CARBOHYDRATE METABOLISM – GLYCOGEN METABOLISM

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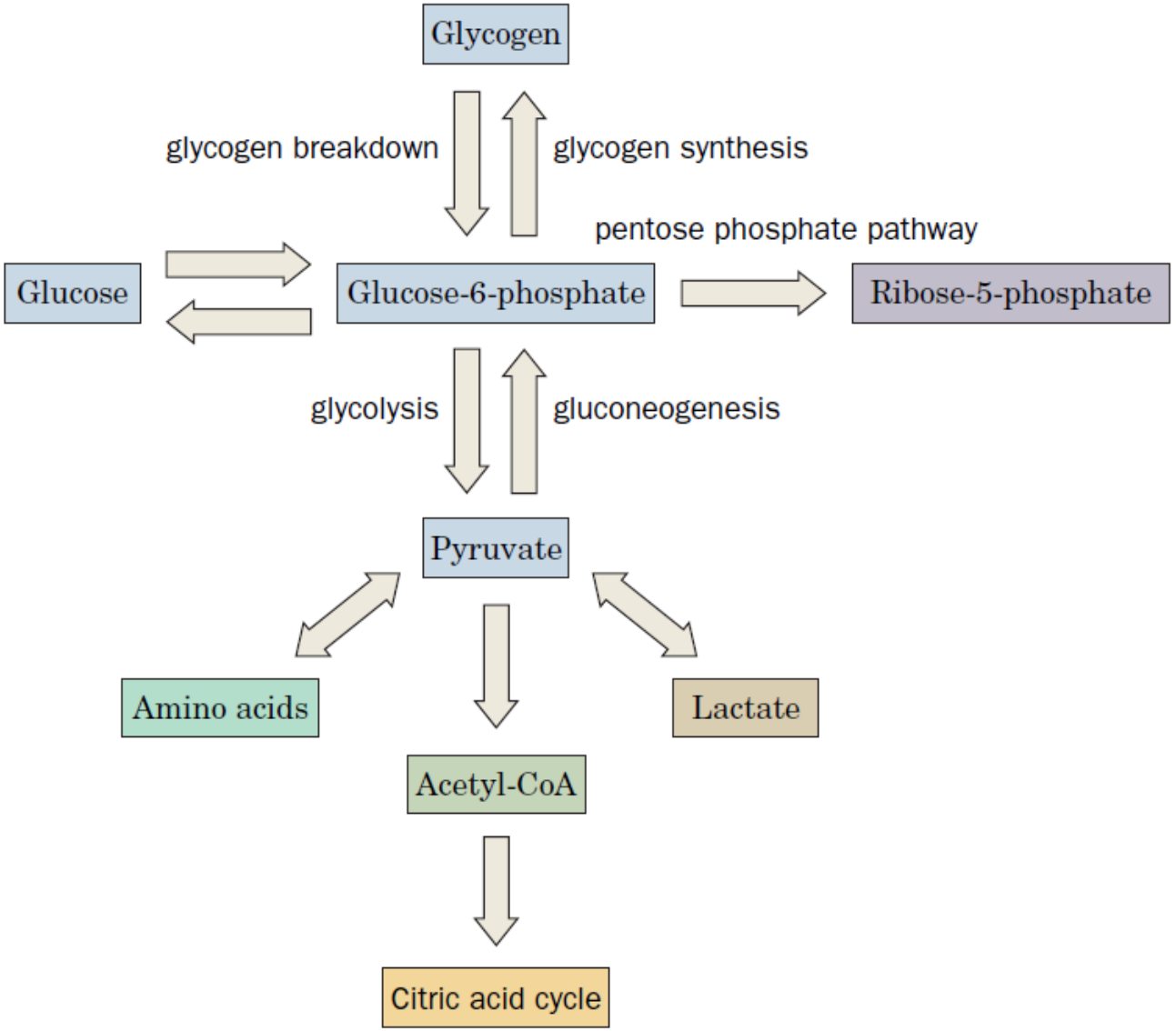
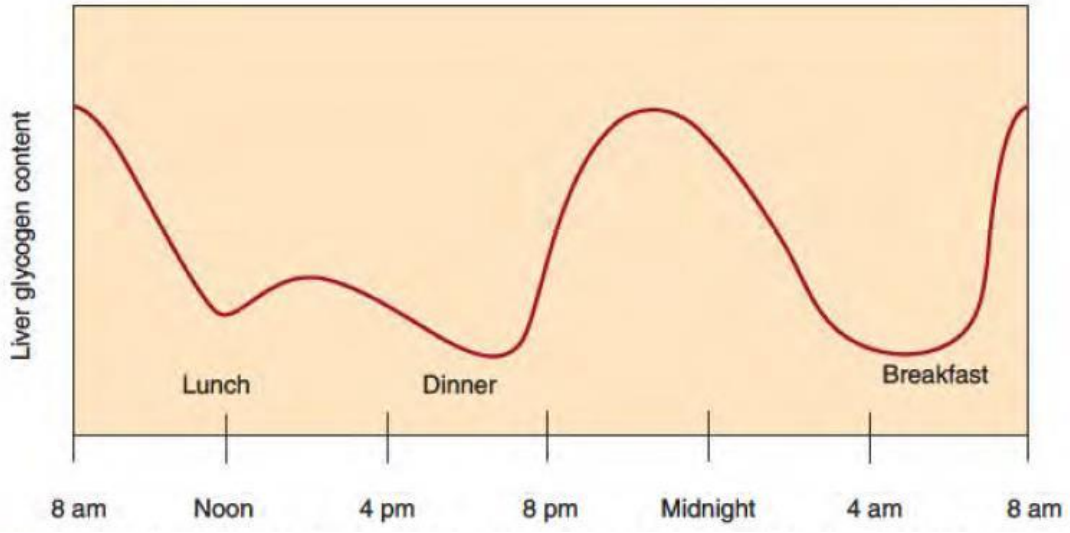
GLYCOGEN METABOLISM



GLYCOGEN METABOLISM

LIVER: Regulation (homeostasis) of blood glucose levels

- *Glycogen synthesis* (after a meal) is promoted by insulin
- *Glycogenolysis* (during fasting) is promoted by glucagon

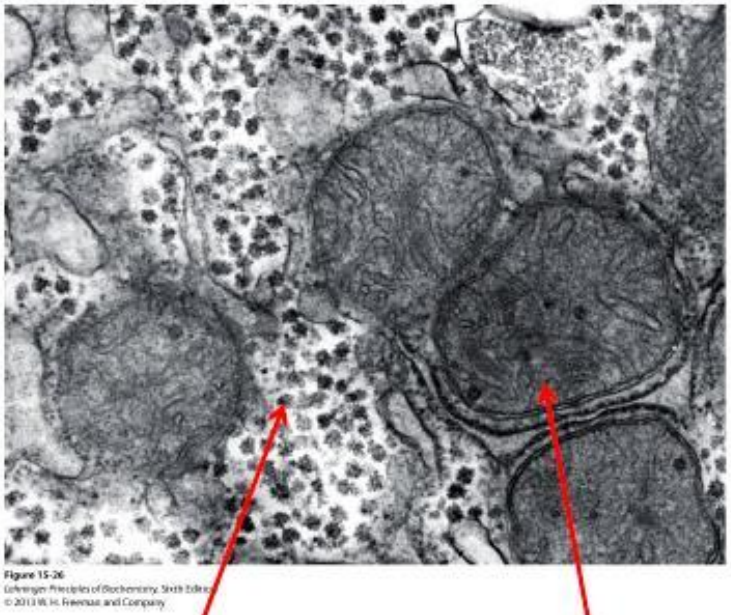


MUSCLE: Metabolic needs for contraction (within seconds)

- *Glycogen synthesis* occurs when ATP is high
- *Glycogenolysis* occurs when ATP is low

GLYCOGEN METABOLISM

Glycogen granules in a hepatocyte



Granules contain:

- Glycogen
- Enzymes that synthesize & degrade glycogen
- Machinery for regulating glycogen synthesis & degradation enzymes

GLYCOGEN SYNTHESIS (glycogenesis)

Glucose + ATP → glucose-6-P + ADP

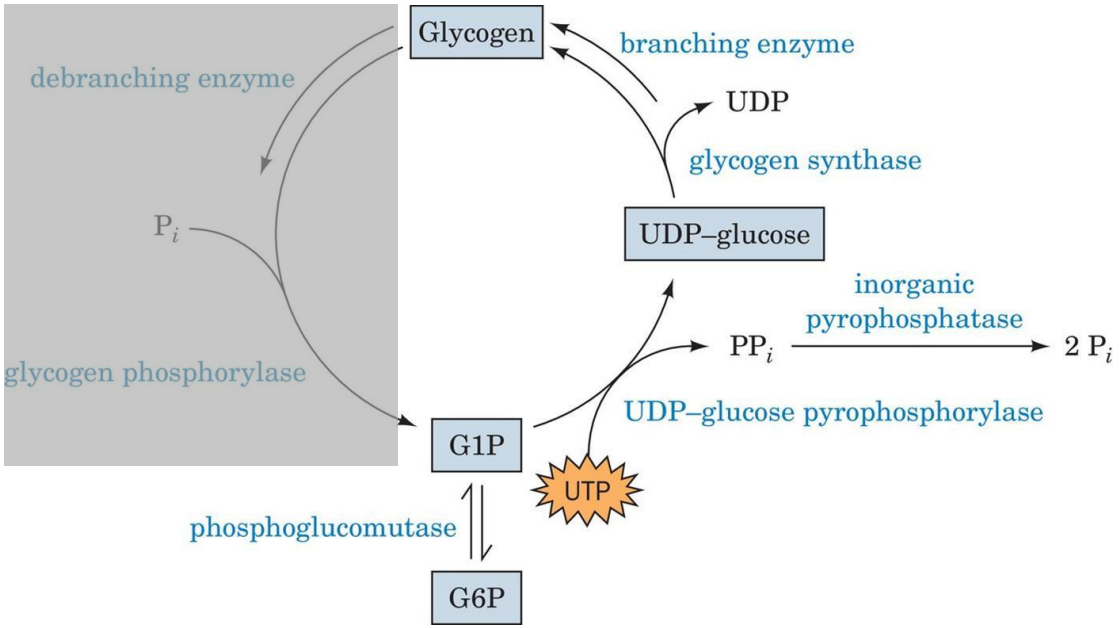
Glucose-6-P → glucose-1-P

Glucose-1-P + UTP → UDP-glucose + PP_i

UDP-glucose + $glycogen_n$ → UDP + $glycogen_{n+1}$

UDP + ATP → UTP + ADP

Branching: transglycosylation (α 1-4 → α 1-6)



GLYCOGEN SYNTHESIS (glycogenesis)

- **Adenylate kinase** (myokinase)

$$AMP + ATP \leftrightarrow ADP + ADP$$

- **Nucleoside monophosphokinase** (NMPK)

$$GMP + ATP \leftrightarrow GDP + ADP$$

$$UMP + ATP \leftrightarrow UDP + ADP$$

$$CMP + ATP \leftrightarrow CDP + ADP$$

- **Nucleoside diphosphokinase** (NDPK)

$$GDP + ATP \leftrightarrow GTP + ADP$$

$$UDP + ATP \leftrightarrow UTP + ADP$$

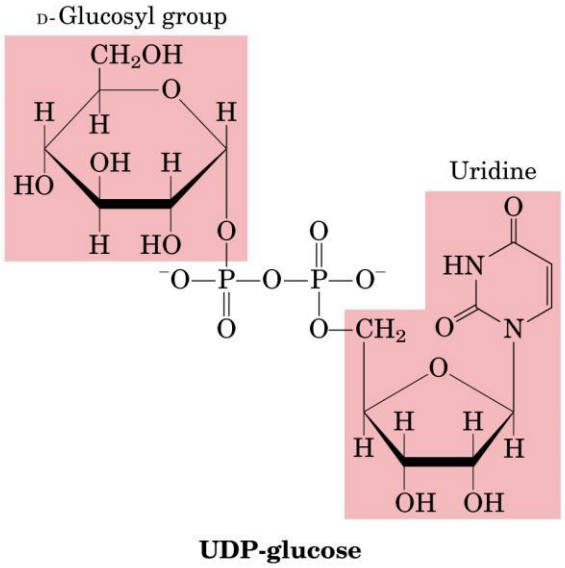
$$CDP + ATP \leftrightarrow CTP + ADP$$

GLYCOGEN SYNTHESIS (glycogenesis)

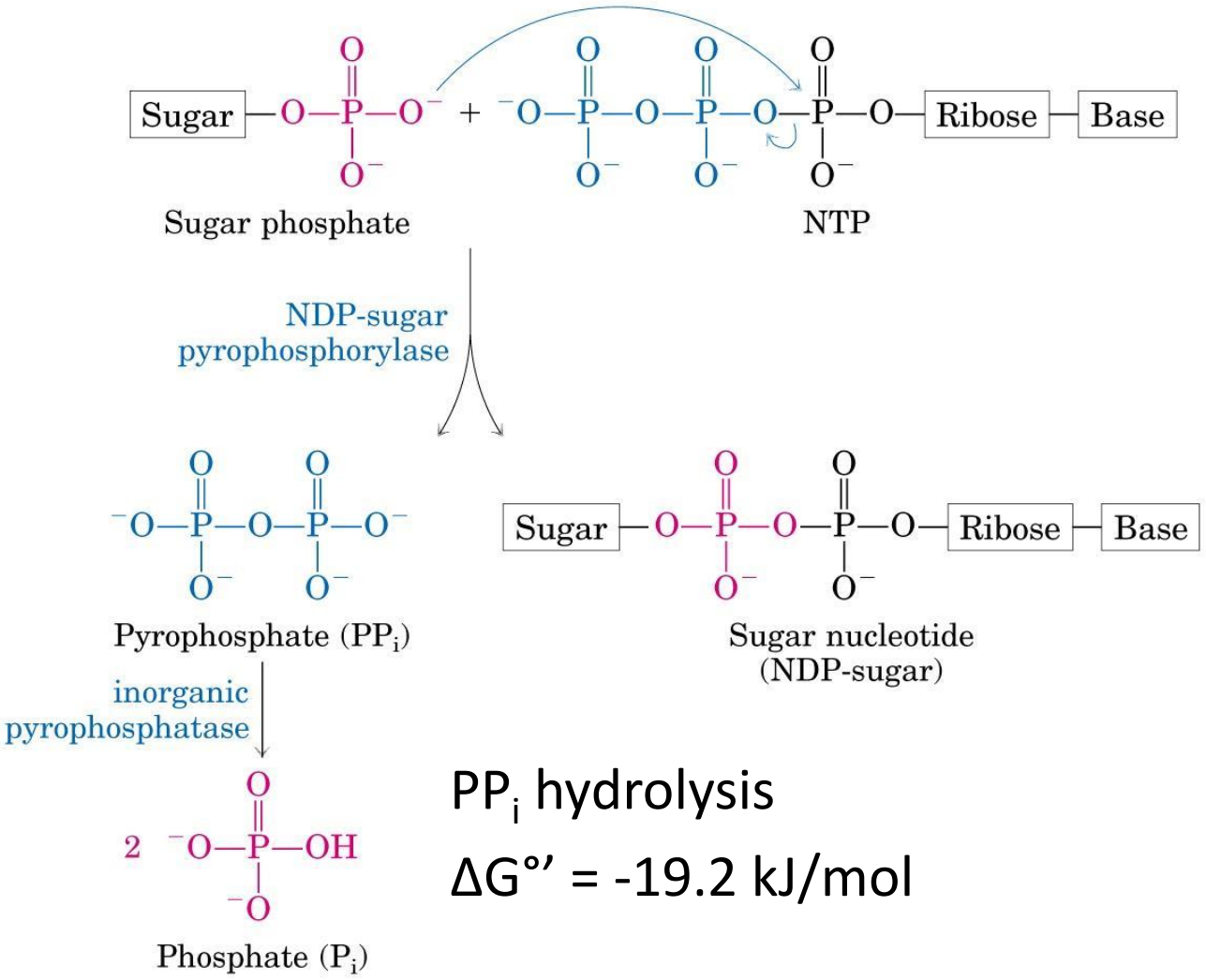
Formation of a **sugar nucleotide**: the anomeric C is activated by the attachment of a nucleotide (phosphodiester bond).

Advantages:

- irreversible formation;
- good leaving group in nucleophilic reactions;
- tag for glucose molecules destined for glycogen synthesis.



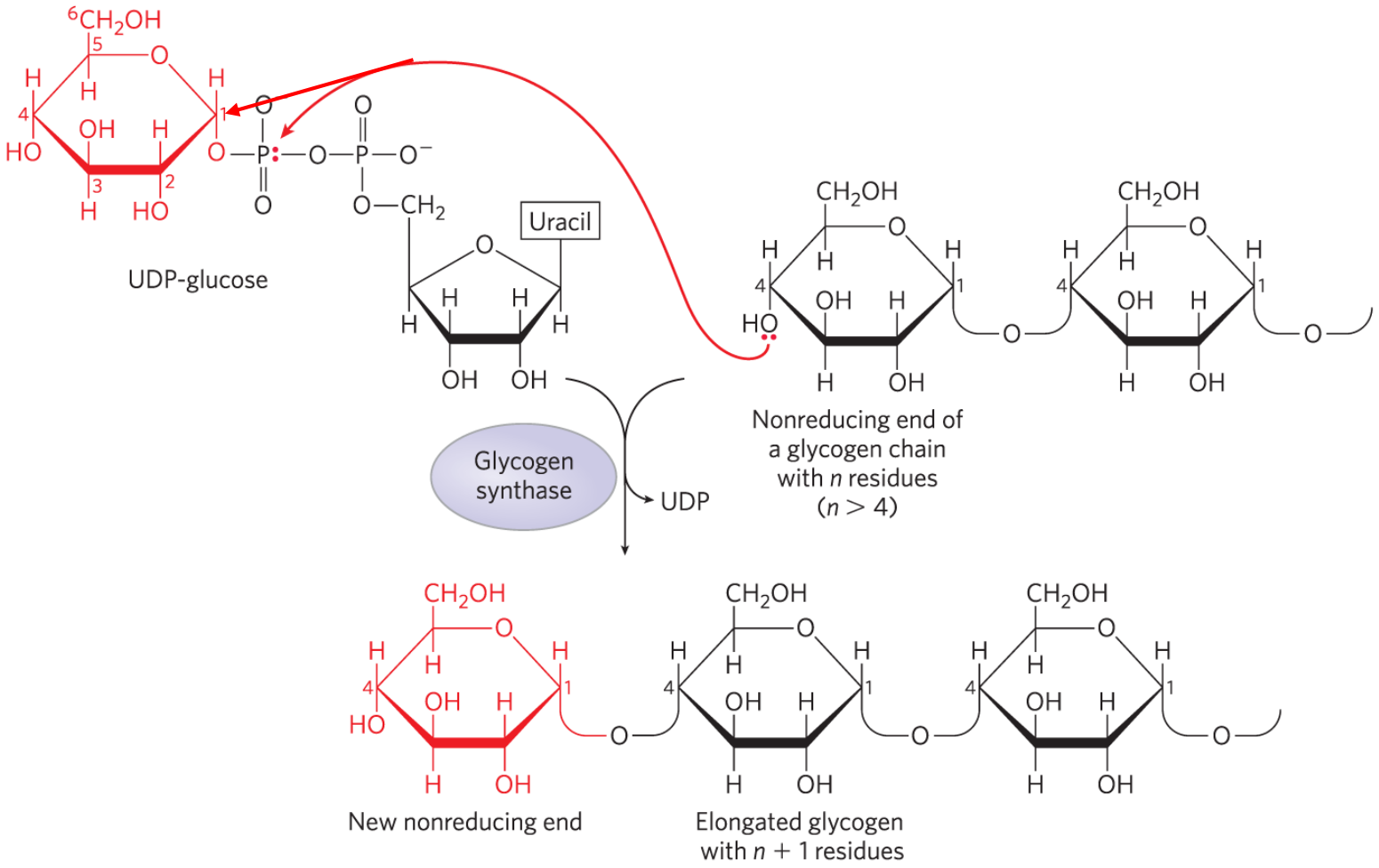
GLYCOGEN SYNTHESIS (glycogenesis)



PP_i hydrolysis

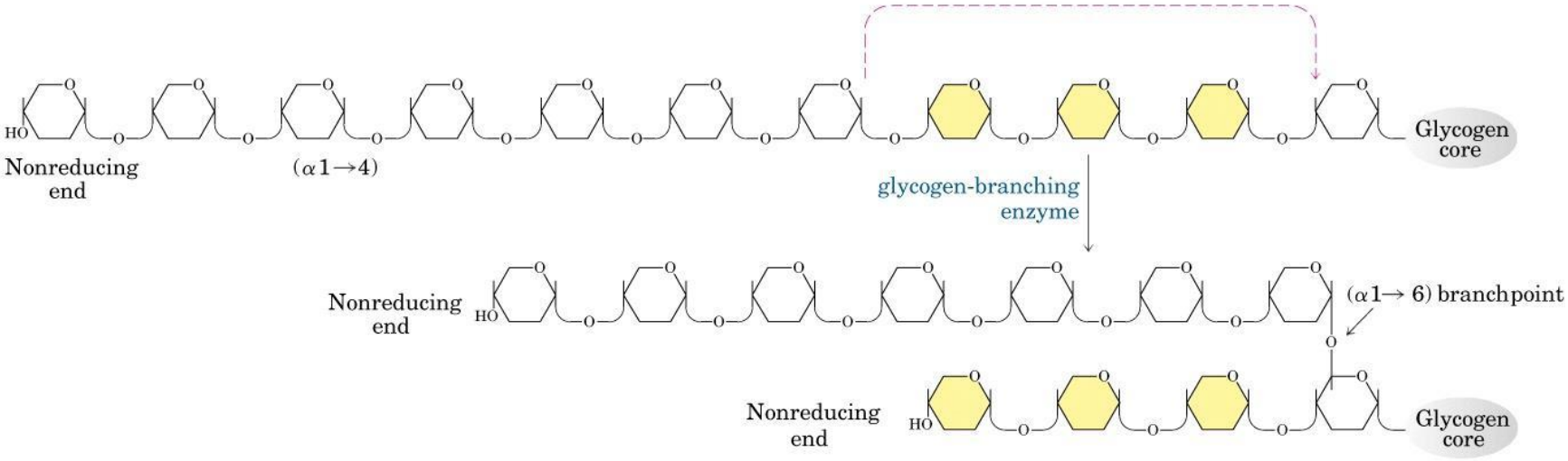
$\Delta G^{\circ\prime} = -19.2$ kJ/mol

GLYCOGEN SYNTHESIS (glycogenesis)



GLYCOGEN SYNTHESIS (glycogenesis)

Glycogen-branching enzyme: formation of α 1→6 bonds (transglycosylation reaction)



GLYCOGEN SYNTHESIS (glycogenesis)

Glycogen synthase is a glycosyl transferase: it transfers a glucose unit from UDP-glucose to preformed glycogen.

Note the difference with Synthetase: Synthetases (or ligases) utilize ATP to energize the condensation of two molecules.

$$A + B + \mathit{ATP} \rightarrow A\text{-}B + ADP + P_i$$

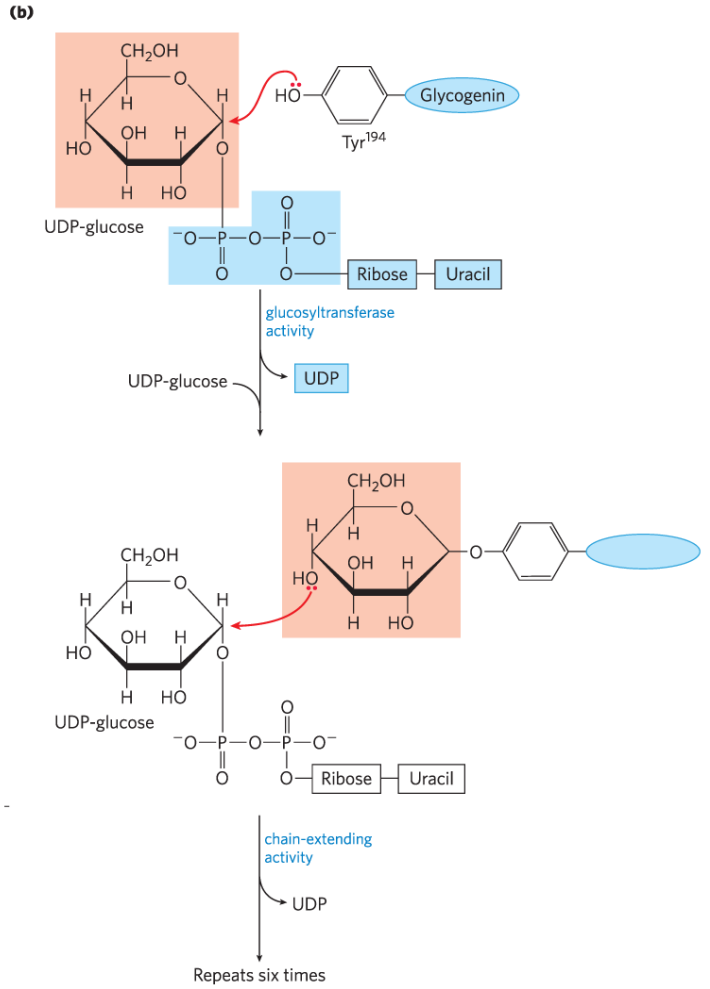
$$A + B + \mathit{ATP} \rightarrow A\text{-}B + AMP + PP_i$$

GLYCOGEN SYNTHESIS (glycogenesis)

Glycogenin is a protein that serves as a primer for glycogen.

1) Formation of a glycosidic bond between UDP-glucose and Tyr^{194} of glycogenin.

2) Addition of 7 more UDP-glucose molecules, follwed by the action of glycogen synthase.



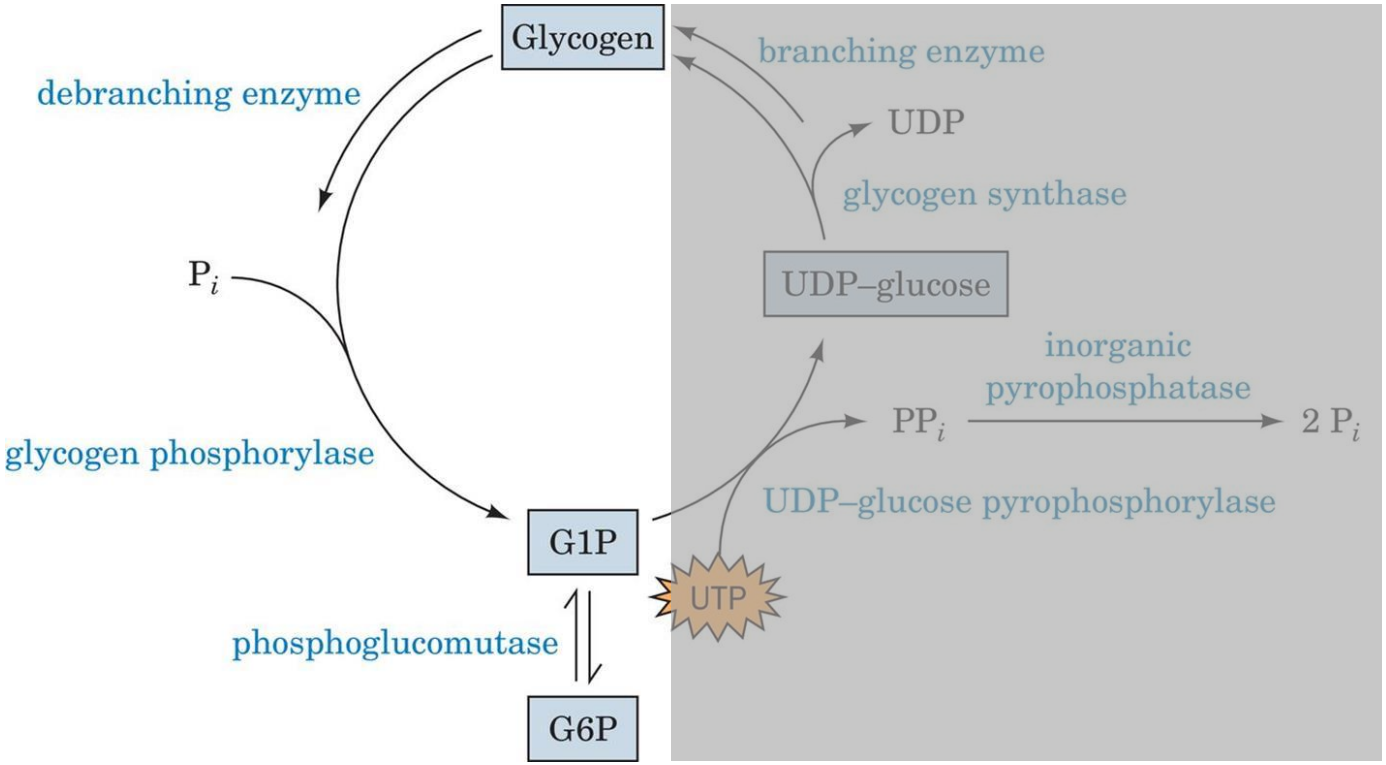
GLYCOGENOLYSIS

$Glycogen_n + P_i \rightarrow glycogen_{n-1} + glucose\text{-}1\text{-}P$

$Glucose\text{-}1\text{-}P \rightarrow glucose\text{-}6\text{-}P$

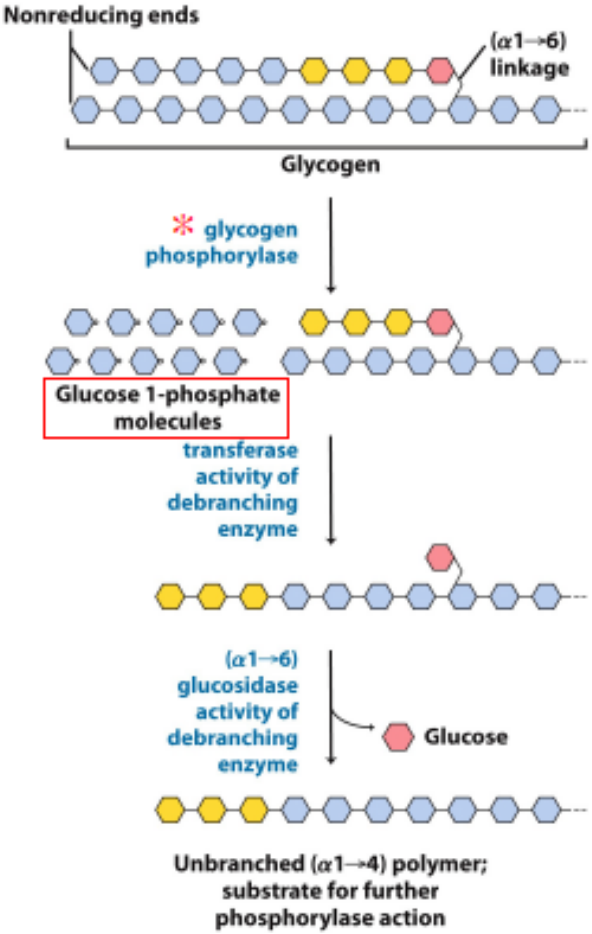
$Glucose\text{-}6\text{-}P + H_2O \rightarrow glucose + P_i$

De-branching: transglycosylation 1—4 → 1—4 + hydrolysis 1—6



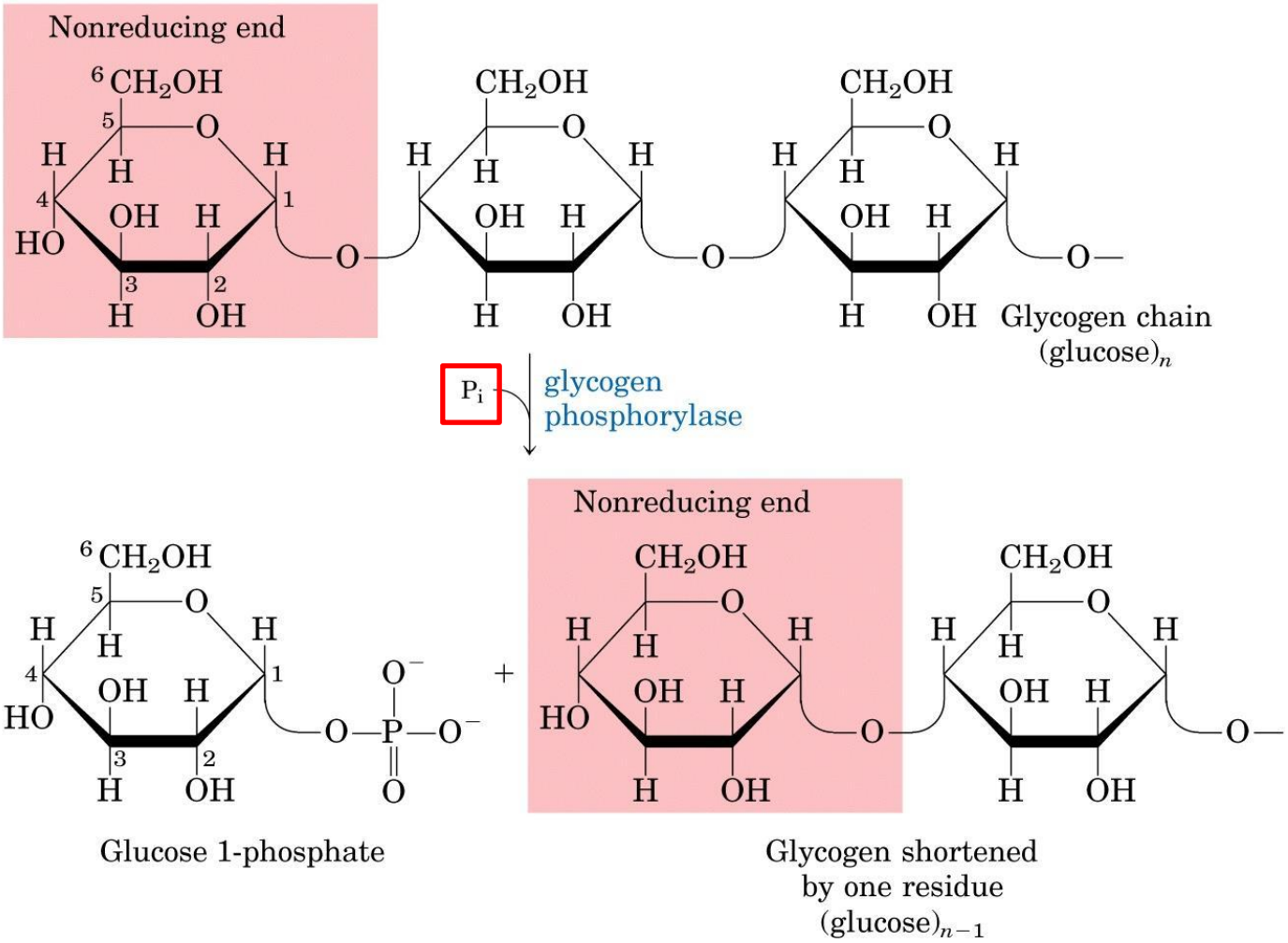
GLYCOGENOLYSIS

Glycogen breakdown



- The enzymes that break down glycogen in liver and muscle are different than the enzymes that break down dietary glycogen.
- The breakdown of glycogen in liver and muscle generates Glucose 1-phosphate molecules.
- Glycogen phosphorylase can only work on branches >4 glucose monomers long.

GLYCOGENOLYSIS



GLYCOGEN PHOSPHORYLASE

Active site: glycogen and P_i

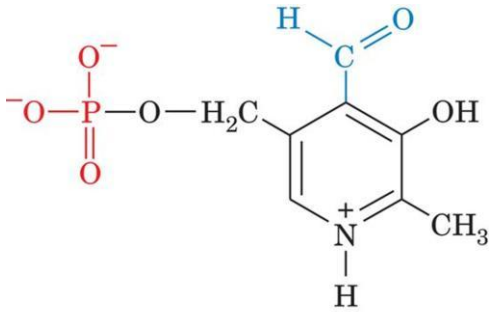
Allosteric site: AMP (activator)

ATP (inhibitor)

Phosphorylation site (Ser^{14})

- Ser-OP (*glycogen phosphorylase a*, active)
- Ser-OH (*glycogen phosphorylase b*, inactive)

Requires pyridoxal phosphate.



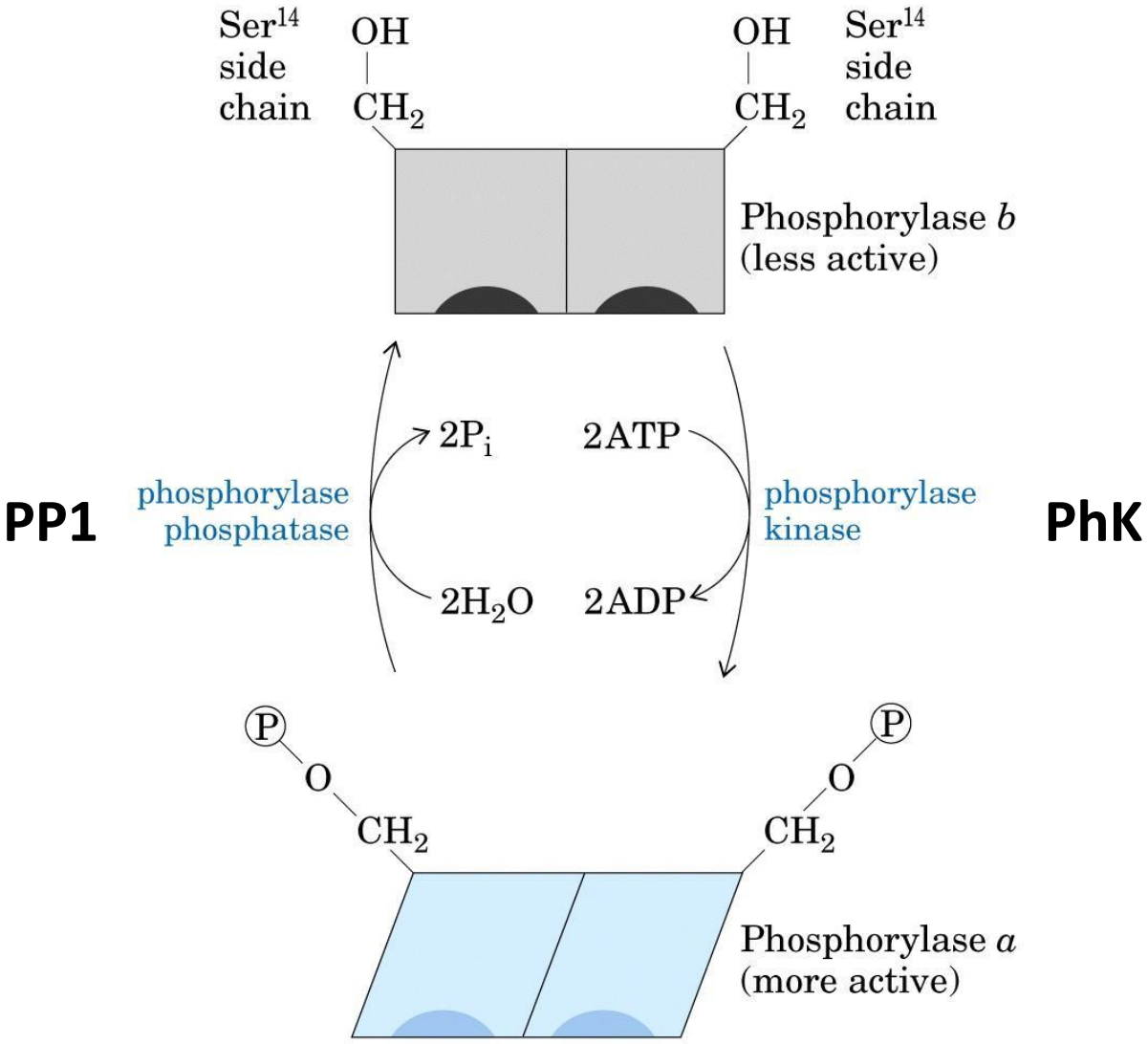
Pyridoxal-5′-phosphate (PLP)

GLYCOGEN PHOSPHORYLASE

Allosteric regulation (ATP; AMP) prevails in **muscle**: control of energy production.

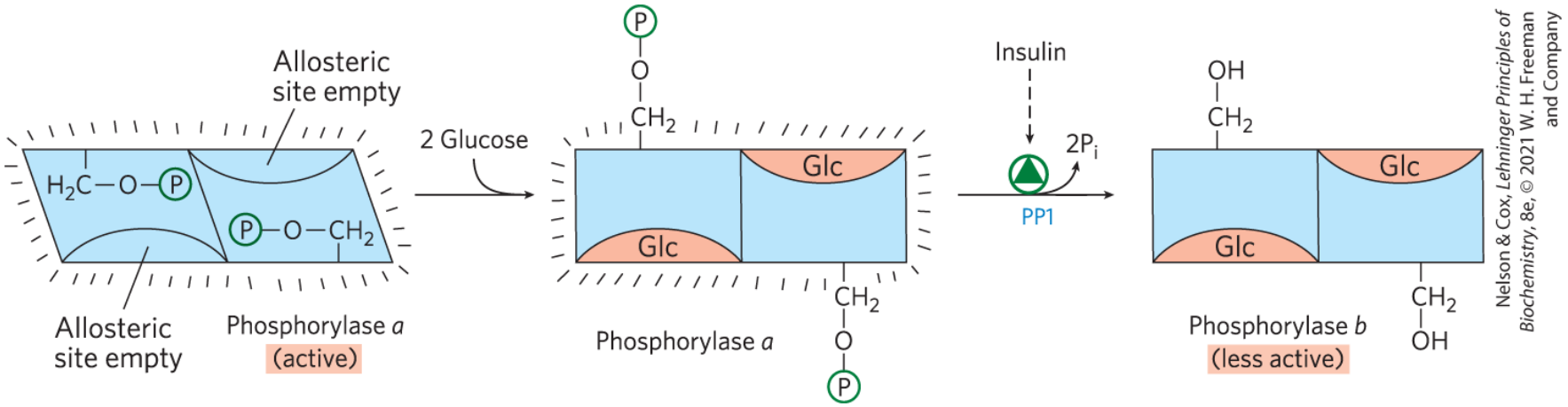
Regulation by **phosphorylation** prevails in **liver**: control of blood glucose.

GLYCOGEN PHOSPHORYLASE



GLYCOGEN PHOSPHORYLASE

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



GLYCOGEN PHOSPHORYLASE

Hormone regulation:

- **Glucagon** or adrenaline → adenylate cyclase ↑

$$ATP \rightarrow cAMP + PP_i$$

- cAMP → PKA (cAMP-dependant Protein Kinase A)↑

Phosphorylase b kinase + ATP → phosphorylase b kinase–P (active) + ADP

- Phosphorylase b kinase–P (active) → Glycogen phosphorylase ↑

Phosphorylase b + ATP → phosphorylase-P (a) + ADP

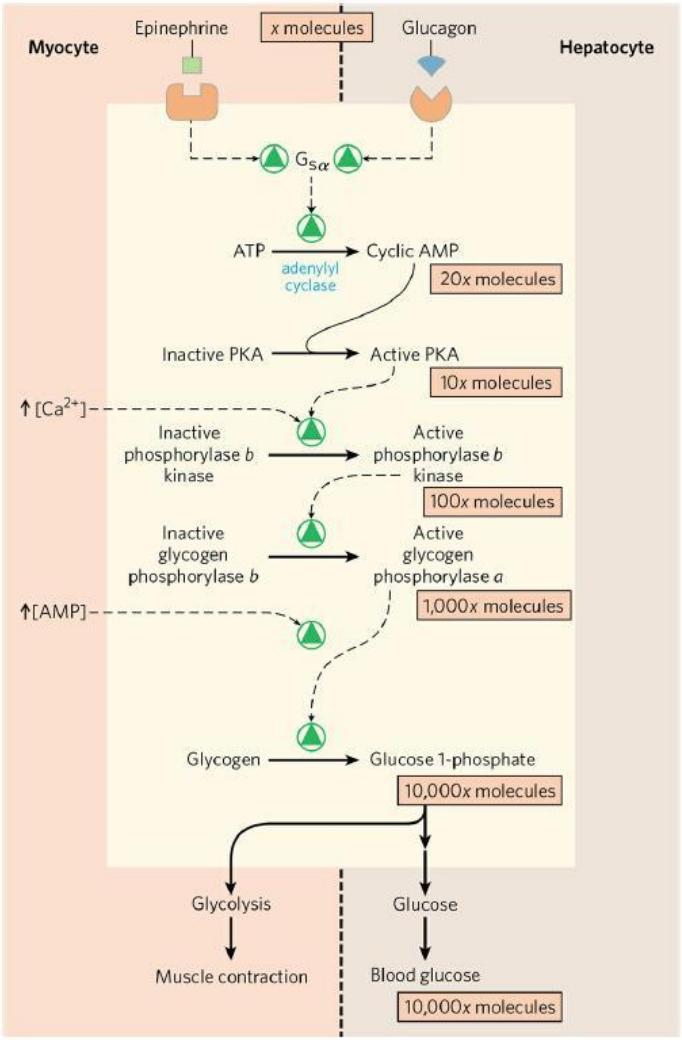
- Phosphorylase a → Glycogenolysis ↑

$$Glycogen_n + Pi \rightarrow Glycogen_{n-1} + glucose\text{-}1\text{-}P$$

GLYCOGEN PHOSPHORYLASE

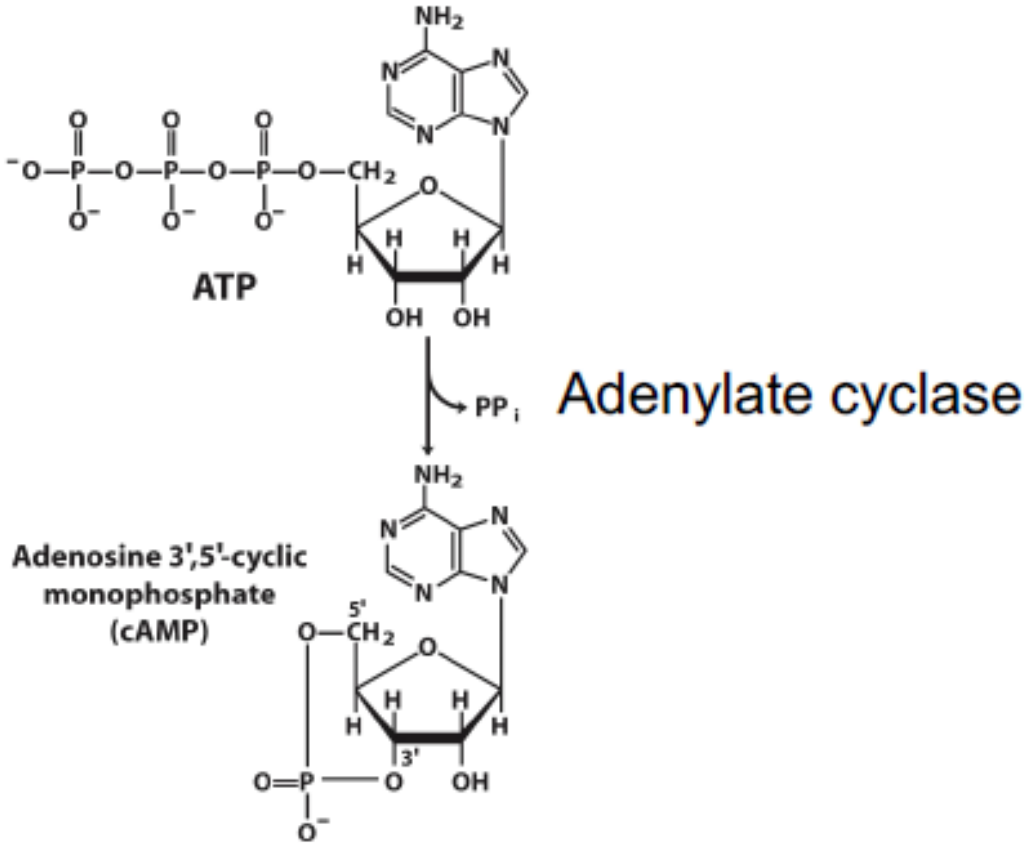
Enzyme cascade (sequence of enzymatic reactions in which a catalyst activates a catalyst, which activates a catalyst)

- rise in [cAMP] activates PKA, which phosphorylates phosphorylase b kinase
- phosphorylase b kinase catalyzes the phosphorylation of glycogen phosphorylase b



GLYCOGEN PHOSPHORYLASE

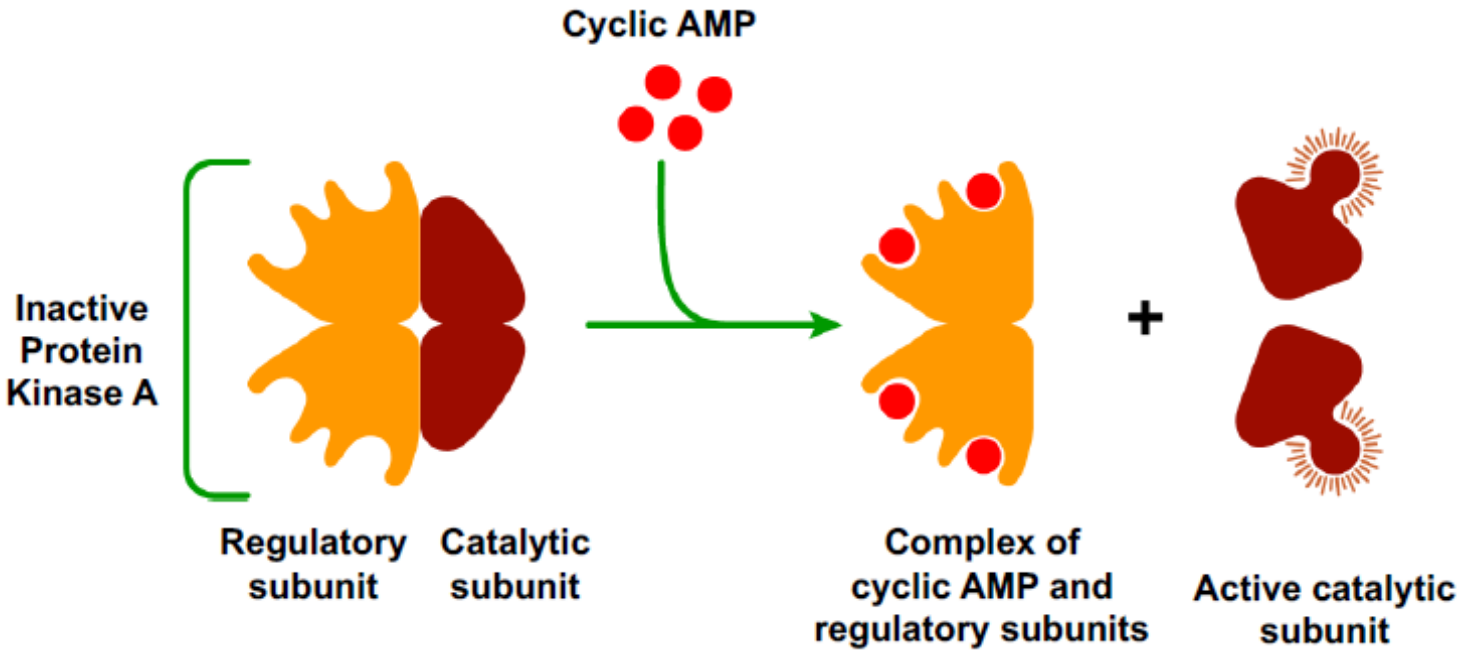
Intracellular signalling by glucagon and epinephrine through cyclic AMP, a universal starvation signal.



cAMP phosphodiesterase (PDE) hydrolyses to 5’ AMP

GLYCOGEN PHOSPHORYLASE

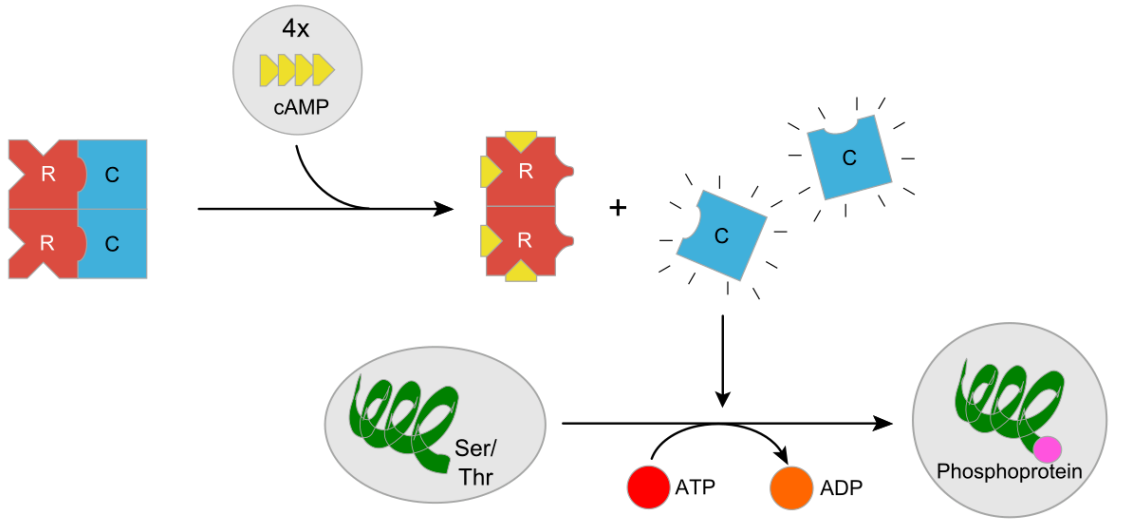
Activation of Ser/Thr protein kinase A (PKA) by cAMP



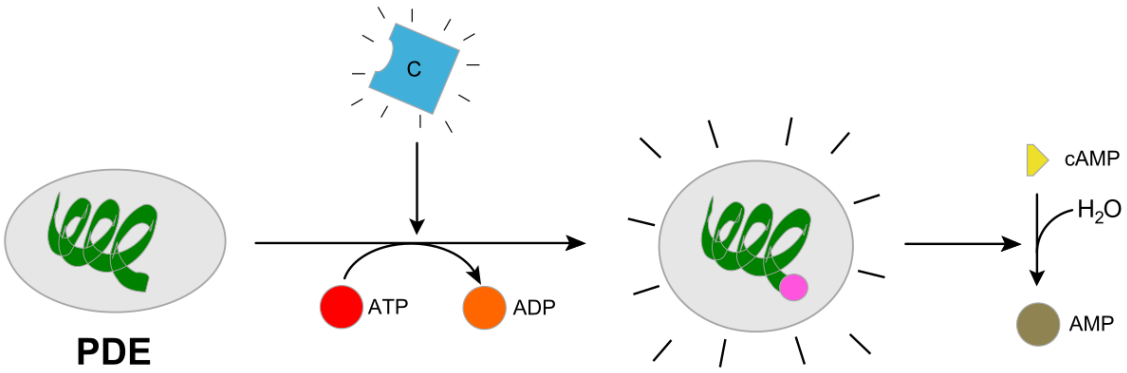
Further amplification: 1 cAMP may cause the phosphorylation of many proteins.

Kinase phosphorylates many different targets.

GLYCOGEN PHOSPHORYLASE



Activation of Ser/Thr protein kinase A (**PKA**) by cAMP.
PKA can phosphorylate phosphorylase b kinase (PhK).



The **activated PDE** catalyses the hydrolysis of cAMP.
The activity of PKA is reduced or terminated (feedback control).

COORDINATION OF GLYCOGEN METABOLISM

In **LIVER**:

- *Insulin*: both enzymes NOT phosphorylated

  Phosphorylase INACTIVE

  Synthase ACTIVE

  Result: *glycogen is synthesized*

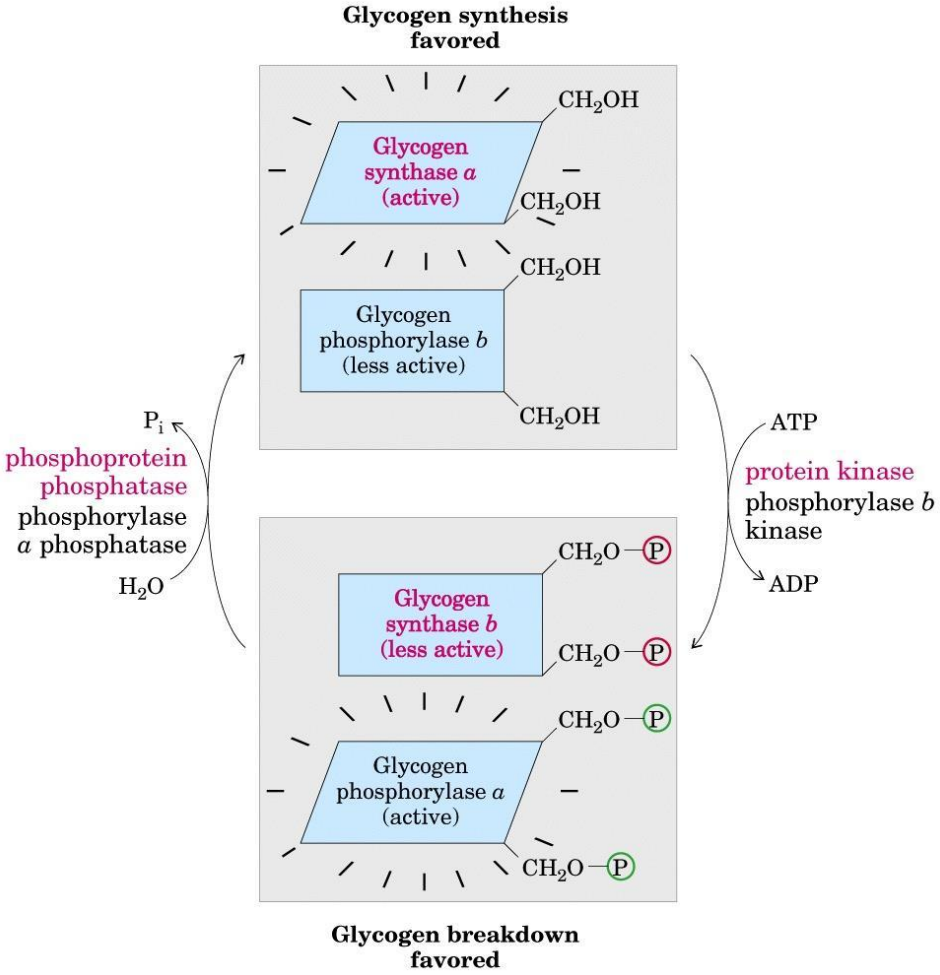
- *Glucagon*: both enzymes are phosphorylated

  Phosphorylase-P ACTIVE

  Synthase-P INACTIVE

  Result: *glycogen is broken down*

COORDINATION OF GLYCOGEN METABOLISM



Glycogen synthase (GS) has two forms:

- *glycogen synthase a* unphosphorylated and catalytically active
- *glycogen synthase b* phosphorylated and inactive

Glycogen synthase kinase 3 (GSK3) catalyzes the phosphorylation of glycogen synthase a.

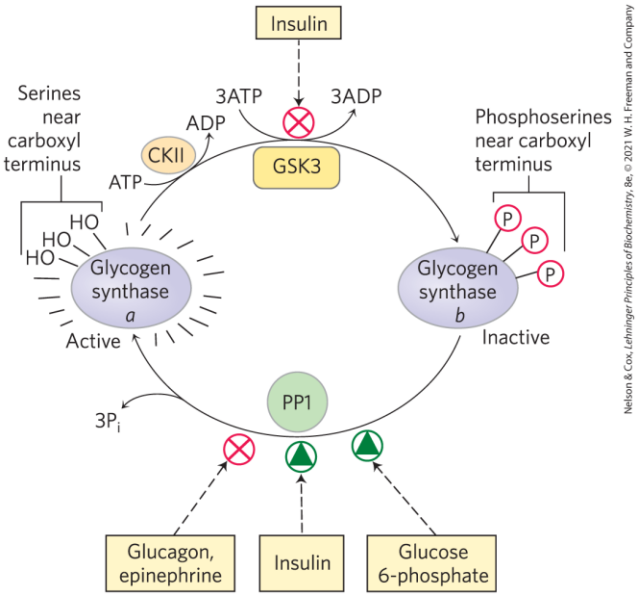
REGULATION OF GLYCOGEN METABOLISM

In **LIVER**:

- *insulin:*

  PKB (protein B kinase) phosphorylates GSK3 (inactivated) → GS remains dephosphorylated ACTIVE

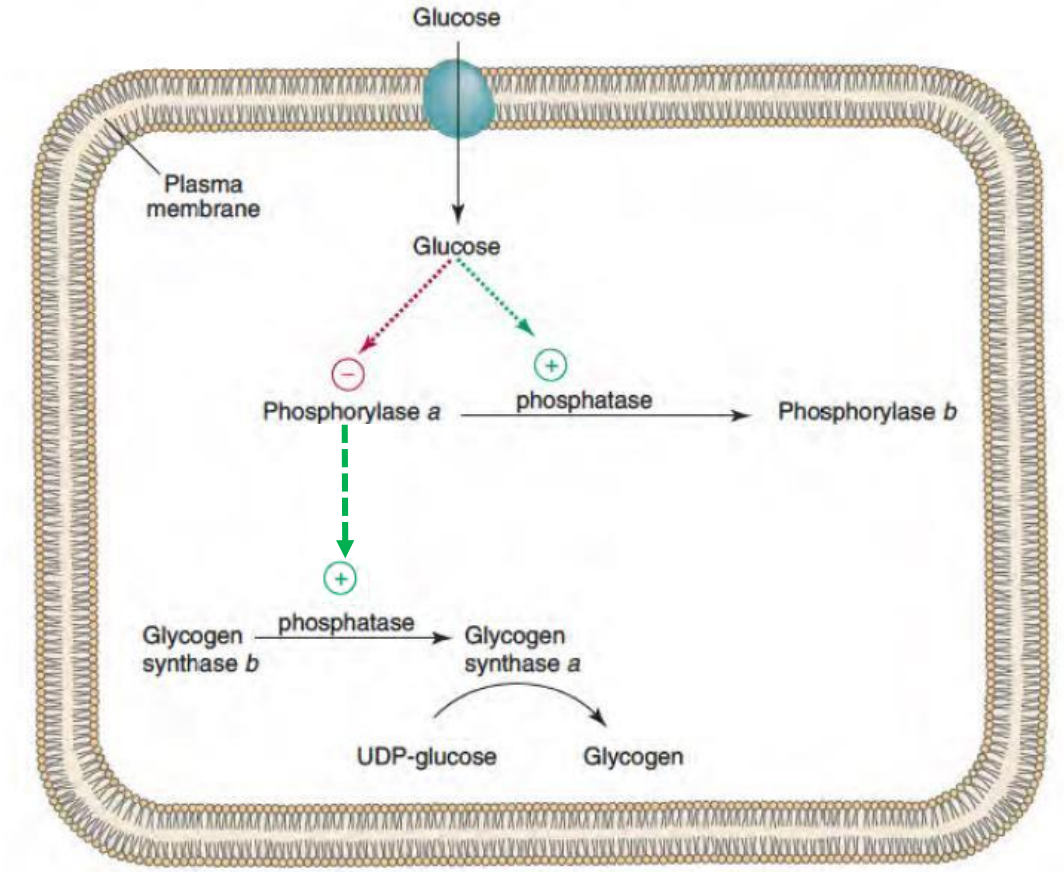
Phosphoprotein phosphatase-1: activated → GS dephosphorylated ACTIVE and Glycogen phosphorylase dephosphorylated INACTIVE



REGULATION OF GLYCOGEN METABOLISM

In **LIVER**:

- *glucose can stimulate glycogenesis*



REGULATION OF GLYCOGEN METABOLISM

In **LIVER**:

- *glucagon*

  PKA → Phosphorylase b kinase → Phosphorylase a ACTIVE

  PKA → GSK3 → GS phosphorylated INACTIVE

REGULATION OF GLYCOGEN METABOLISM

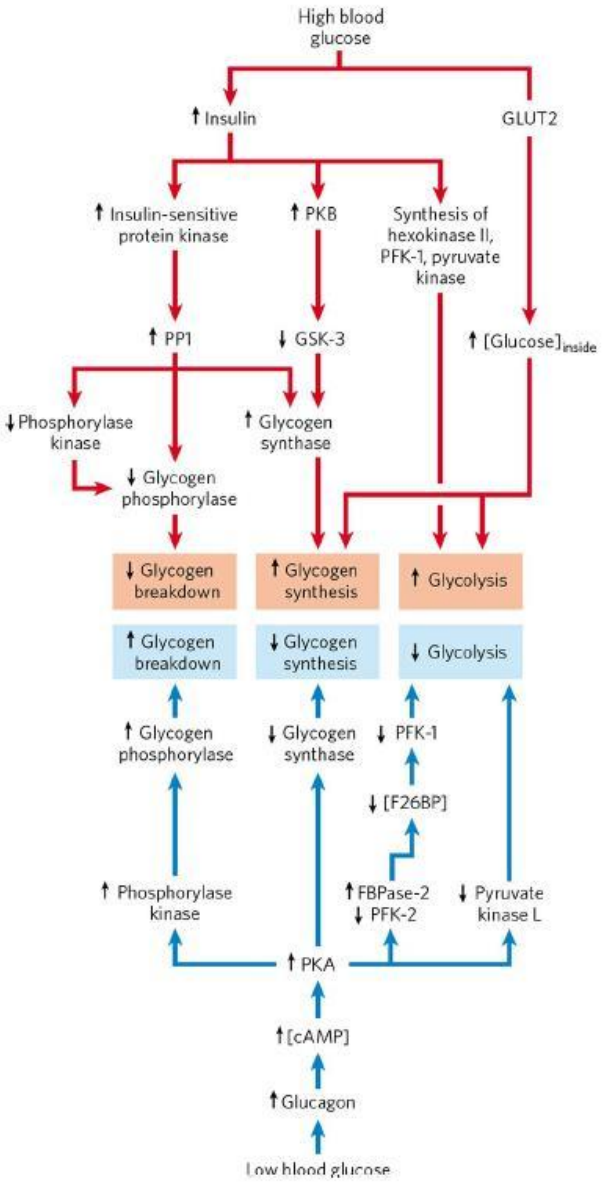
Like most signal transduction cascades, glucagon-stimulated signaling regulates many downstream targets.

TABLE 23–4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	Effect on glucose metabolism	Target enzyme
↑ Glycogen breakdown (liver)	Glycogen → glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate → glucose	↑ FBPase-2 ↓ Pyruvate kinase ↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Hormone-sensitive lipase
		↑ PKA (perilipin–Ⓟ)
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↓ Acetyl-CoA carboxylase

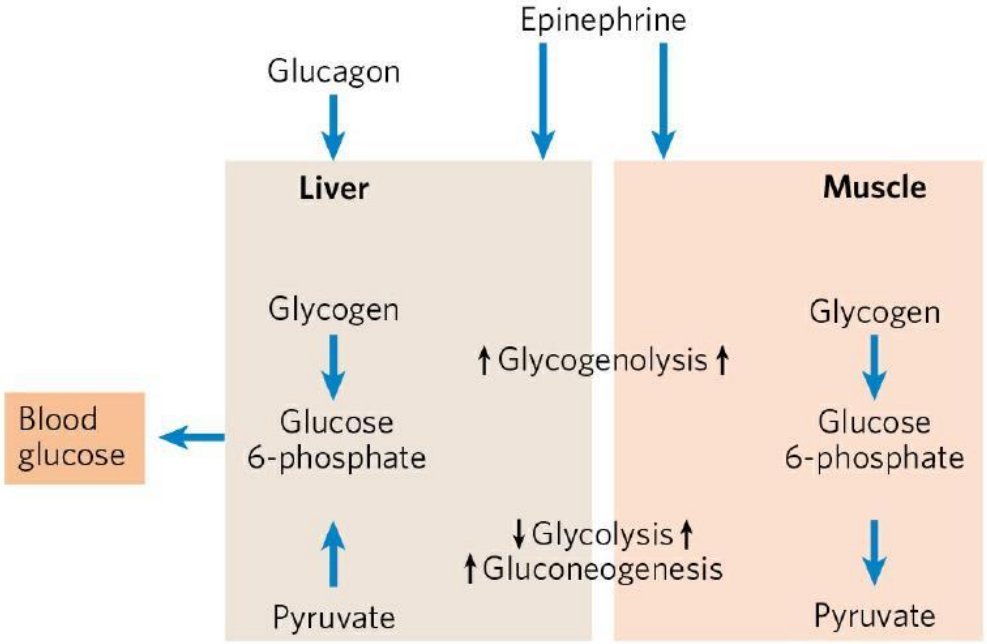
Table 23-4
Lehninger Principles of Biochemistry, Sixth Edition

REGULATION OF GLYCOGEN METABOLISM

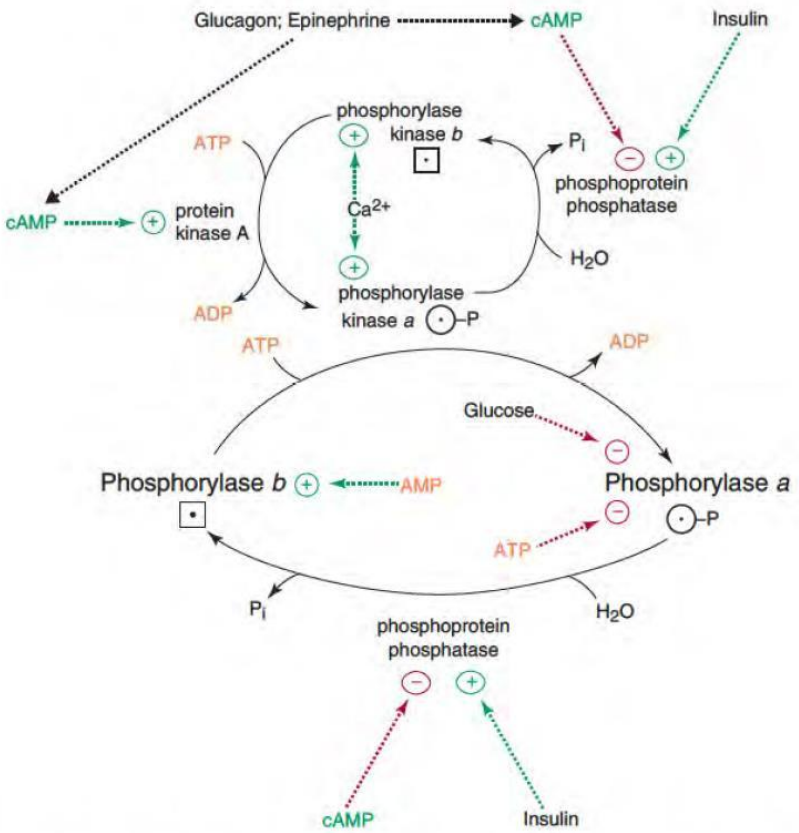


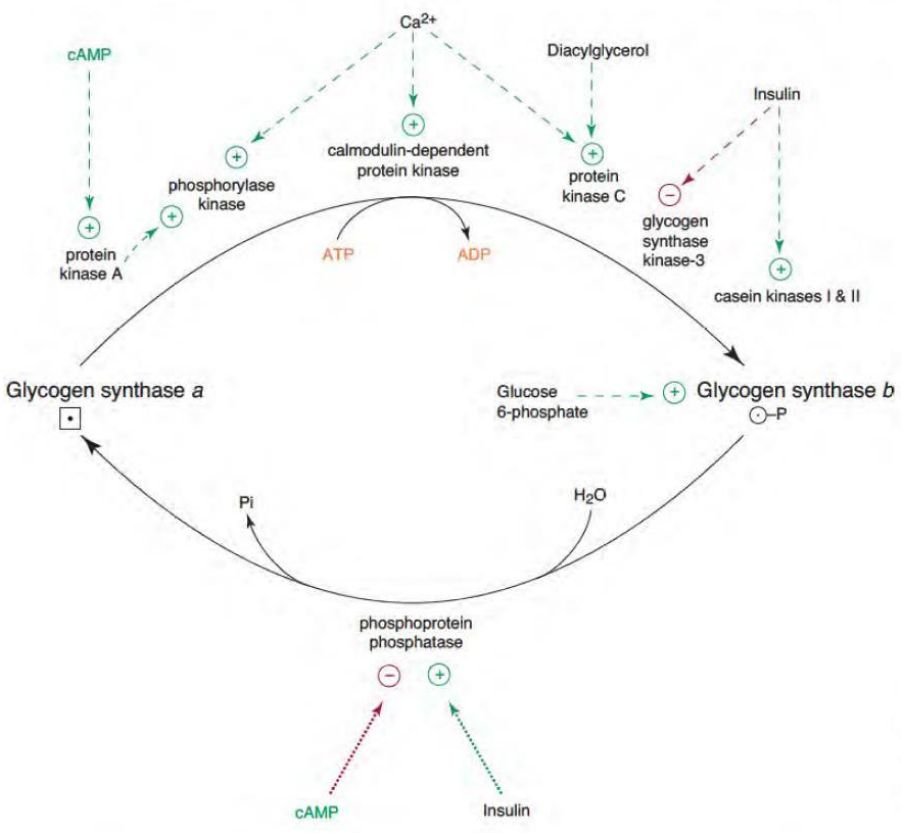
Regulation of carbohydrate metabolism in the liver.

Difference in the regulation of carbohydrate metabolism in liver and muscle.



REGULATION OF GLYCOGEN METABOLISM





GLYCOGEN METABOLISM IN MUSCLE

Glucose entering from bloodstream (GLUT4) is phosphorylated by low K_m hexokinase. There is **no glucose-6-Pase** in muscle.

Glycogen metabolism is mainly controlled by **ATP/AMP**.

At rest, **ATP** level is **high** and drives **glycogen synthesis**.

When muscle contracts, **AMP** stimulates **glycogen phosphorylase**; Calcium ions stimulate phosphorylase b kinase for further activation of phosphorylase.

At the same time also glycogen synthase is phosphorylated and becomes inactive: glucose-6-P can only follow glycolysis for ATP synthesis.

REGULATION OF ATP PRODUCTION IN SKELETAL MUSCLE

Contraction: ATP → ADP + P_i

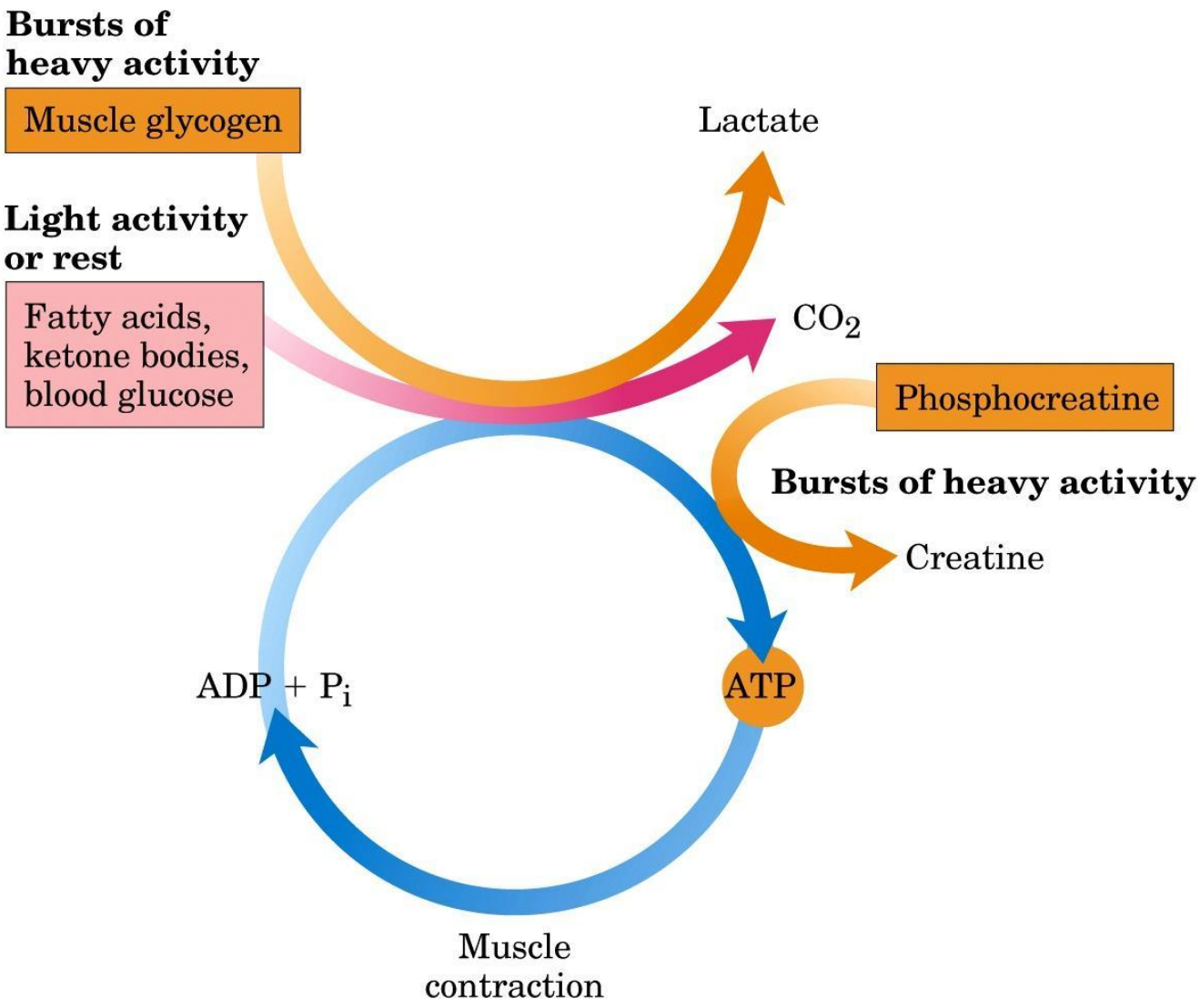
Adenylate kinase: 2 ADP → AMP + ATP

P-creatine reserve: P-creatine + ADP → creatine + ATP

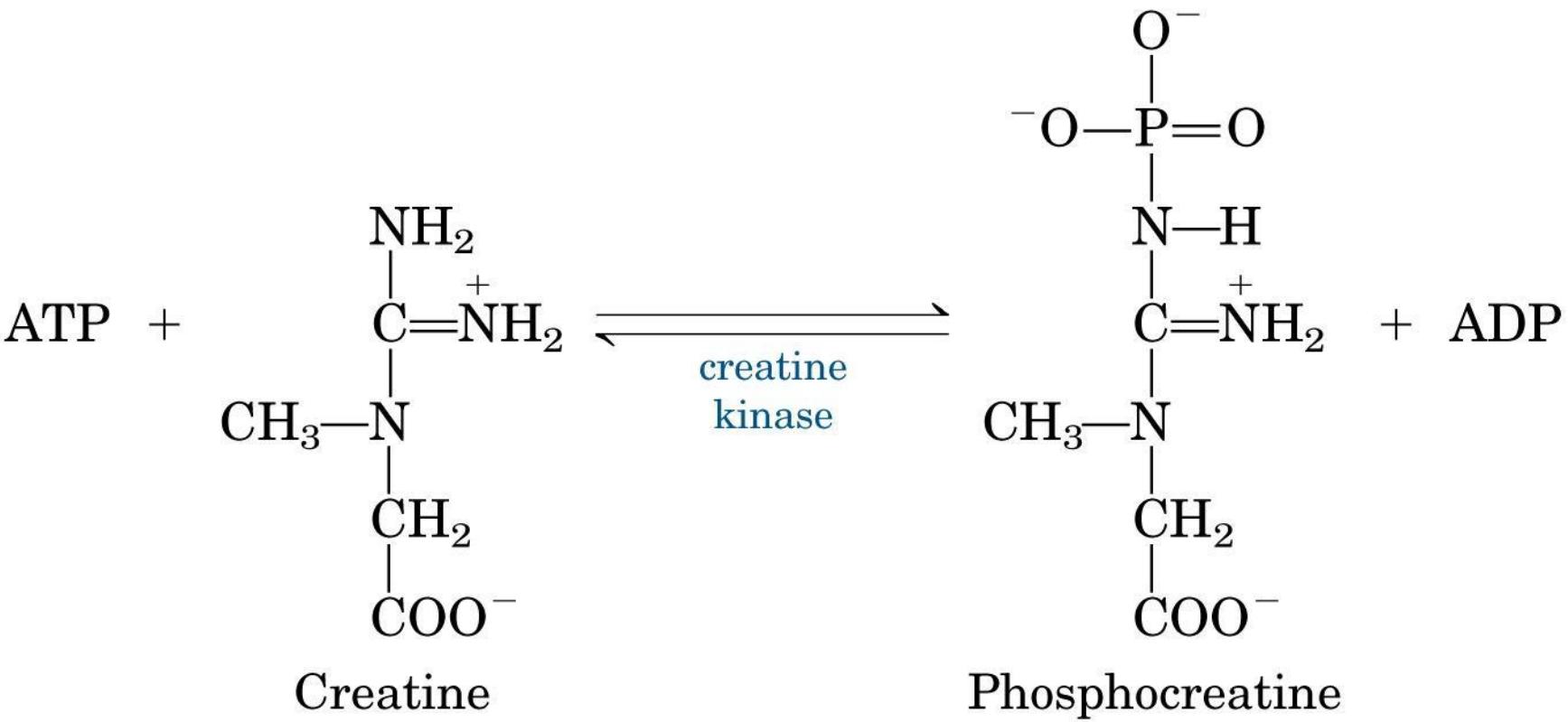
Activation of carbohydrate metabolism:

- AMP activates phosphorylase b (allosteric site)
- Ca^{2+} activates phosphorylase b kinase: phosphorylase b → phosphorylase a
- Adrenalin activates adenylate cyclase: cAMP → PKA → phosphorylase b kinase → phosphorylase a

REGULATION OF ATP PRODUCTION IN SKELETAL MUSCLE



REGULATION OF ATP PRODUCTION IN SKELETAL MUSCLE



REGULATION OF ATP PRODUCTION IN SKELETAL MUSCLE

table 23–2

Physiological and Metabolic Effects of Epinephrine: Preparation for Action

Physiological	
↑ Heart rate	Increased delivery of O_2 to tissues (muscle)
↑ Blood pressure	
↑ Dilation of respiratory passages	
Metabolic	
↑ Glycogen breakdown (muscle, liver)	Increased production of glucose for fuel
↓ Glycogen synthesis (muscle, liver)	
↑ Gluconeogenesis (liver)	
↑ Glycolysis (muscle)	Increased ATP production in muscle
↑ Fatty acid mobilization (adipose tissue)	Increased availability of fatty acids as fuel
↑ Glucagon secretion	Reinforce metabolic effects of epinephrine
↓ Insulin secretion	

GLYCOGEN STORAGE DISEASES IN HUMANS

TABLE 1 Glycogen Storage Diseases of Humans

Type (name)	Enzyme affected	Primary organ 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_i 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

Box 15-4 table 1
Lehninger Principles of Biochemistry, Sixth Edition

EXAM-TYPE QUESTION

Reaction ATP + creatine → ADP + creatine-P proceeds in the direction written above (left to right):

a. During muscle contraction
b. When the respiratory chain is uncoupled
c. In muscle at rest
d. If the content of the enzyme creatine kinase is increased

Answer c is correct. At rest ATP is not used and is stored as P-creatine. In contracting muscles P-creatine transfers the phosphate group to ADP to recover ATP for contraction (a). If mitochondria are uncoupled no ATP is formed (b). The amount of enzyme cannot affect the direction of the reaction (d).

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