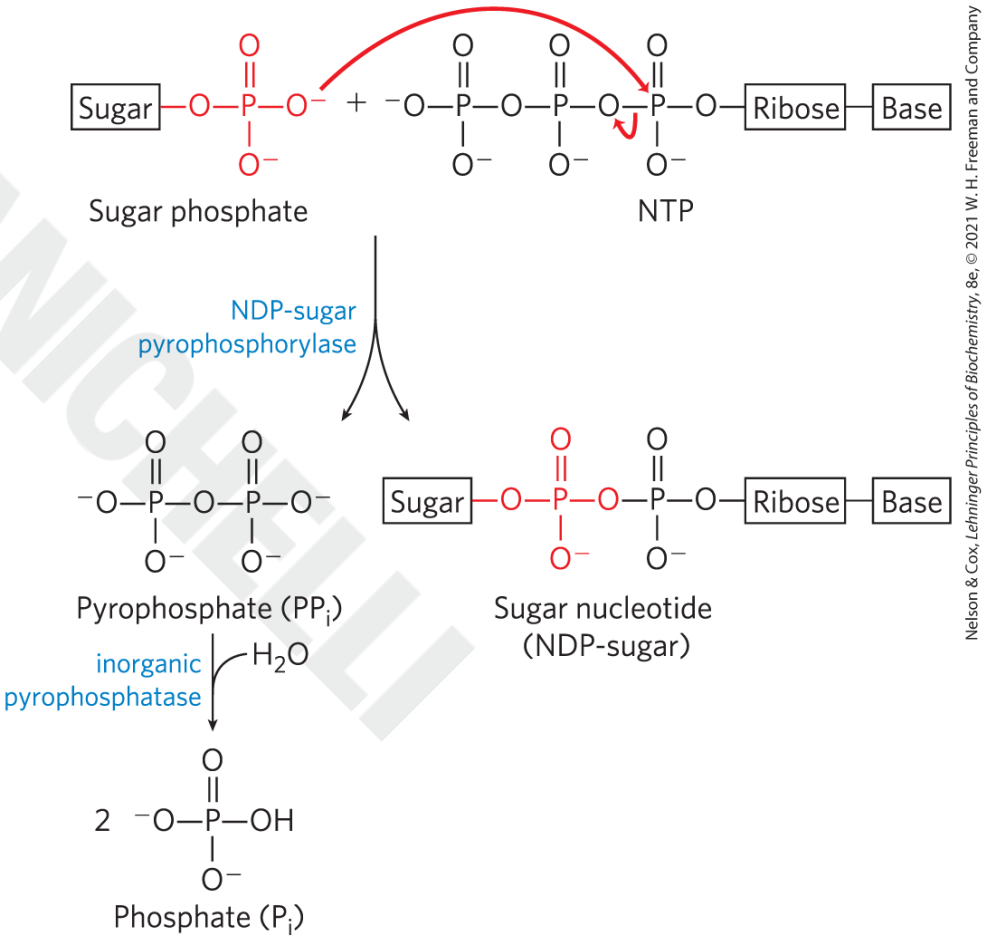
Glycogen synthesis requires a protein primer and an activated glucose precursor. Individual glucose molecules activated as sugar nucleotides are added to the nonreducing end of the growing linear chains in the outer tiers of the glycogen *β*-granules, and a branching enzyme adds branches periodically.

Properties of Sugar Nucleotides

- sugar nucleotides are suitable for biosynthetic reactions because:
  - their formation is metabolically irreversible
  - the nucleotide moiety has many groups that can undergo noncovalent interactions with enzymes
  - the nucleotidyl group (UDP, ADP) is an excellent leaving group, facilitating nucleophilic attack
  - “tagging” with nucleotidyl groups distinguishes the hexoses from hexoses destined for other purposes

Formation of a Sugar Nucleotide

- rapid removal of the product, driven by the large, negative free-energy change of PP_i ($\Delta G'° = -19.2$ kJ/mol) hydrolysis, pulls the synthetic reaction forward



Net reaction: Sugar phosphate + NTP ⟶ NDP-sugar + $2P_i$

Glycogen Synthesis Begins With Glucose 6-Phosphate

- sources of glucose 6-phosphate:
  - hexokinase isozymes derive glucose 6-phosphate from glucose
  - lactate taken up by the liver is converted to glucose 6-phosphate by gluconeogenesis

- phosphoglucomutase = converts glucose 6-phosphate to glucose 1-phosphate

UDP-Glucose Pyrophosphorylase Catalyzes A Key Step of Glycogen Biosynthesis

- **UDP-glucose pyrophosphorylase** = converts glucose 1-phosphate to UDP-glucose

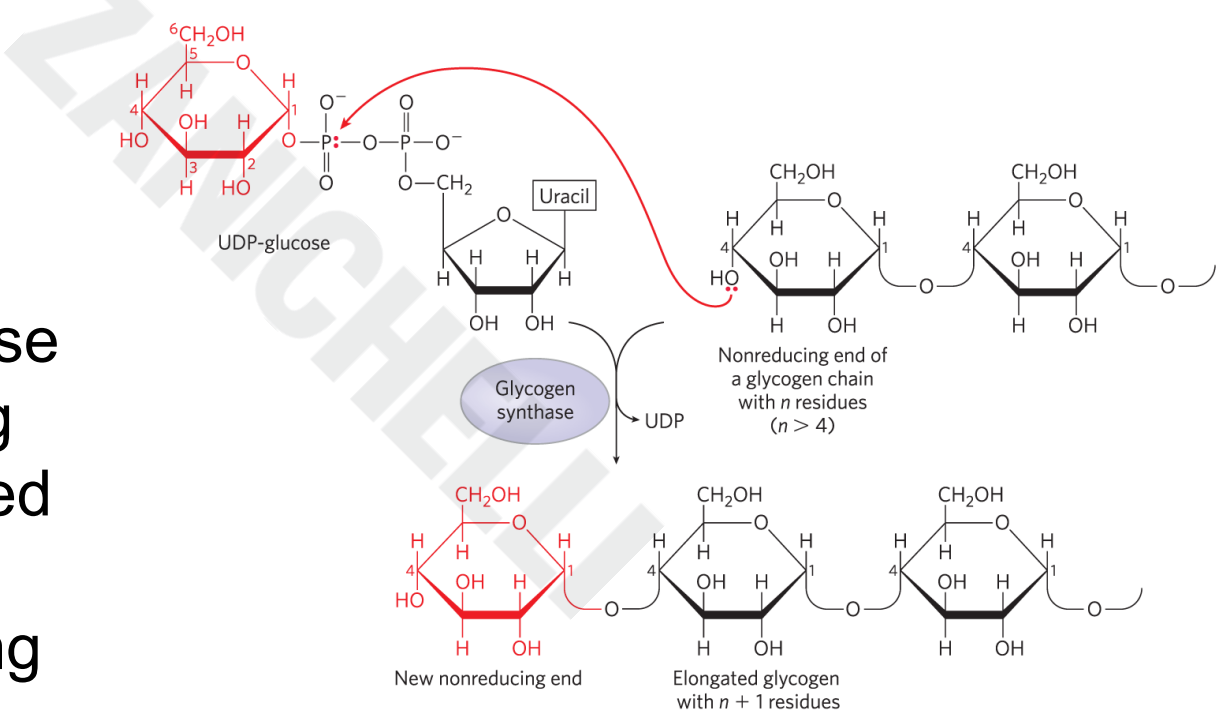
glucose 1-phosphate + UTP ⟶ UDP-glucose + PP_i

P3 Principle 3 (3 of 4)

Glycogen synthesis requires a protein primer and an activated glucose precursor. Individual glucose molecules activated as sugar nucleotides are added to the nonreducing end of the growing linear chains in the outer tiers of the glycogen *β*-granules, and a branching enzyme adds branches periodically.

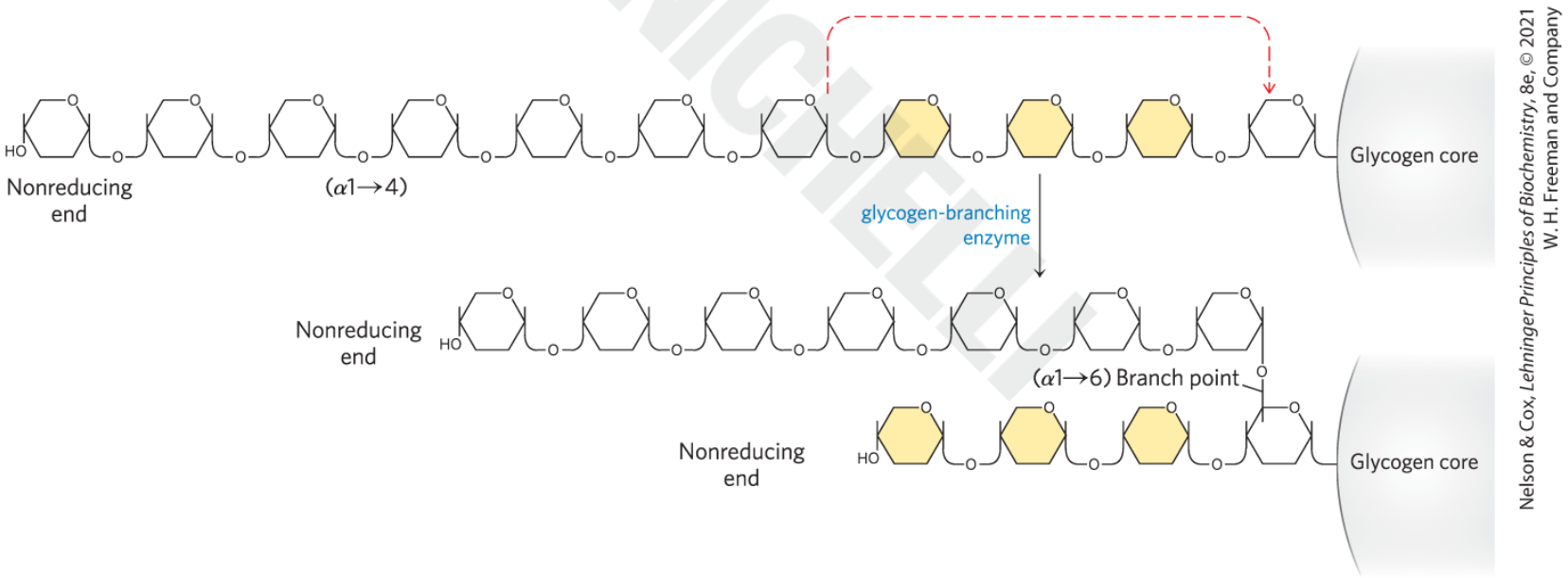
UDP-Glucose Donates Glucose to a Nonreducing End of Glycogen

- **glycogen synthase** = catalyzes the transfer of the glucose residue from UDP-glucose to a nonreducing end of a branched glycogen molecule, forming an (α1⟶ 4) linkage



Glycogen-Branching Enzyme

- **glycogen-branching enzyme** = catalyzes the formation of the (α1⟶6) bonds found at the branch points of glycogen



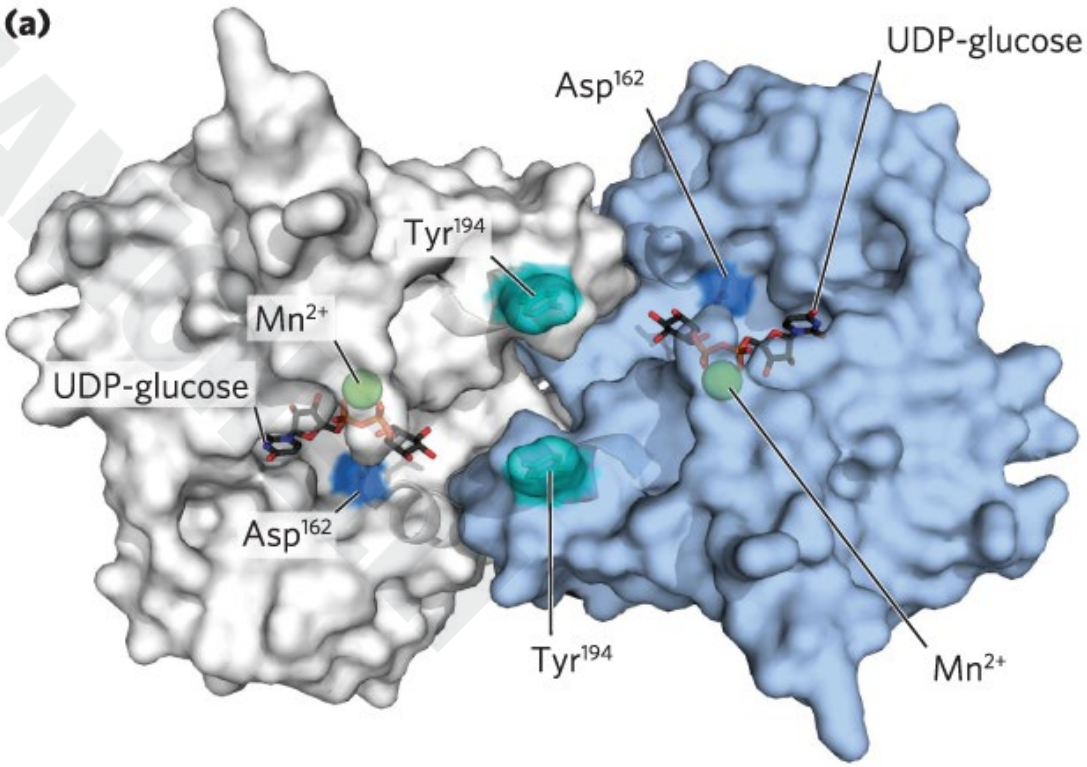
P3 Principle 3 (4 of 4)

Glycogen synthesis requires a protein primer and an activated glucose precursor. Individual glucose molecules activated as sugar nucleotides are added to the nonreducing end of the growing linear chains in the outer tiers of the glycogen *β*-granules, and a branching enzyme adds branches periodically.

Glycogenin Primes the Initial Sugar Residues in Glycogen

- glycogen synthase requires a primer

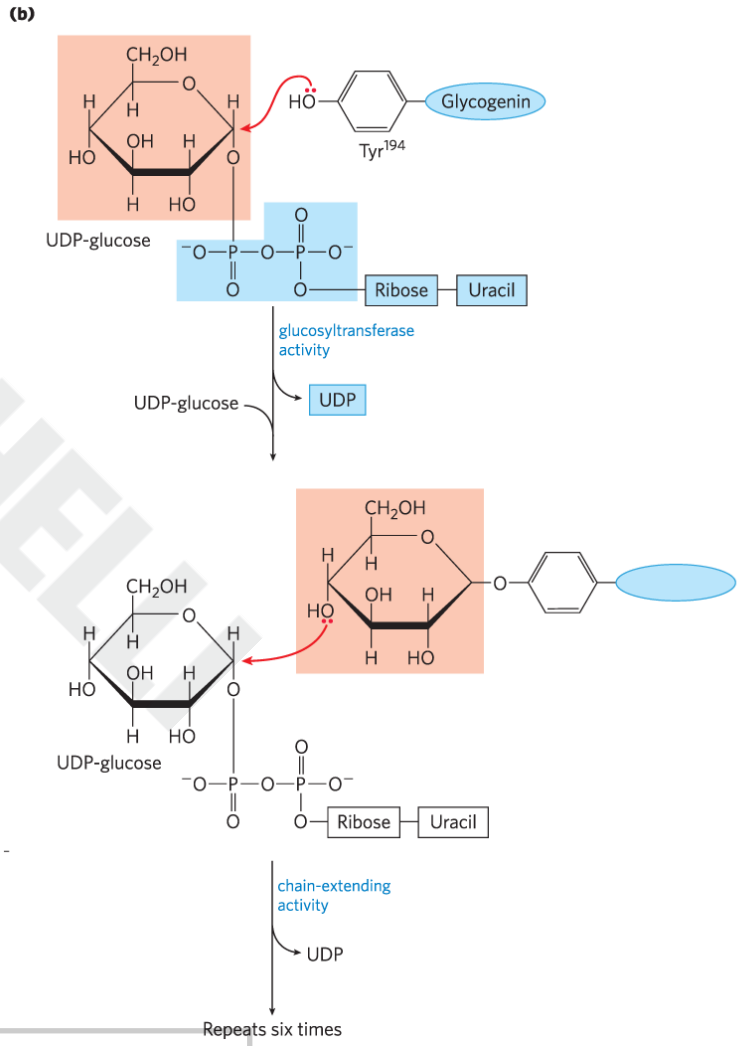
- **glycogenin** = the primer on which new chains are assembled and the enzyme that catalyzes their assembly



The Glycogenin Mechanism

- 1st reaction = autocatalytic formation of a glycosidic bond between the glucose of UDP-glucose and Tyr194 of glycogenin

- 2nd reaction = addition of seven more glucose residues, each from UDP-glucose, to form a primer that can be acted on by glycogen synthase



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15.3 Coordinated Regulation of Glycogen Breakdown and Synthesis

P4 Principle 4 (2 of 7)

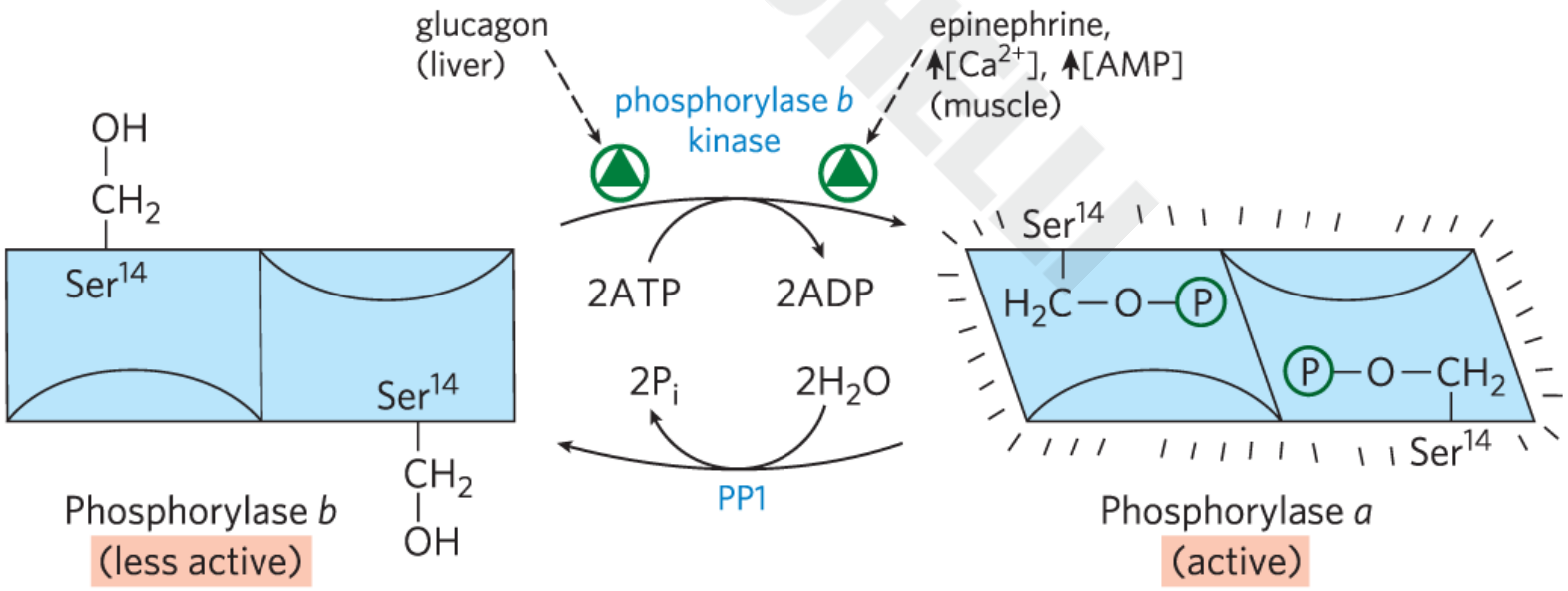
Regulation of the balance between the formation of glycogen from excess glucose and the release of glucose from glycogen polymers when it is needed in metabolism is a critical function of cellular and organismal homeostasis. This balance, ultimately controlled by the hormones epinephrine, glucagon, and insulin, is achieved through allosteric regulation and phosphorylation of the synthetic and degradative enzymes. These enzymes and the regulatory proteins that act on them are integral parts of the glycogen granule.

Glycogen Phosphorylase Is Regulated by Hormone-Stimulated Phosphorylation and by Allosteric Effectors

- skeletal glycogen phosphorylase has two forms:
  - **glycogen phosphorylase *a*** = catalytically active
  - **glycogen phosphorylase *b*** = much less active

Regulation of Muscle Glycogen Phosphorylase by Covalent Modification

- epinephrine (from vigorous muscle activity) and glucagon (in the liver) trigger phosphorylation of phosphorylase *b*, converting it to phosphorylase *a*



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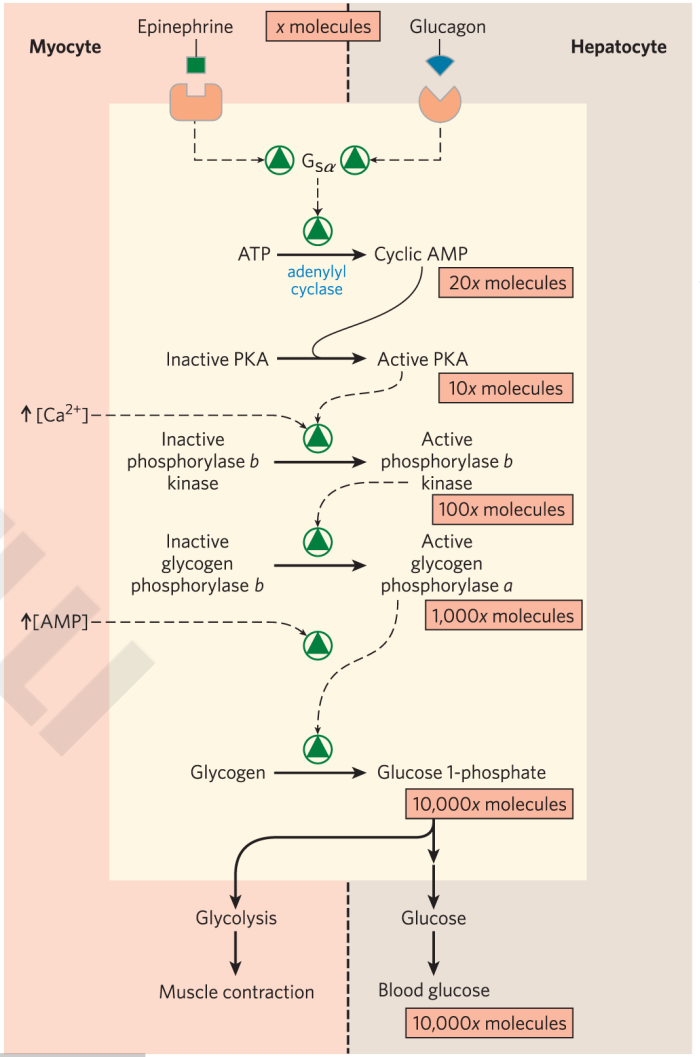
Elevated [cAMP] Initiates an Enzyme Cascade

- **enzyme cascade** = sequence of enzymatic reactions in which a catalyst activates a catalyst, which activates a catalyst

- rise in [cAMP] activates PKA, which phosphorylates **phosphorylase *b* kinase**

- **phosphorylase *b* kinase =** catalyzes the phosphorylation of glycogen phosphorylase *b*



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P4 Principle 4 (3 of 7)

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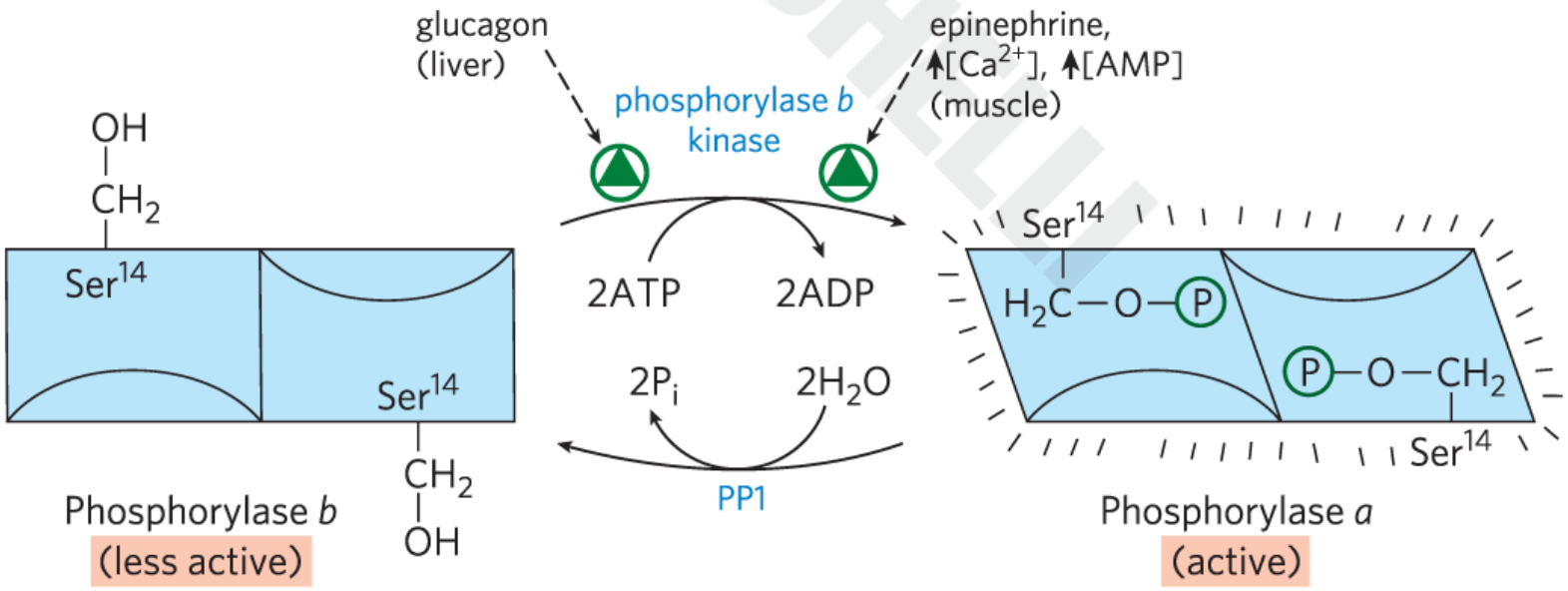
Allosteric Control Mechanisms

- Ca^{2+} is a signal for muscle contraction
  - binds to and activates phosphorylase *b* kinase
- AMP accumulates in vigorously contracting muscle
  - binds to and activates phosphorylase to speed up glucose 1-phosphate release from glycogen
- ATP blocks the allosteric site, inactivating phosphorylase

Phosphoprotein Phosphatase 1 (PP1)

- **phosphoprotein phosphatase 1 (PP1)** = removes phosphoryl groups from phosphorylase *a*, converting it to the less active form, phosphorylase *b*



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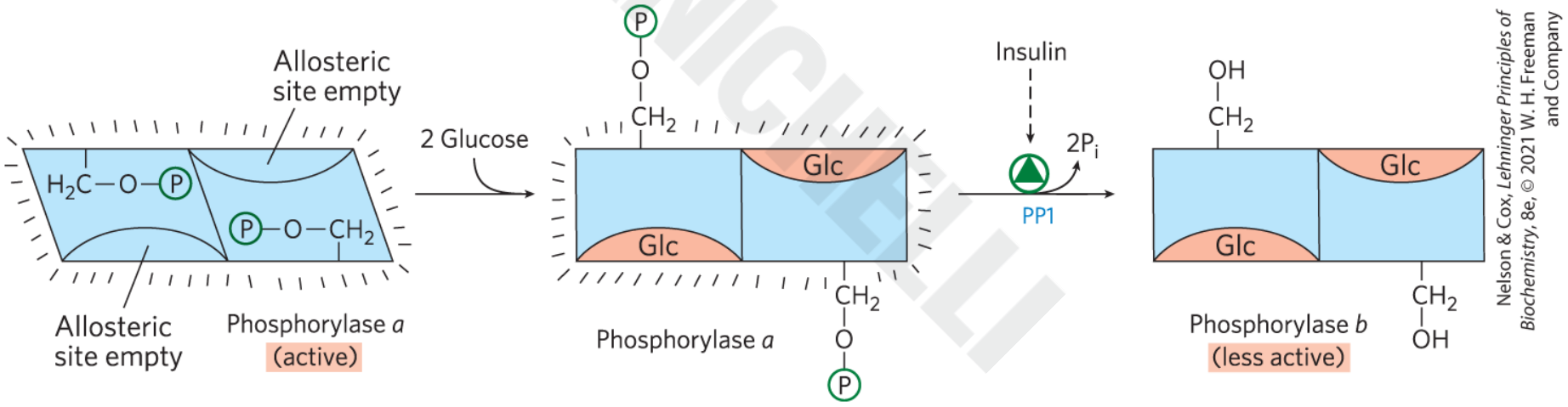
Liver Glycogen Phosphorylase *a* is a Glucose Sensor

- glucose binds to an allosteric site on phosphorylase *a*, making it more susceptible to dephosphorylation by PP1



P4 Principle 4 (4 of 7)

Regulation of the balance between the formation of glycogen from excess glucose and the release of glucose from glycogen polymers when it is needed in metabolism is a critical function of cellular and organismal homeostasis. This balance, ultimately controlled by the hormones epinephrine, glucagon, and insulin, is achieved through allosteric regulation and phosphorylation of the synthetic and degradative enzymes. These enzymes and the regulatory proteins that act on them are integral parts of the glycogen granule.

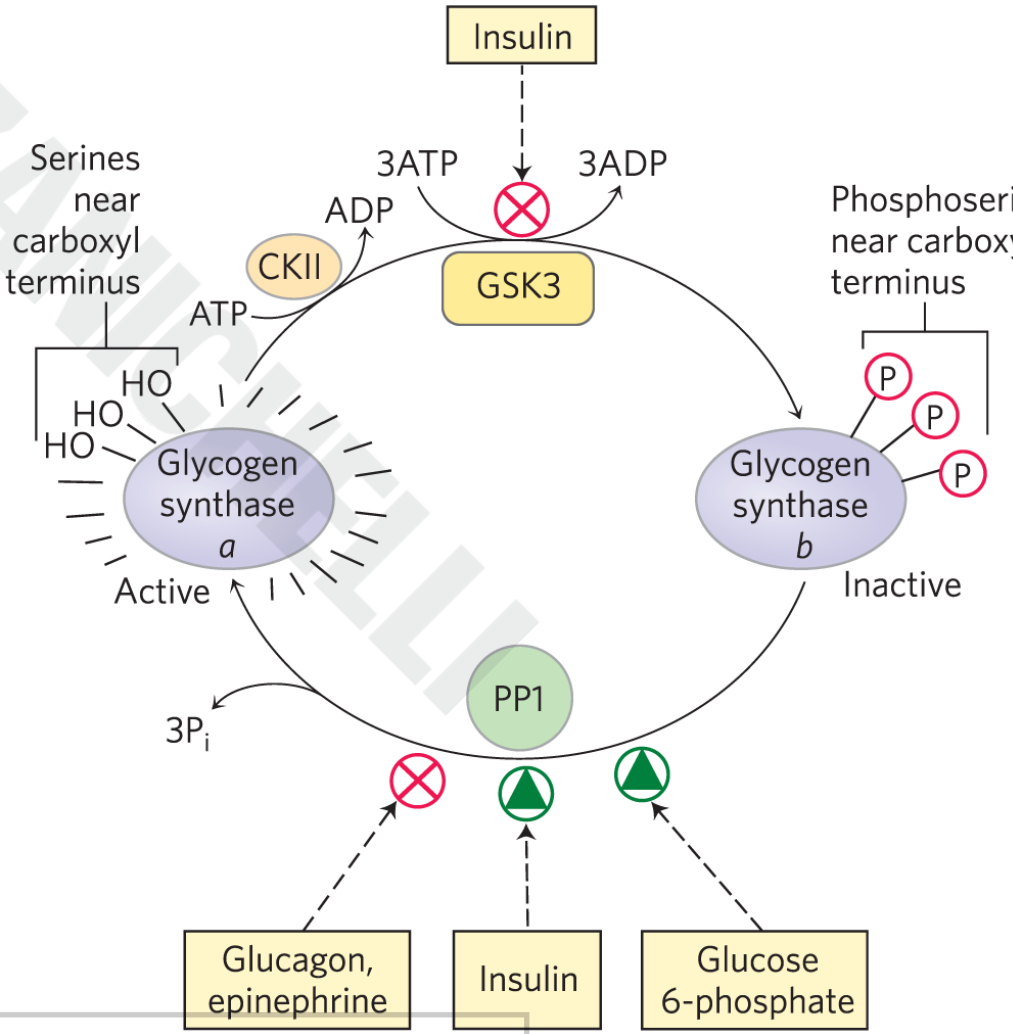
Glycogen Synthase Also Is Subject to Multiple Levels of Regulation

- glycogen synthase has two forms:
  - **glycogen synthase *a*** = unphosphorylated and catalytically active
  - **glycogen synthase *b*** = phosphorylated and inactive unless glucose 6-phosphate is present

- **glycogen synthase kinase 3 (GSK3)** = catalyzes the phosphorylation of glycogen synthase *a*

Effects of GSK3 on Glycogen Synthase Activity

- insulin inactivates GSK3 and activates PP1
- glucose 6-phosphate acts allosterically to make glycogen synthase *b* a better substrate for PP1



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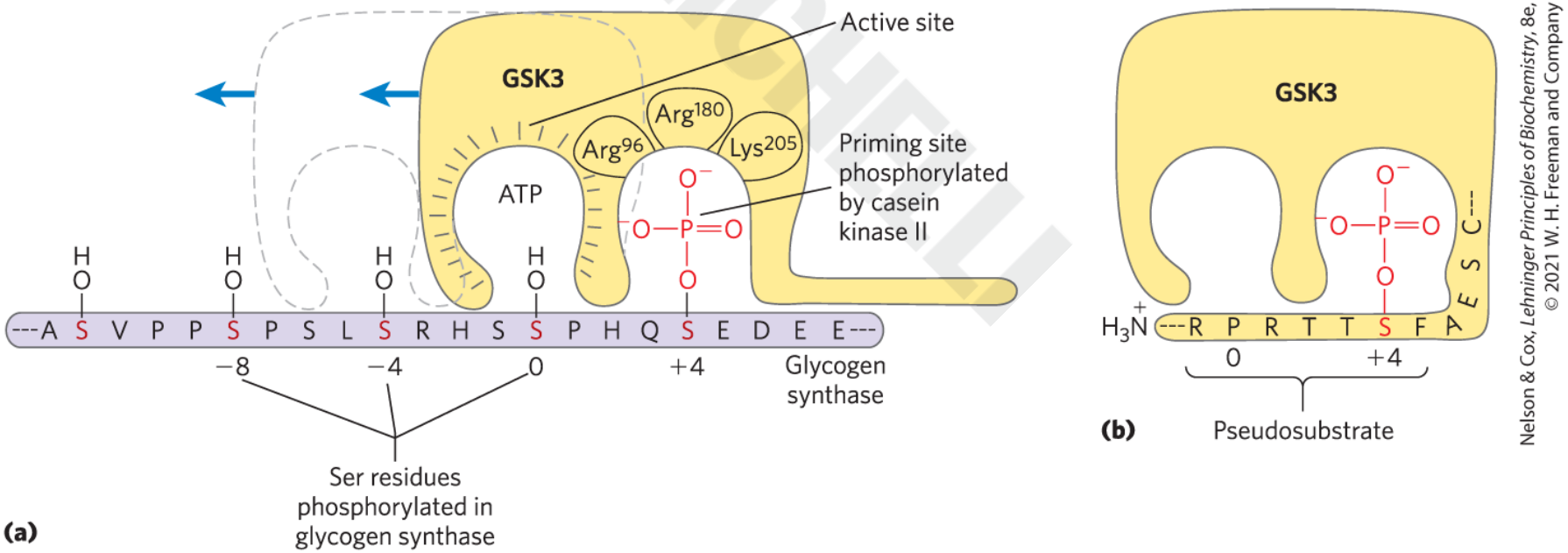
The Action of GSK3 is Hierarchical

- GSK3 cannot phosphorylate glycogen synthase until **casein kinase II (CKII)** has phosphorylated the glycogen synthase on a nearby residue (a **priming** event)



P4 Principle 4 (5 of 7)

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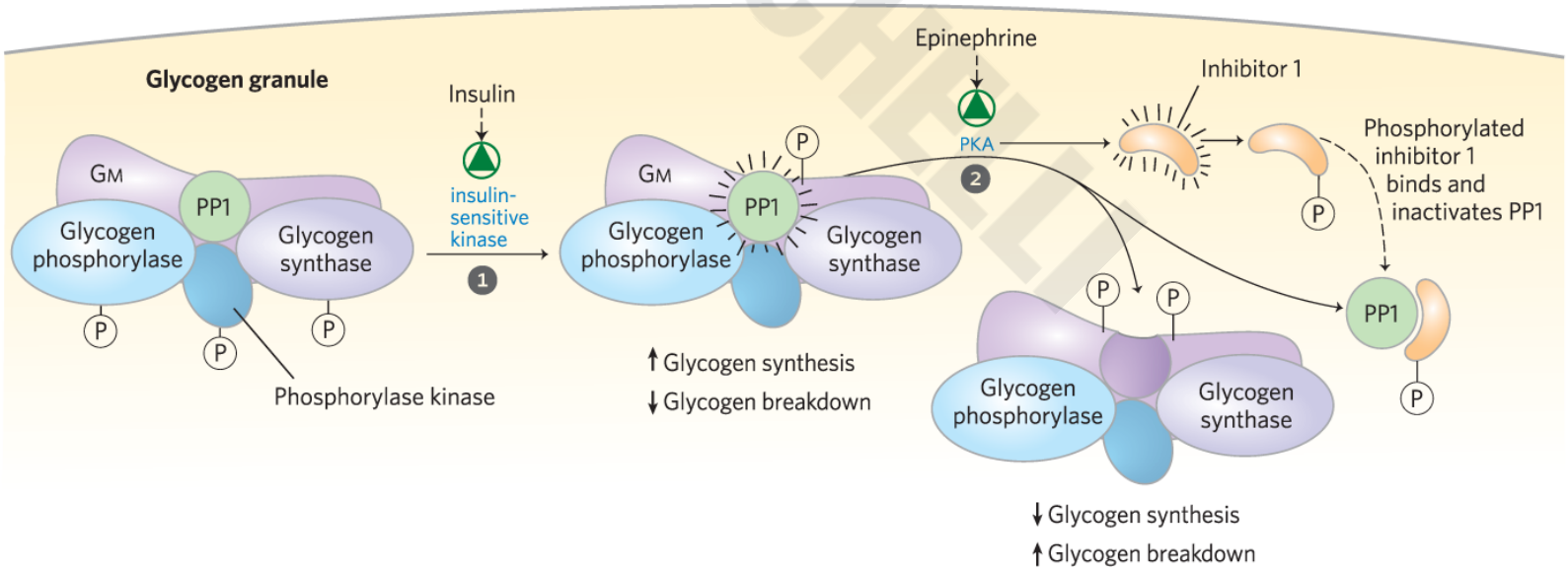
Glycogen-Targeting Proteins

- **glycogen-targeting protein** = regulatory subunit of PP1 that serves as a scaffold, binding glycogen, phosphorylase kinase, glycogen phosphorylase, and glycogen synthase



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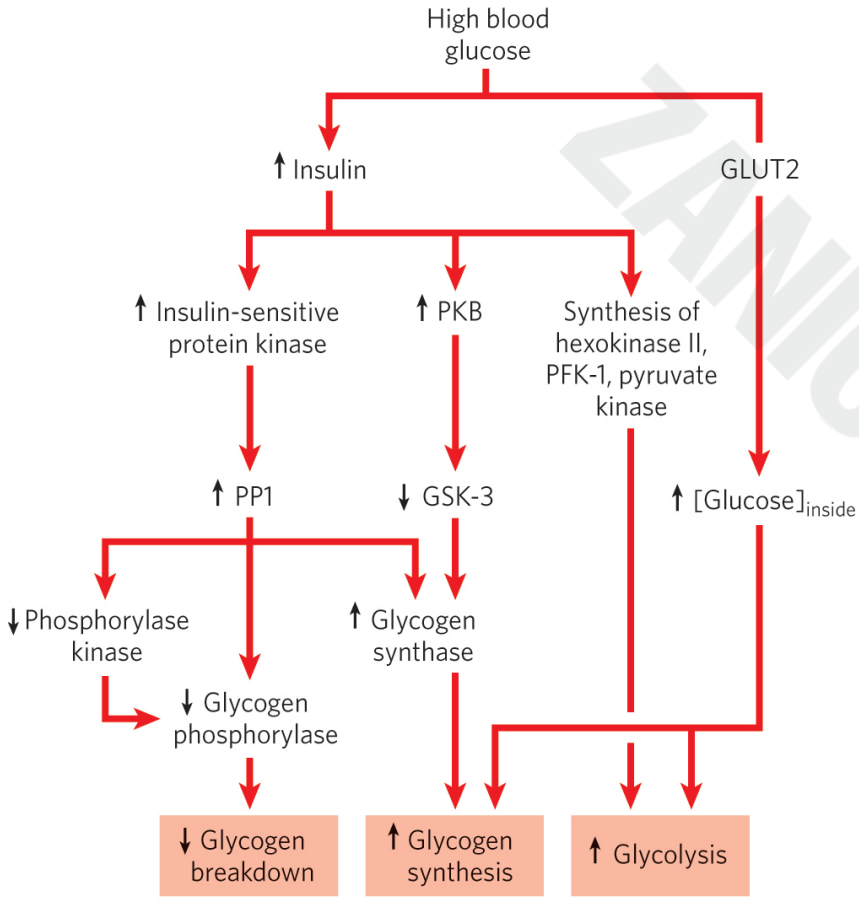
Allosteric and Hormonal Signals Coordinate Carbohydrate Metabolism Globally

- in the liver:
  - insulin activates glycogen synthase by inactivating GSK3 and activating PP1
  - glucagon stimulates glycogen breakdown and gluconeogenesis while blocking glycolysis

- in muscle, epinephrine provides ATP by stimulating glycogen breakdown and glycolysis

Regulation of Carbohydrate Metabolism in the Liver



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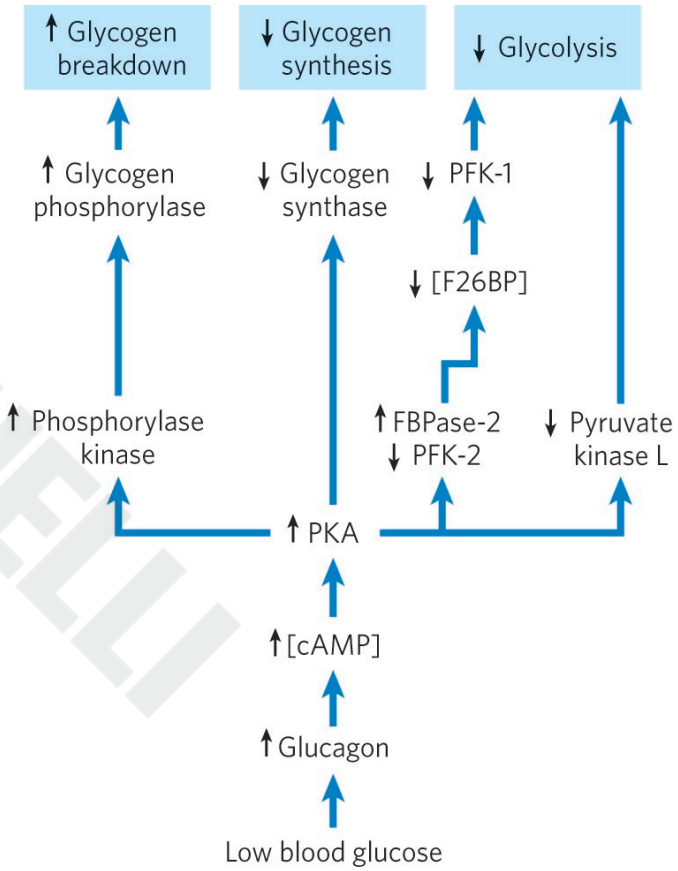

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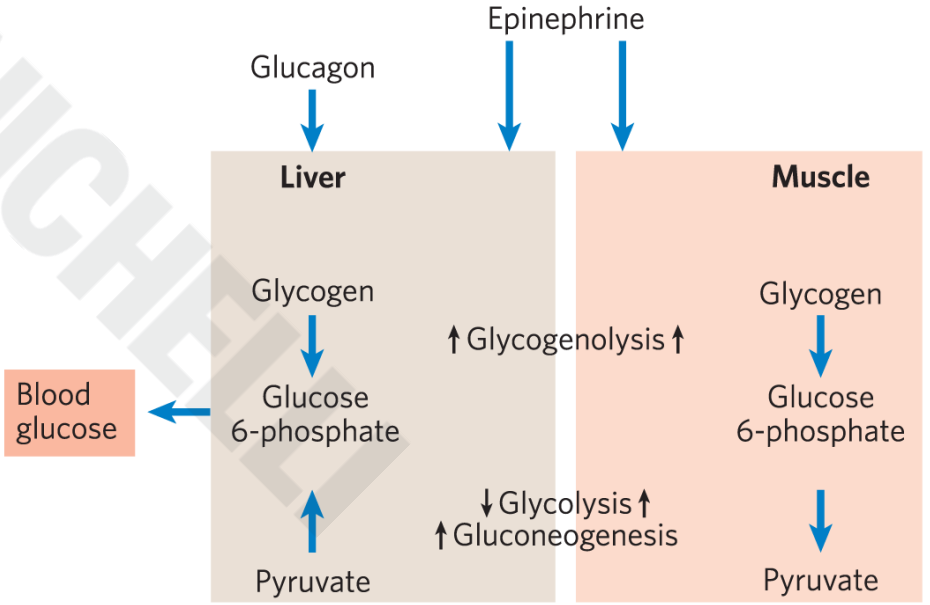
P4 Principle 4 (6 of 7)

Regulation of the balance between the formation of glycogen from excess glucose and the release of glucose from glycogen polymers when it is needed in metabolism is a critical function of cellular and organismal homeostasis. This balance, ultimately controlled by the hormones epinephrine, glucagon, and insulin, is achieved through allosteric regulation and phosphorylation of the synthetic and degradative enzymes. These enzymes and the regulatory proteins that act on them are integral parts of the glycogen granule.

Difference in the Regulation of Carbohydrate Metabolism in Muscle

- skeletal muscle:
  - uses its stored glycogen only for its own needs
  - undergoes very large changes in its demand for ATP
  - lacks the enzymatic machinery for gluconeogenesis



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P4 Principle 4 (7 of 7)

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Carbohydrate and Lipid Metabolism Are Integrated by Hormonal and Allosteric Mechanisms

- the metabolism of fats and fatty acids is very closely tied to that of carbohydrates

- regulatory controls adjust metabolite flow through various metabolic pathways without causing major changes in the concentrations of intermediates shared with other pathways