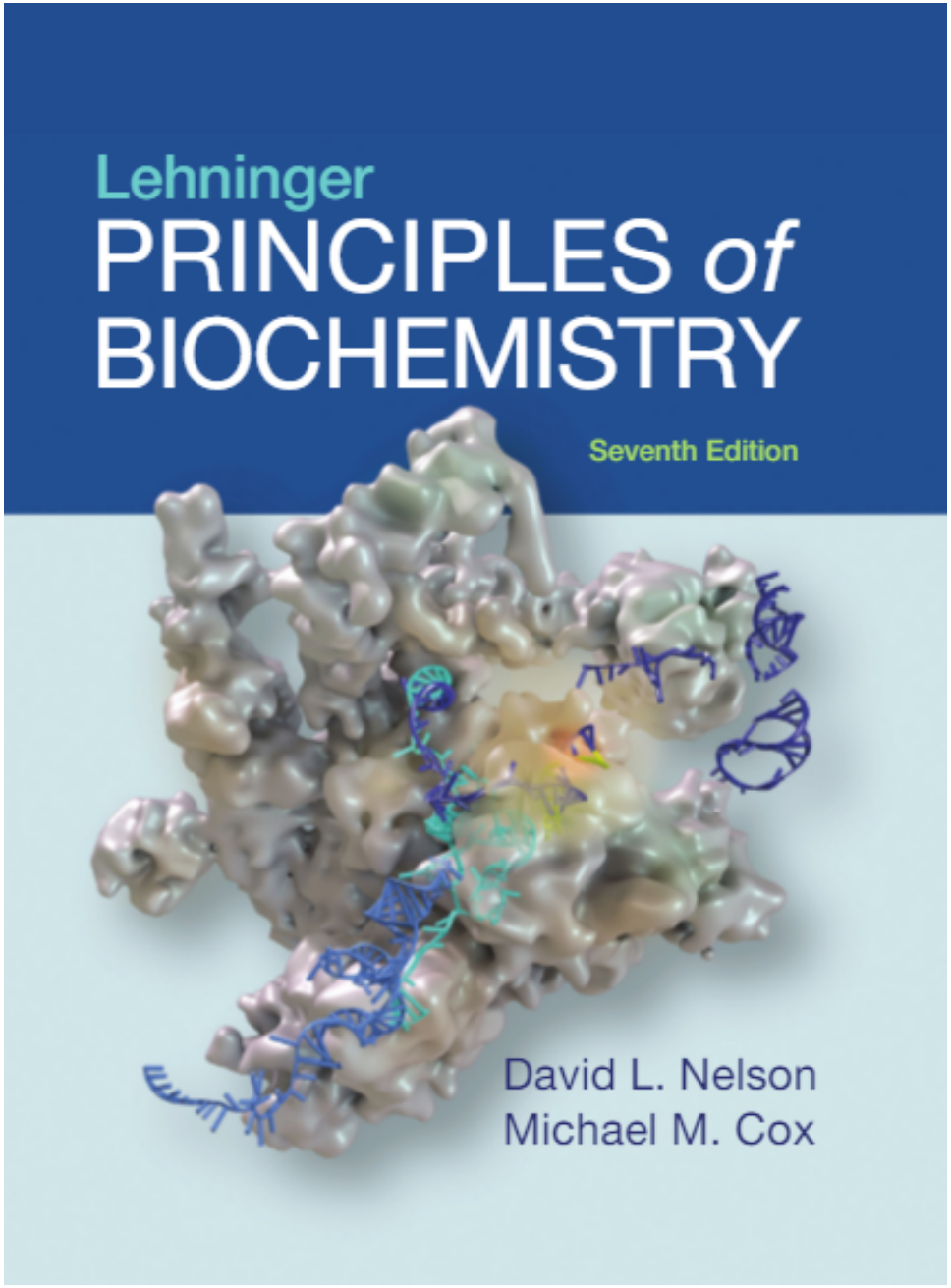
15| Principles of Metabolic Regulation



CHAPTER 15
Principles of Metabolic Regulation

Learning goals:

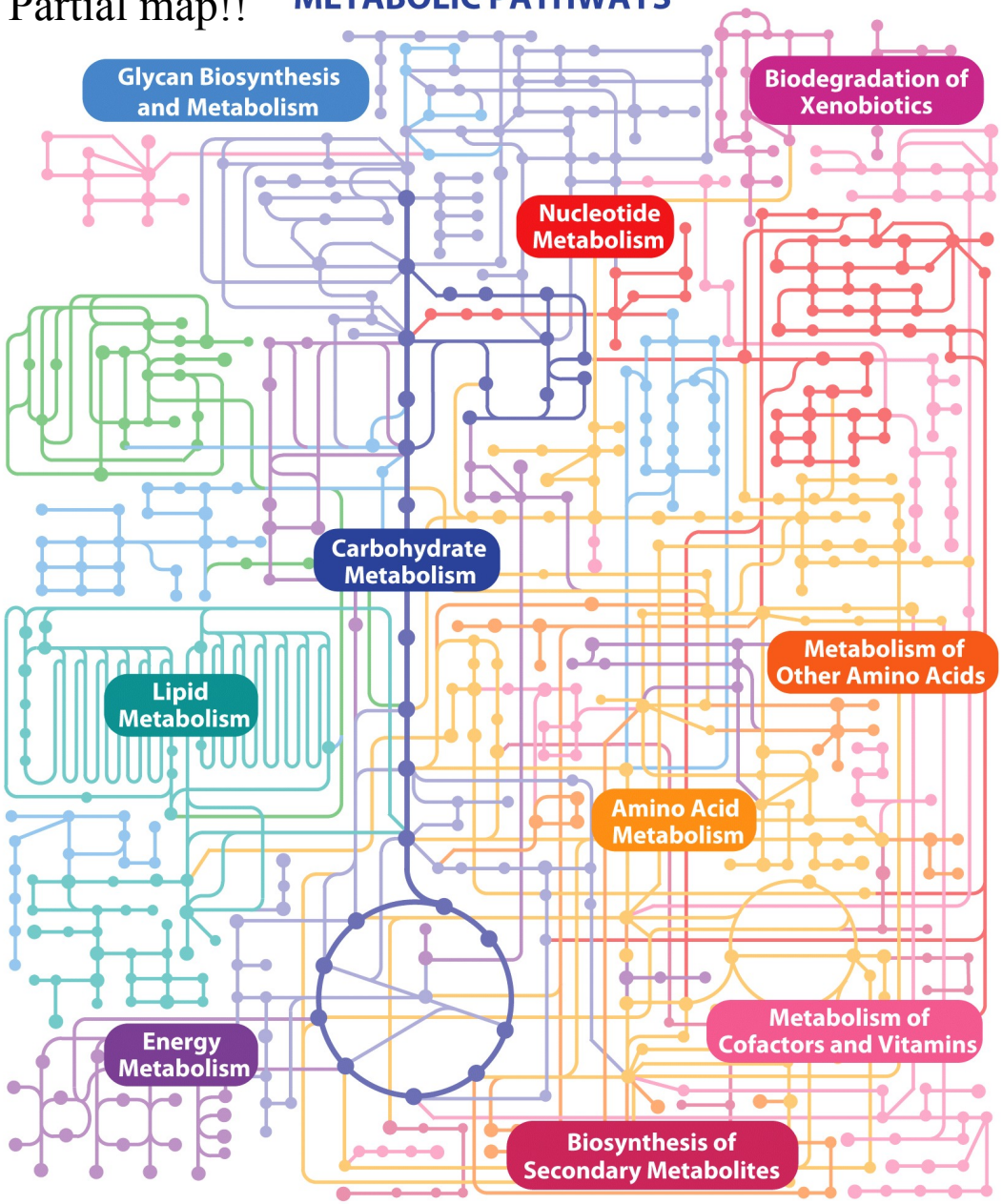
- Principles of regulation in biological systems
- What determines activity of glycolysis versus gluconeogenesis?
- Chemistry and regulation of glycogen metabolism

Metabolic Pathways

- The biochemical reactions in the living cell—metabolism—are organized into metabolic pathways. In the living cell **NO** separation exists!
- The pathways have dedicated purposes:
  - Extraction of energy
  - Storage of fuels
  - Synthesis of important building blocks
  - Elimination of waste materials
- The pathways can be represented as a map
  - Follow the fate of metabolites and building blocks
  - Identify enzymes that act on these metabolites
  - Identify points and agents of regulation
  - Identify sources of metabolic diseases

Map of Metabolic Pathways

Partial map!!



Which one is more complicated?

Principles of regulation

- Organisms maintain **homeostasis** by keeping the concentrations of most metabolites at *steady state*
- In steady state, the rate of synthesis of a metabolite equals the rate of breakdown of this metabolite

$A \xrightarrow{v_1} S \xrightarrow{v_2} P$ (even though the **flux** of metabolite flow (v) may be high, the concentration of S will remain almost constant by the preceding reaction). E.g. $[glc]_{blood}$ ~ 5 mM

- The failure of homeostatic mechanisms leads to human disease (think diabetes: v_1 for glc entry in blood ≠ v_2 glc uptake into cells)
- Pathways are at steady state unless perturbed
- After perturbation a NEW steady state will be established
- The need of regulatory proteins is immense (4000 genes, ~12% of all genes in humans)

Principles of Regulation

- The flow of metabolites through the pathways is regulated to maintain homeostasis
- Flux is modulated by changes in the *number* or *catalytic activity* of regulatory proteins
- Sometimes, the levels of required metabolites must be altered very rapidly
  - Need to increase the capacity of glycolysis during action
  - Need to reduce the capacity of glycolysis after the action
  - Need to increase the capacity of gluconeogenesis after *successful* action

Rates of a Biochemical Reactions

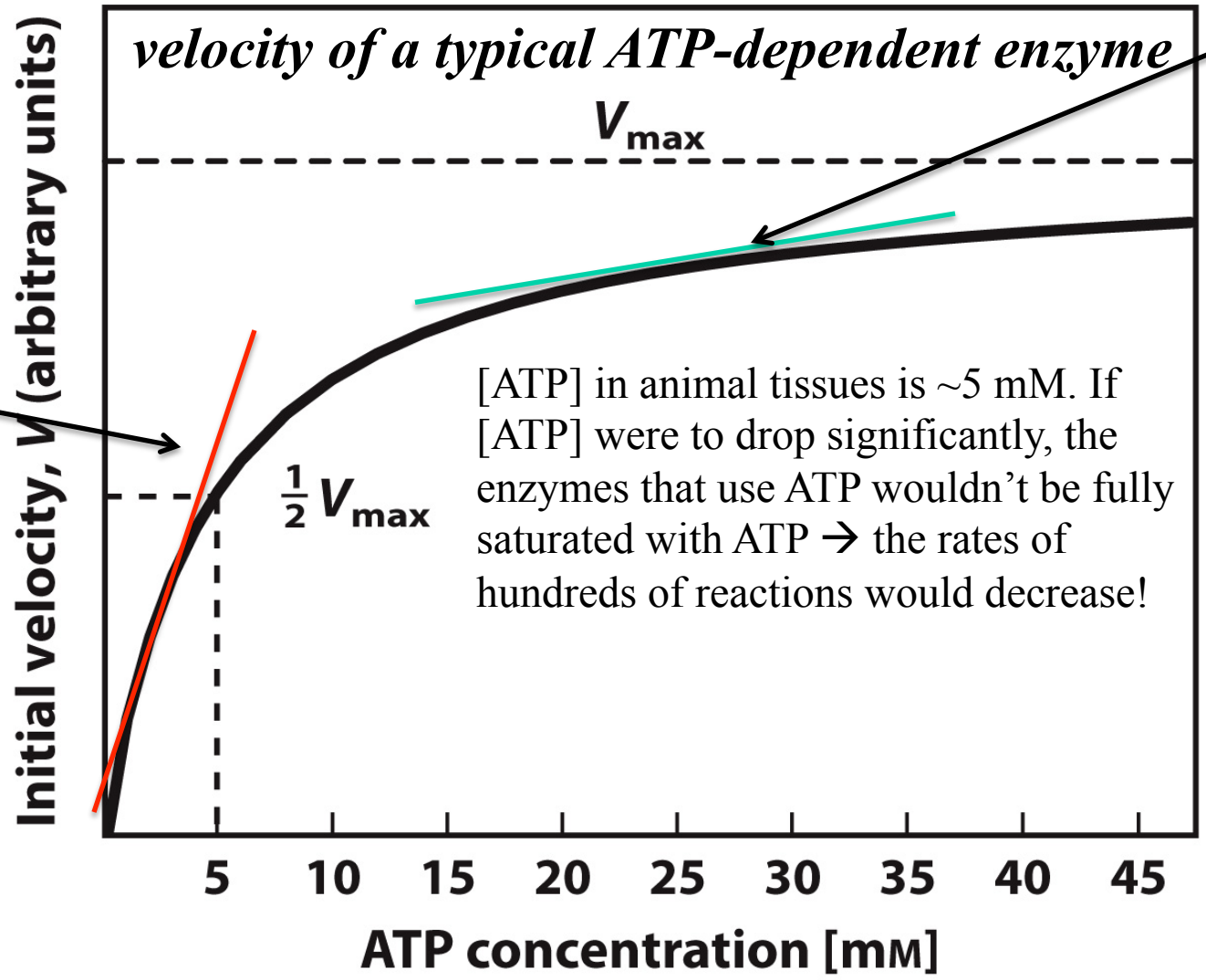
- Rates of a biochemical reactions depend on many factors:
  - Concentration of reactants vs. products
  - Activity of the catalyst
    - Concentration of the enzyme
      - Rate of translation vs. rate of degradation
    - Intrinsic activity of the enzyme
      - Could depend on substrate, effectors or phosphorylation state
  - Concentrations of effectors
    - Allosteric regulators
    - Competing substrates
    - pH, ionic environment
  - Temperature

Rate of reaction depends on the concentration of substrates

- The rate is more sensitive to concentration at low concentrations
  - Frequency of substrate meeting the enzyme matters
- The rate becomes insensitive at high substrate concentrations
  - The enzyme is nearly saturated with substrate

Effect of [Substrate] on Enzyme Activity

At low concentrations, slope (i.e., change in velocity over concentration) increases drastically.



At high concentrations, slope increases more slowly.

[ATP] in animal tissues is ~5 mM. If [ATP] were to drop significantly, the enzymes that use ATP wouldn't be fully saturated with ATP → the rates of hundreds of reactions would decrease!

Figure 15-7
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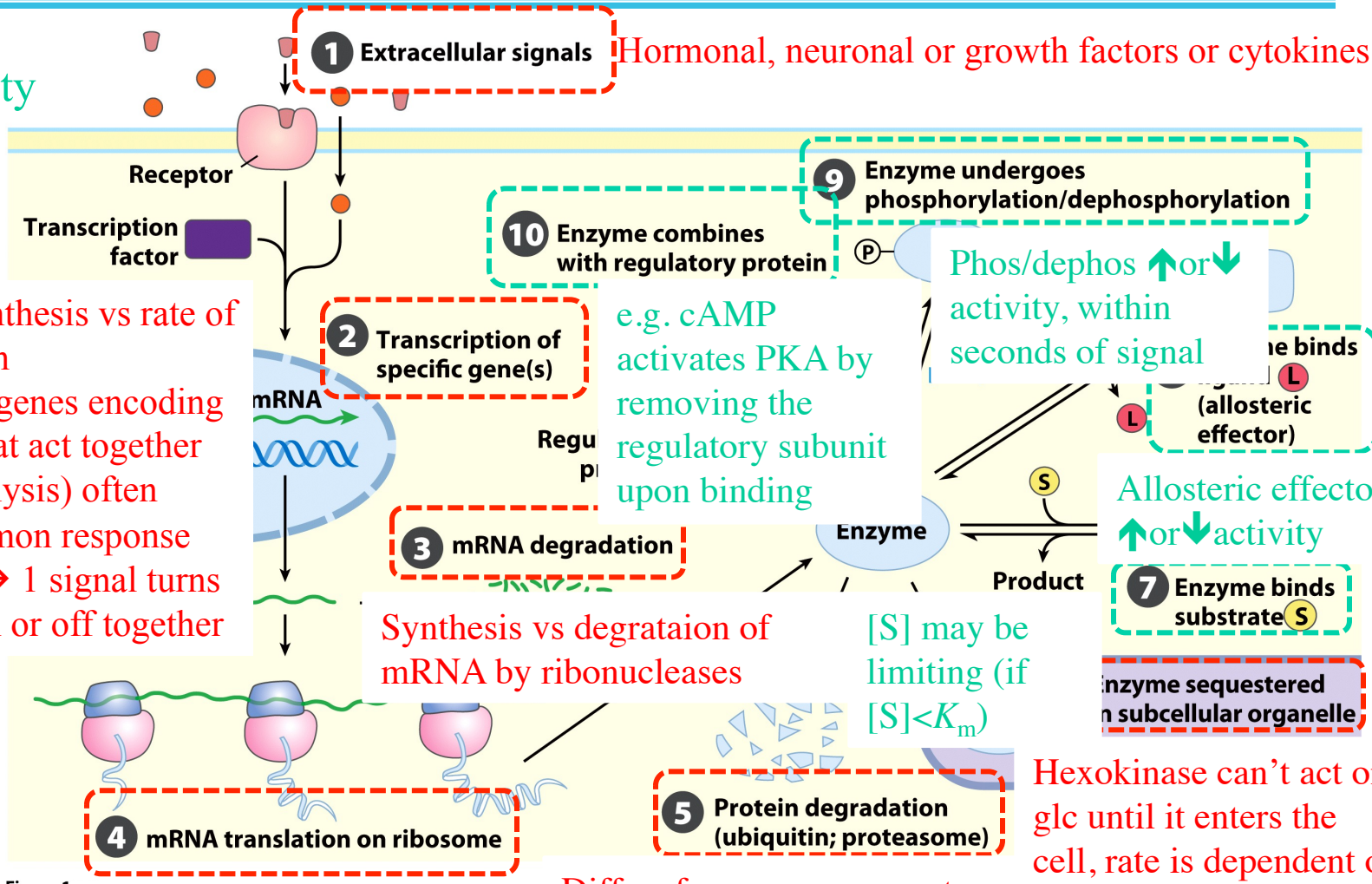
Factors that Determine the Activity of Enzymes

red: number
green: activity



Hormonal, neuronal or growth factors or cytokines

- Rate of synthesis vs rate of degradation
- Groups of genes encoding proteins that act together (e.g. glycolysis) often share common response elements → 1 signal turns them all on or off together

e.g. cAMP activates PKA by removing the regulatory subunit upon binding

Phos/dephos ↑or↓ activity, within seconds of signal

Allosteric effectors ↑or↓activity

Synthesis vs degrataion of mRNA by ribonucleases

[S] may be limiting (if [S]<K_m)

Hexokinase can't act on glc until it enters the cell, rate is dependent on activity of GLUT

Translation is regulated by many factors

Differs from one enzyme to another and depends on cellular conditions

Figure 1
Lehninge
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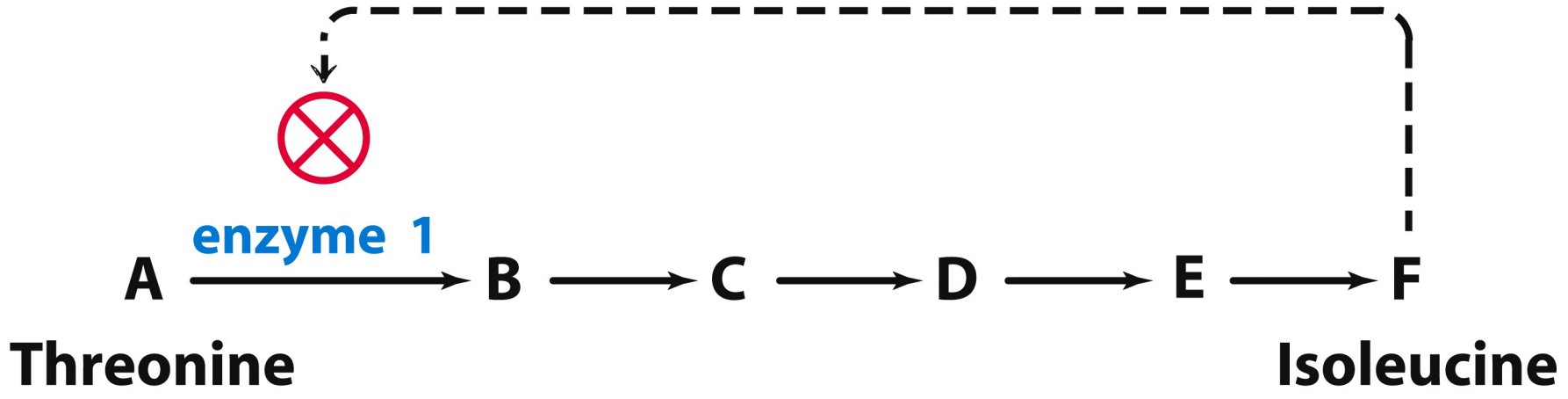
Feedback Inhibition

In many cases, ultimate products of metabolic pathways directly or indirectly inhibit their own biosynthetic pathways

– ATP inhibits the commitment step of glycolysis



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Phosphorylation of enzymes affects their activity

- Phosphorylation is catalyzed by protein kinases
- Dephosphorylation is catalyzed by protein phosphatases, or can be spontaneous
- Typically, proteins are phosphorylated on the hydroxyl groups of Ser, Thr or Tyr

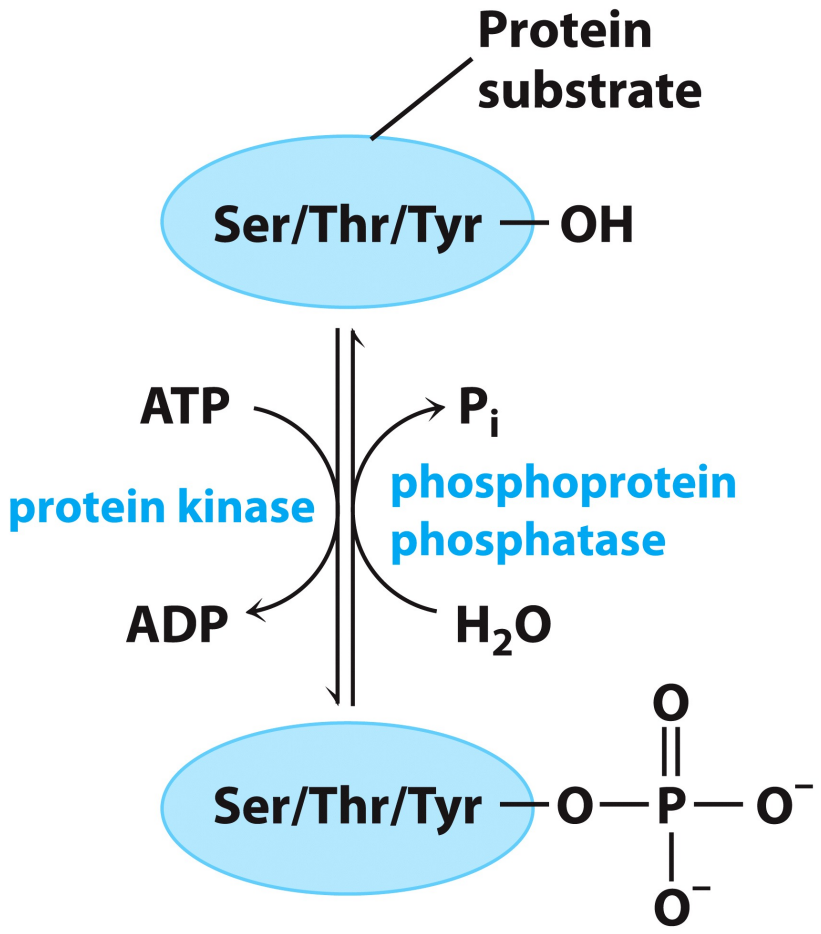

Figure 15-5
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Enzymes are also regulated by regulatory proteins

Binding of regulatory protein subunits affects specificity.

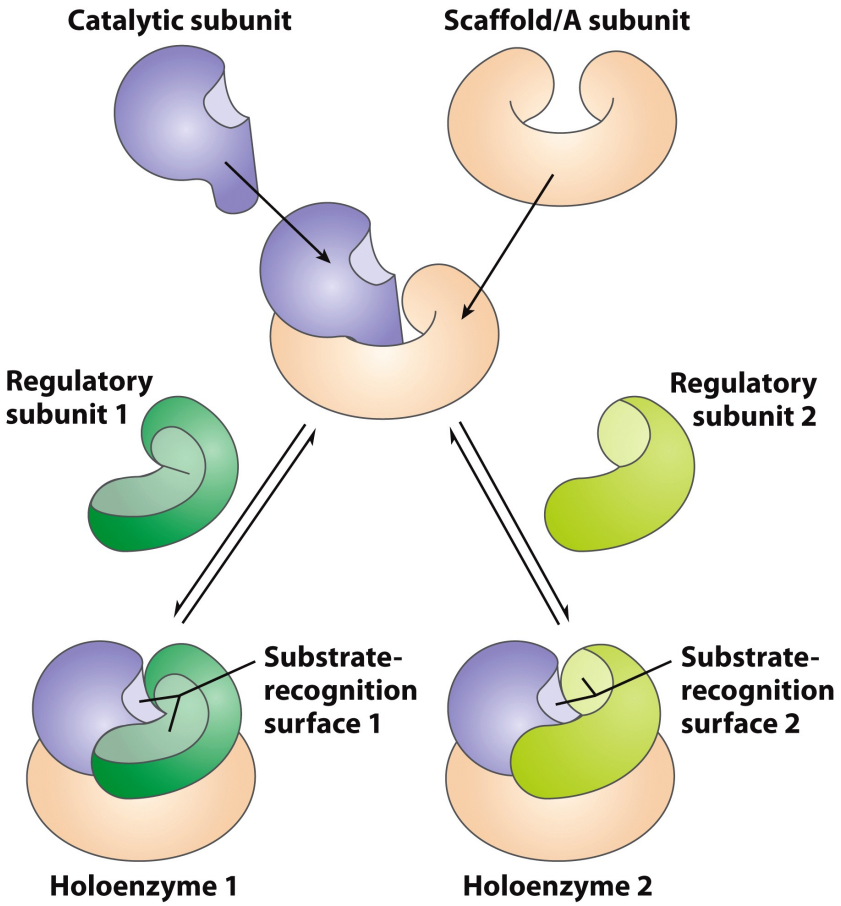

Figure 15-20b
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Proteins have a finite lifespan

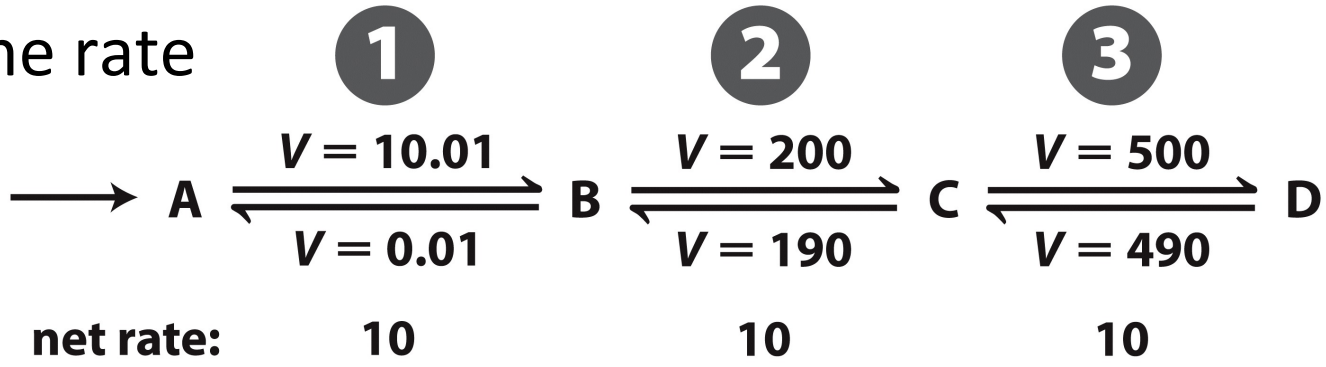
- Different proteins in the same tissue have very different half-lives
  - Less than an hour to about a week for liver enzymes
  - Rapid turnover is expensive but proteins with short half-lives can reach new steady state levels faster → better responsiveness to signals
- Some proteins are as old as you are
  - Crystallins in the eye lens

TABLE 15–1 **Average Half-Life of Proteins in Mammalian Tissues**

Tissue	Average half-life (days)
Liver	0.9
Kidney	1.7
Heart	4.1
Brain	4.6
Muscle	10.7

Reactions far from equilibrium are common points of regulation

- Within a metabolic pathway most reactions operate near equilibrium (e.g. “2” and “3”) (small changes in [S] or [P] can change the rate or even reverse the direction)
- Key enzymes operate far from equilibrium (e.g. “1”)
  - These are the sites of regulation
  - Control flow through the pathway
- To maintain steady state all enzymes operate at the same rate



Step **1** is far from equilibrium $V_{forward} >> V_{reverse}$. The net rate of step **1** (10) >> $V_{reverse}$ (0.01) and is identical to the net rates of steps **2** and **3** when the pathway is operating in the steady state. *Step 1 has a large, negative ΔG.*

ATP and AMP are key cellular regulators

- Cells need to keep a constant supply of ATP
- A 10% decrease in [ATP] can greatly affect the activity of ATP utilizing enzymes
- A 10% decrease in [ATP] leads to a dramatic increase in [AMP]
  - AMP can be a more potent allosteric regulator

TABLE 15-4 Relative Changes in [ATP] and [AMP] When ATP Is Consumed

Adenine nucleotide	Concentration before ATP depletion (mM)	Concentration after ATP depletion (mM)	Relative change
ATP	5.0	4.5	10%
ADP	1.0	1.0	0
AMP	0.1	0.6	600%

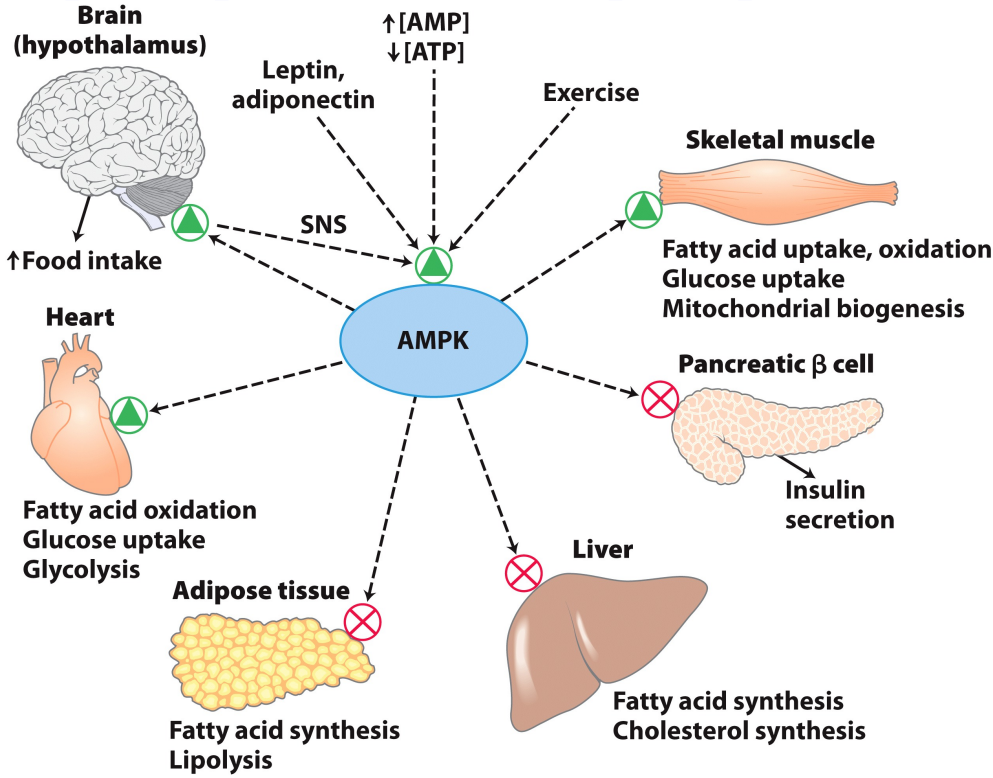
[AMP] is more sensitive indicator of a cell's energetic state than [ATP]

Why??

AMP differentially affects pathways in different tissues via AMPK

- When ATP is consumed (e.g. contraction) AMP is produced from ATP in 2 steps
1. ATP → ADP + P_i (ATP consuming process)
2. 2ADP → ATP + AMP (**adenylate kinase**)
- The most important mediator of regulation by AMP is AMP-activated protein kinase (**AMPK**)
  - ↓nutrients or ↑exercise ↑[AMP] ↑AMPK ↑glucose transport ↑glycolysis ↓fatty acid, cholesterol and protein synthesis

AMPK is activated by elevated [AMP] or decreased [ATP] et. al.



Shifts metabolism in many tissues away from energy-consuming processes to the use of fatty acids as a fuel (extrahepatic tissues) and gluconeogenesis (liver)

Concentrations of other metabolic intermediates must also be adjusted

- ATP is not the only metabolite that has to be present at appropriate levels
- Hundreds of other metabolites change their concentrations according to the needs of the organism
- E.g. Dihydroxyacetone and 3-phosphoglycerate (glycolytic intermediates).
    - DHA is a precursor of triacylglycerols
    - 3-PG is a precursor of the amino acid serine
    - When TAGs or Ser are needed, *the rate of glycolysis must be adjusted* to provide them, *WITHOUT reducing glycolytic production of ATP*

Some Enzymes in the Pathway Limit the Flux of Metabolites More Than Others

- Enzymes that are far from equilibrium (regulated)
- Not all regulated enzymes have the same affect on the entire pathway.
  - Some control flux through the pathway.
  - Others regulate steady state concentrations of metabolites in response to changes in flux.
- Hexokinase and phosphofructokinase are appropriate targets for regulation of glycolytic flux.
  - Increased hexokinase activity enables activation of glucose.
  - Increased phosphofructokinase-1 activity enables catabolism of activated glucose via glycolysis.

Why are we interested in what limits the flux though a pathway?

- To understand the action of hormones or drugs, or the pathology that results from a failure of metabolic regulation, we MUST know where the control is present.

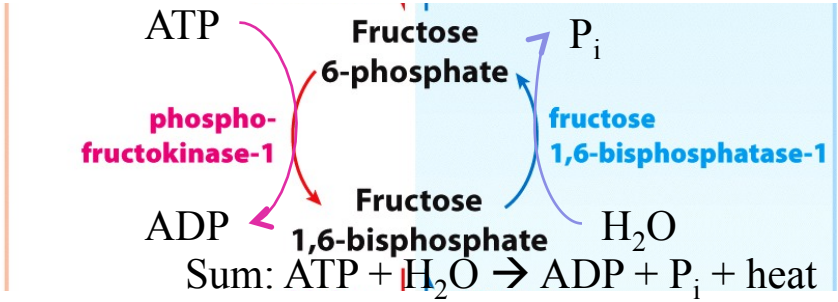
- If YOU want to design a drug to inhibit a pathway, it is logical to target the enzyme that has the GREATEST impact on the flux through that pathway!

- **15.2 Analysis of metabolic control** *is experimental metabolic biochemistry and is not required for the purposes of this course*

Glycolysis vs. Gluconeogenesis

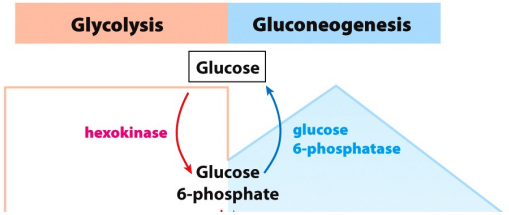
- *Gluconeogenesis* – in the liver to supply bodily tissues with glc when glycogen stores are depleted or no dietary glc is available

- *3 glycolytic* steps are irreversible (large –ve $\Delta G'$), bypass reactions



- Simultaneous operation of both pathways consumes ATP without production of biological work! A large amount of chemical energy will be lost as heat (**futile cycle/substrate cycle** is a better term)

- Need to regulate both pathways where they diverge



Hexokinase

- 4 isozymes in humans
- Isozymes differ in affinity for glc
- HK II (muscles) ↑ affinity (K_m~ 0.1 mM)
- $[glc]_{blood}$ ~ 5 mM → HK II is saturated → operates at V_{max}
- Both HK I and HK II (muscles) are allosterically inhibited by their product (Glc-6-P) to balance the rate of glc-6-P formation and utilization (to reestablish the steady state)

- HK IV (glucokinase) ↓ affinity (K_m~ 10 mM)
- HK IV works at ~ 2x less than K_m → not at V_{max} → regulated by $[glc]_{blood}$
- Under low $[glc]_{blood}$, glc (with glc from gluconeogenesis) leaves the liver before being trapped by phosphorylation to go to other tissues
- Under high $[glc]_{blood}$ (after a carb meal), HK IV activity continues to increase as [glc] increases

Kinetic Properties of HK I vs. HK IV

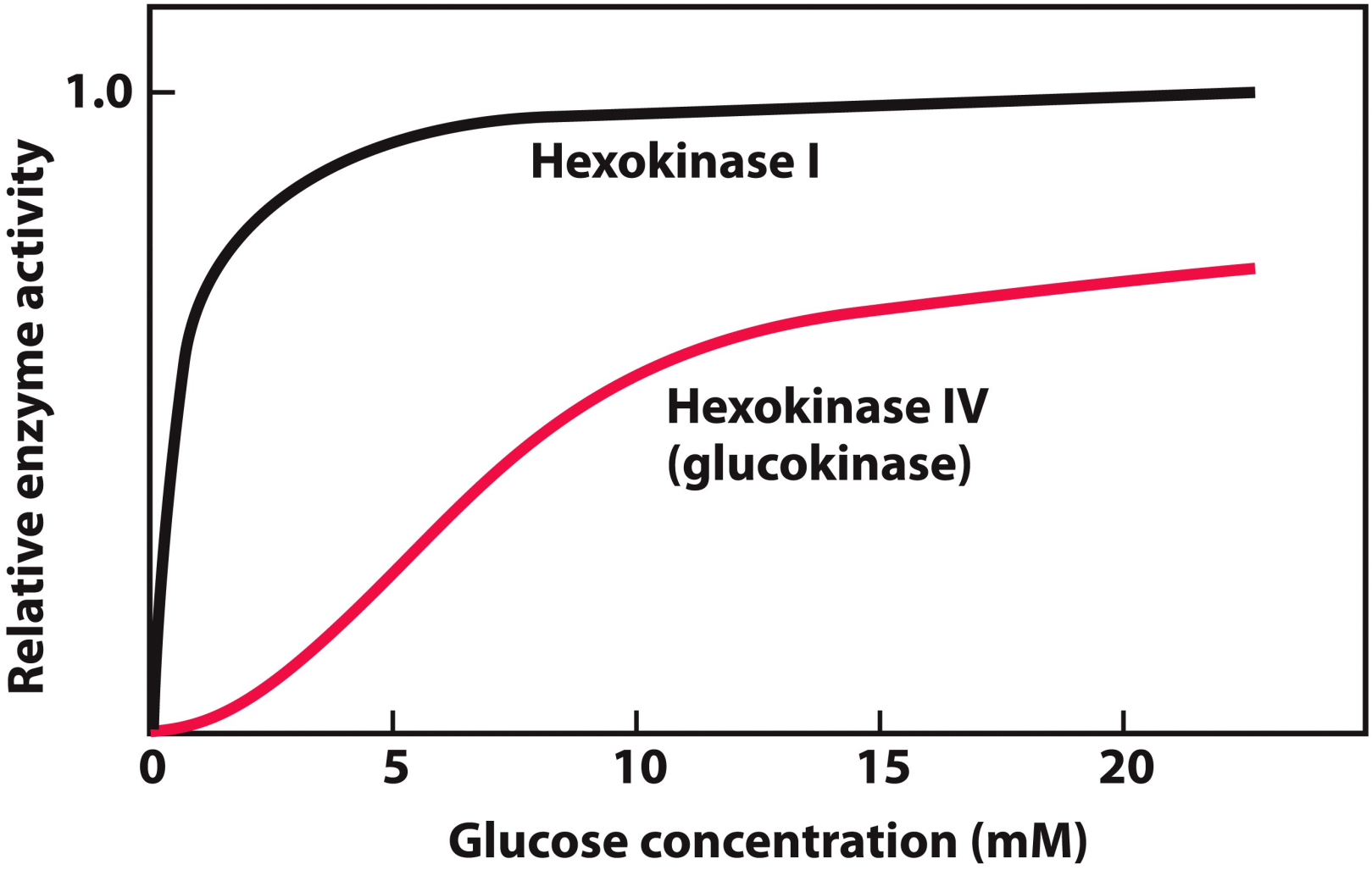


Figure 15-14
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Hexokinase

- HK IV is not inhibited by glc-6-P, so it can function at the higher [glc-6-P] which totally inhibits HK I – III
- Only HK IV is inhibited by the reversal binding of a regulatory protein in the liver
- Binding is **tighter** with fru-6-P. Glc competes with fru-6-P ➔ relieving the inhibition
- When glc is under 5 mM, HK IV is inhibited by this mechanism to prevent the liver from competing with other organs for glc

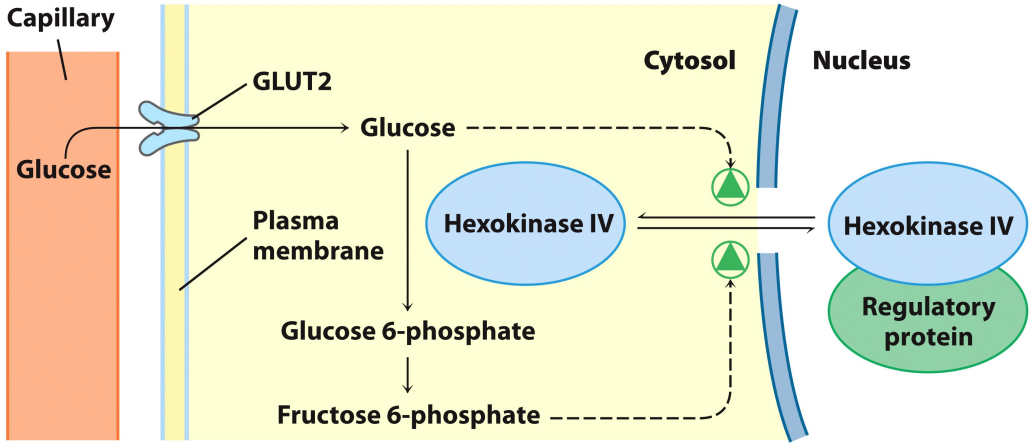

Figure 15-15
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PFK-1

- Fructose-6-phosphate → fructose 1,6-bisphosphate is the commitment step in glycolysis
- While ATP is a substrate, ATP is also a negative effector
  - *Do not spend glucose in glycolysis if there is plenty of ATP*

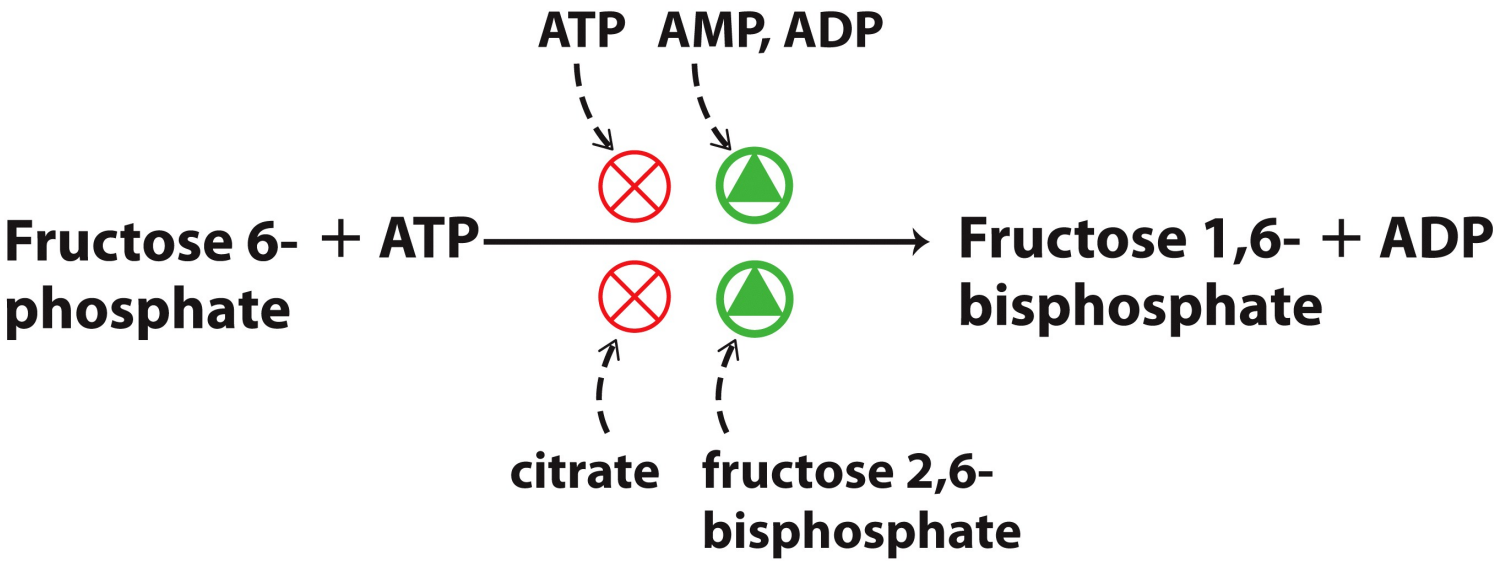

Figure 15-16c
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Effect of ATP on Phosphofructokinase-1

ATP inhibits PFK-1 by binding to an *allosteric site* and lowering the affinity to fru-6-P

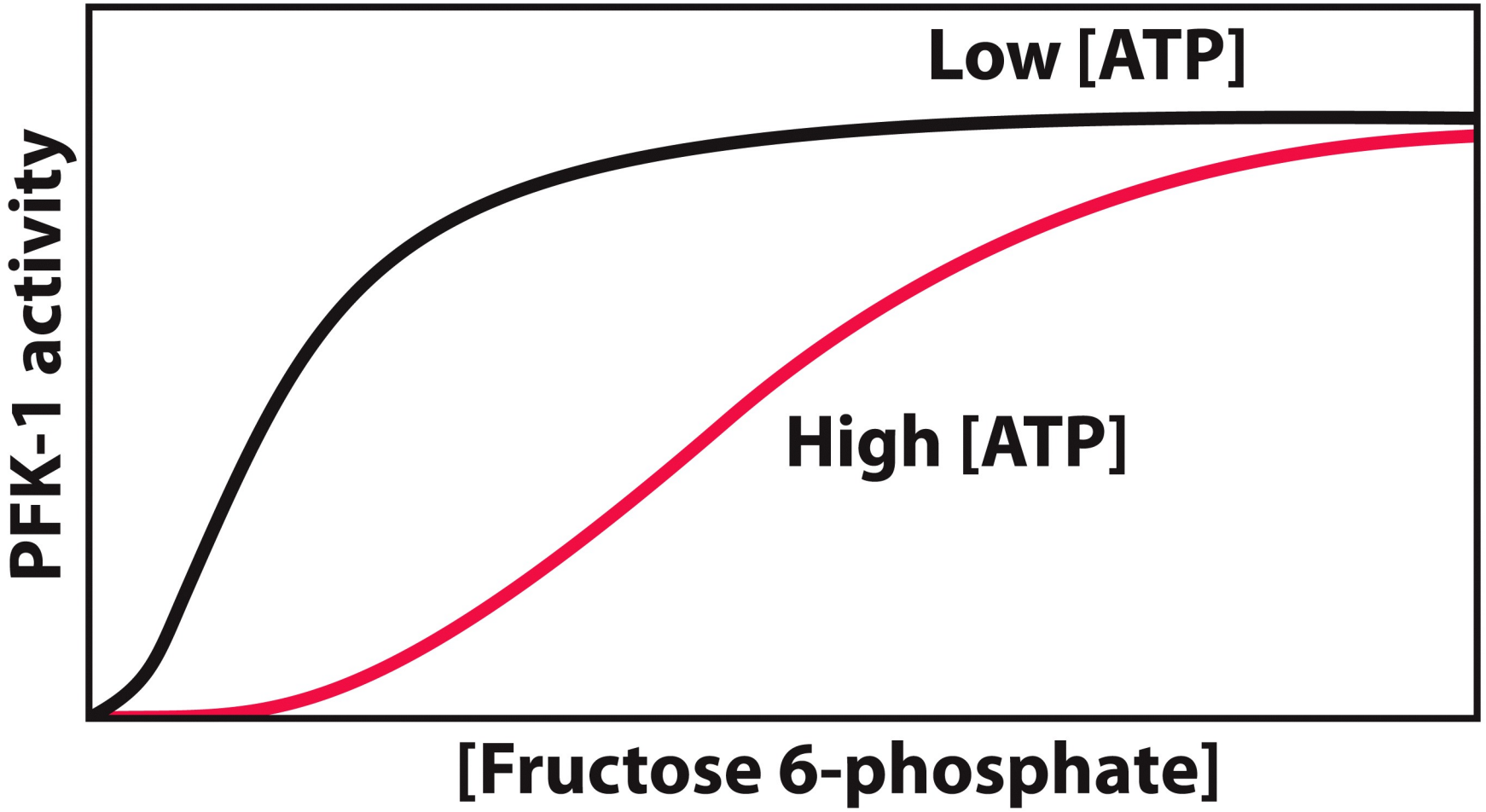

Figure 15-16b
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PFK-1 & FBPase-1

- High [citrate] increases the inhibitory effects of ATP, reducing the flow of glc through glycolysis even more
- Serves as an intracellular signal that the cell is meeting its current needs for energy

- FBPase-1 is allosterically inhibited by AMP

➢ *At low [ATP], cells funnel glc into glycolysis and inhibit gluconeogenesis*

Regulation of Phosphofructokinase 1 and Fructose 1,6-Bisphosphatase

- Go glycolysis if AMP is high and ATP is low (not enough energy)
- Go gluconeogenesis if AMP is low (plenty of energy)

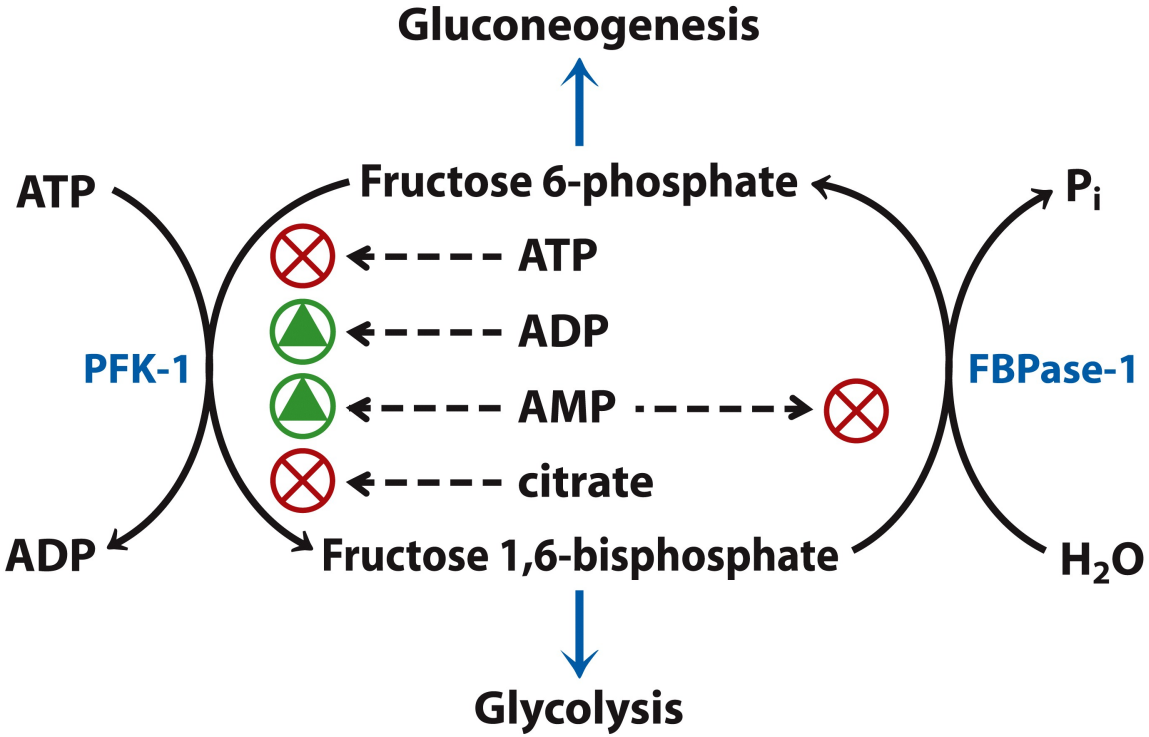

Figure 15-17
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Fructose 2,6-Bisphosphate

- ↓$[glc]_{blood}$ → **glucagon** signals the liver to stop using glc and to produce and release more into the blood
- ↑$[glc]_{blood}$ → **insulin** signals the liver to use glc a fuel and as a precursor for glycogen and TAG
- *This hormonal regulation is mediated by **F26BP***

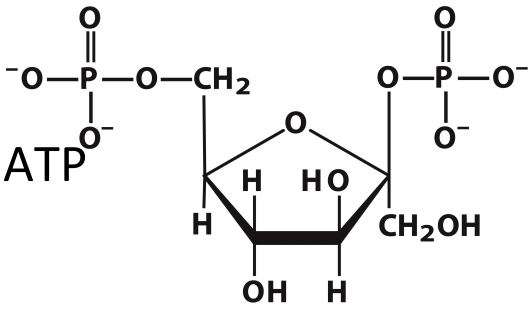
- **NOT** a glycolytic intermediate, only a regulator
- Produced specifically to regulate glycolysis and gluconeogenesis
  - activates PFK-1 (glycolysis)

↑PFK affinity to Fru-6-P and↓ affinity for citrate and ATP

PFK is virtually INACTIVE in the absence of F26BP!

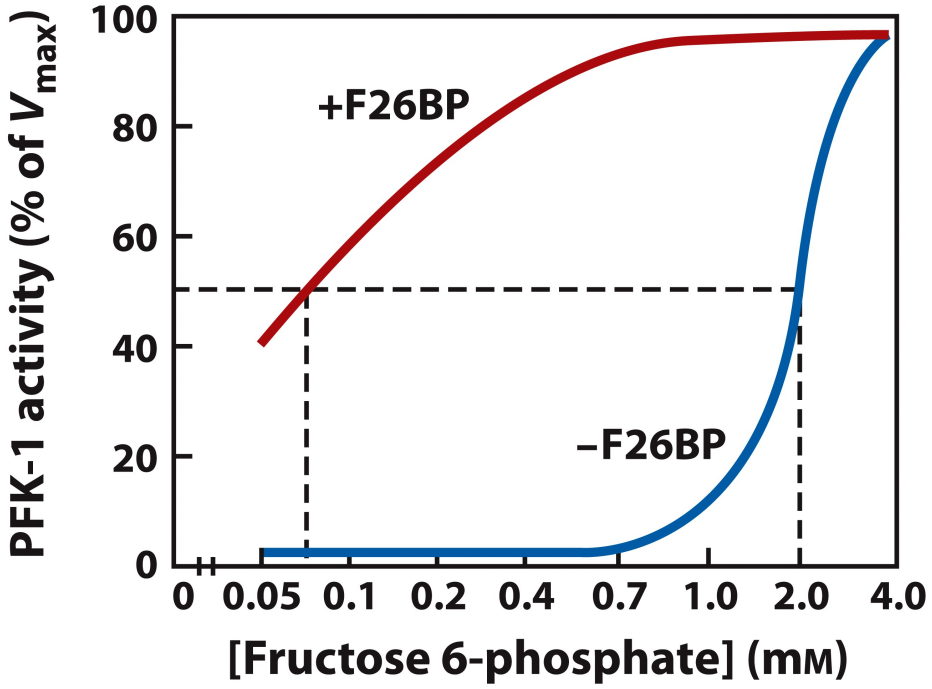
  - inhibits FBPase-1 (gluconeogenesis)

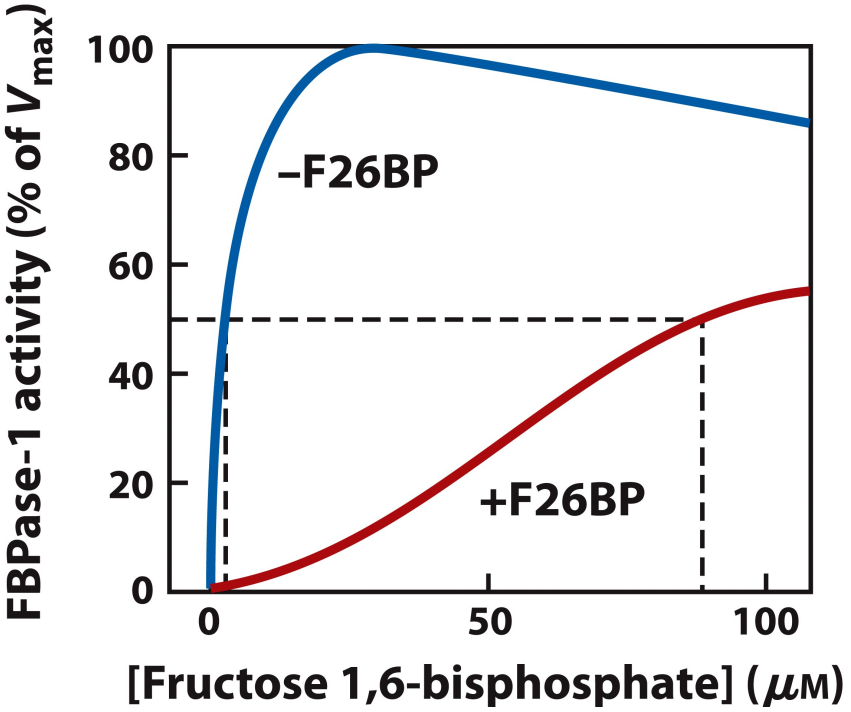
↓FBPase affinity to its substrate



Fructose 2,6-bisphosphate

Glycolysis and gluconeogenesis are differentially regulated by F-2,6-BP





F26BP is produced from fructose-6-phosphate

- **Bifunctional enzyme**: a subunit carries the PFK-2 activity and the other has the FBPase-2 activity
- Regulated by insulin and glucagon

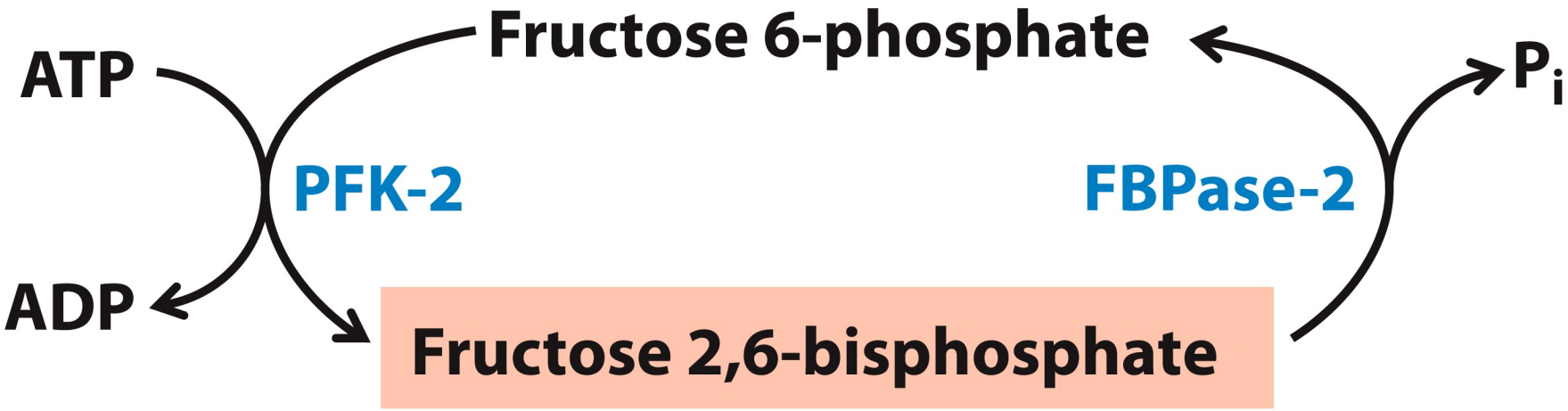


Figure 15-19a
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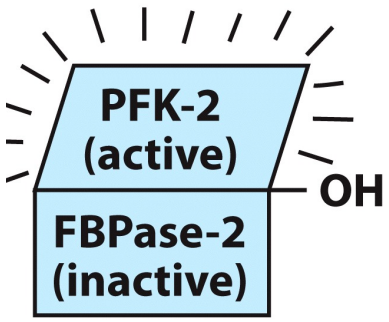
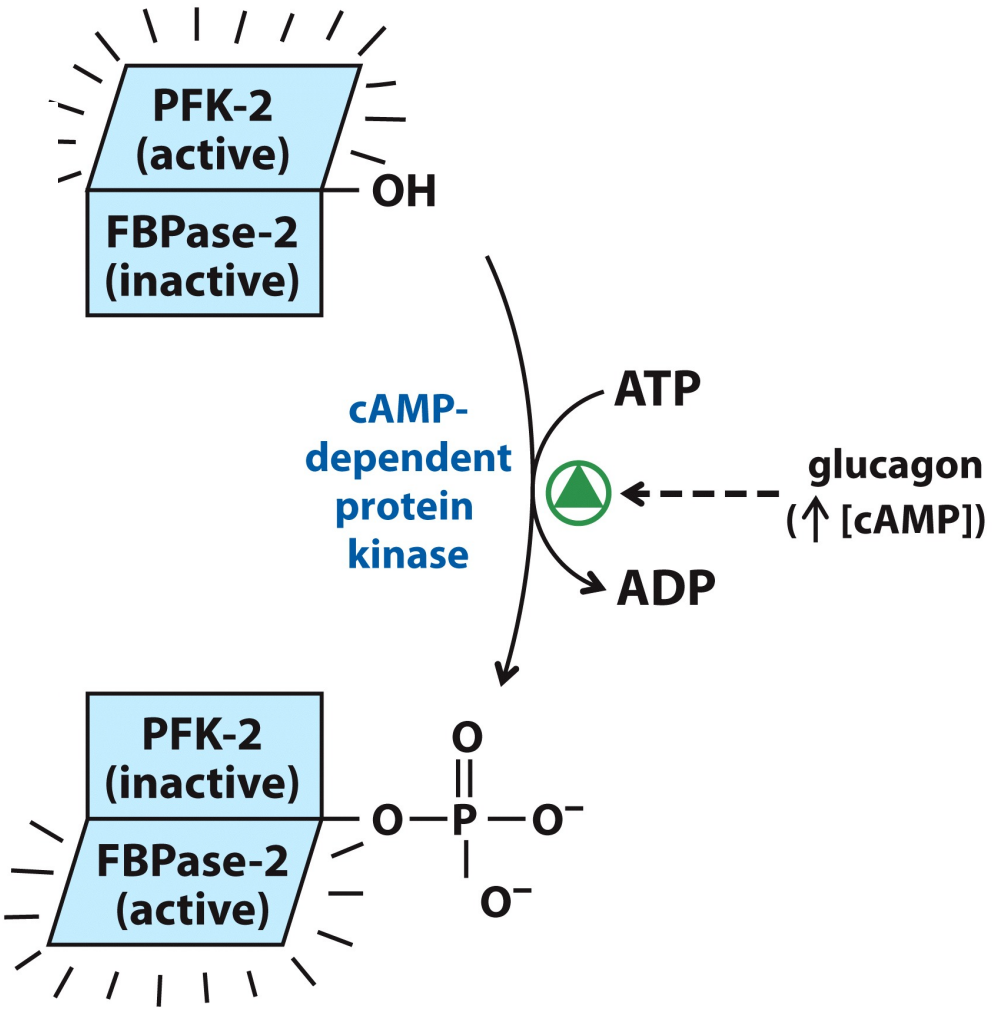
Regulation of F26BP Levels

Structurally, these two enzymes are **different** than those in glycolysis and gluconeogenesis (i.e., they are **conjoined**, rather than independent) and are **regulated via phosphorylation.**



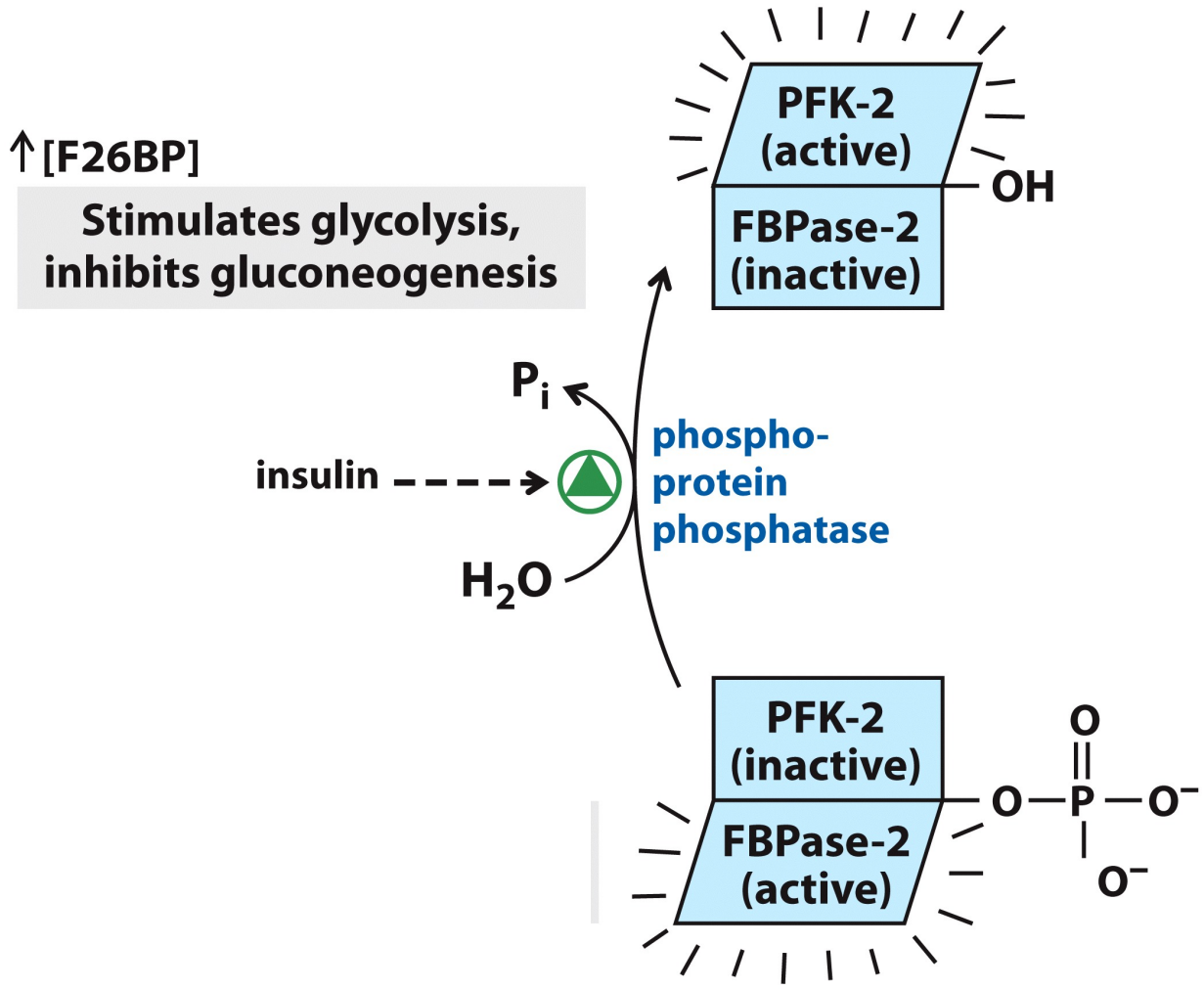
Regulation of F26BP Levels



↓[F26BP]

Inhibits glycolysis, stimulates gluconeogenesis

Regulation of F26BP Levels



Regulation of Pyruvate Kinase

- 3 isozymes in vertebrates
- **Allosterically activated by fructose-1,6-bisphosphate**
  - *Increase* flow through glycolysis
- Allosterically inhibited by signs of abundant energy supply (all tissues)
  - ATP
  - Acetyl-CoA and long-chain fatty acids
  - Alanine (enough amino acids)
- **Inactivated by phosphorylation** in response to signs of glucose depletion (glucagon) (liver isozyme only)
  - The use of glc in the liver is slowed and glc is exported to brain and other vital organs
  - *In muscles, cAMP in response to adrenaline activates glycogen breakdown and glycolysis ➔ provides fuel needed for fight-or-flight*

Regulation of Pyruvate Kinase

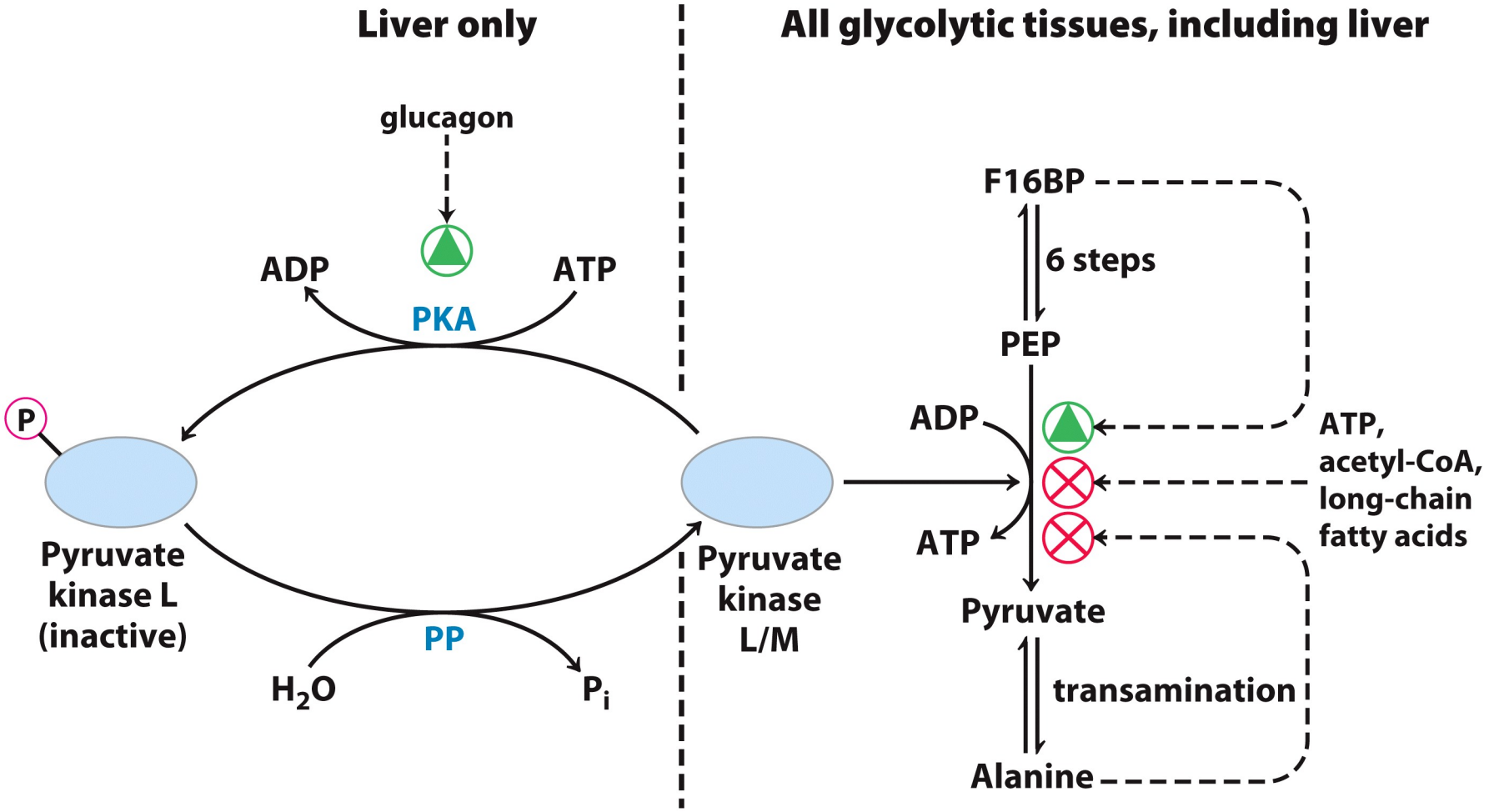


Figure 15-21
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Two Alternative Fates for Pyruvate

- Pyruvate can be a source of new glucose
  - Store energy as glycogen
  - Generate NADPH via pentose phosphate pathway
- Pyruvate can be a source of acetyl-CoA
  - Store energy as body fat
  - Make ATP via citric acid cycle
- *Acetyl-CoA stimulates glucose synthesis by activating pyruvate carboxylase* (high under abundant energy from fats: breakdown of fats → acetyl-CoA, also CAC is inhibited → acetyl-CoA accumulation)
- PEP carboxykinase is regulated by transcription (fasting or high glucagon ↑ transcription and mRNA stabilization; insulin has the opposite effect)

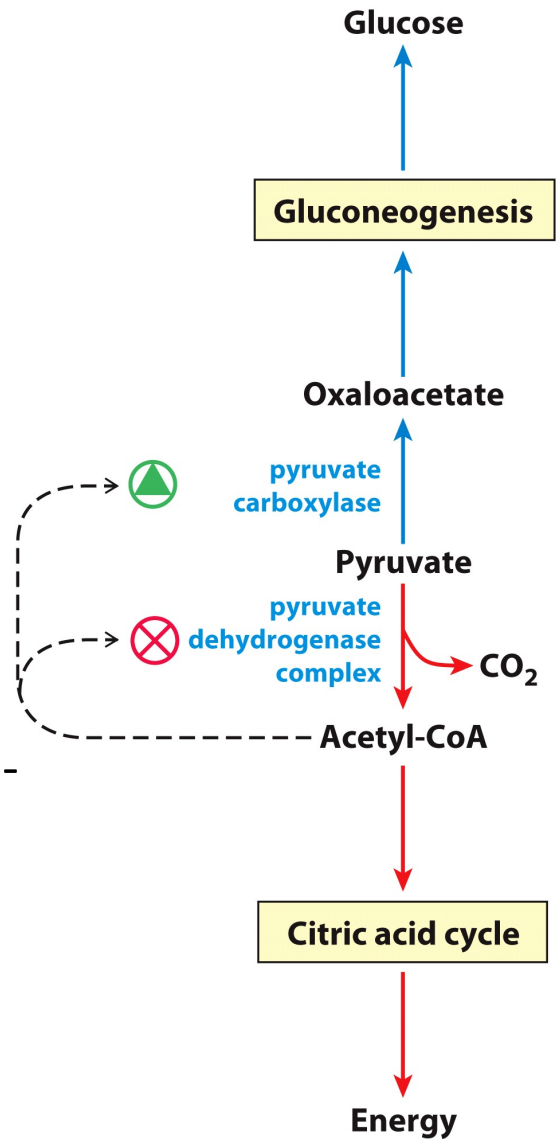

Figure 15-22
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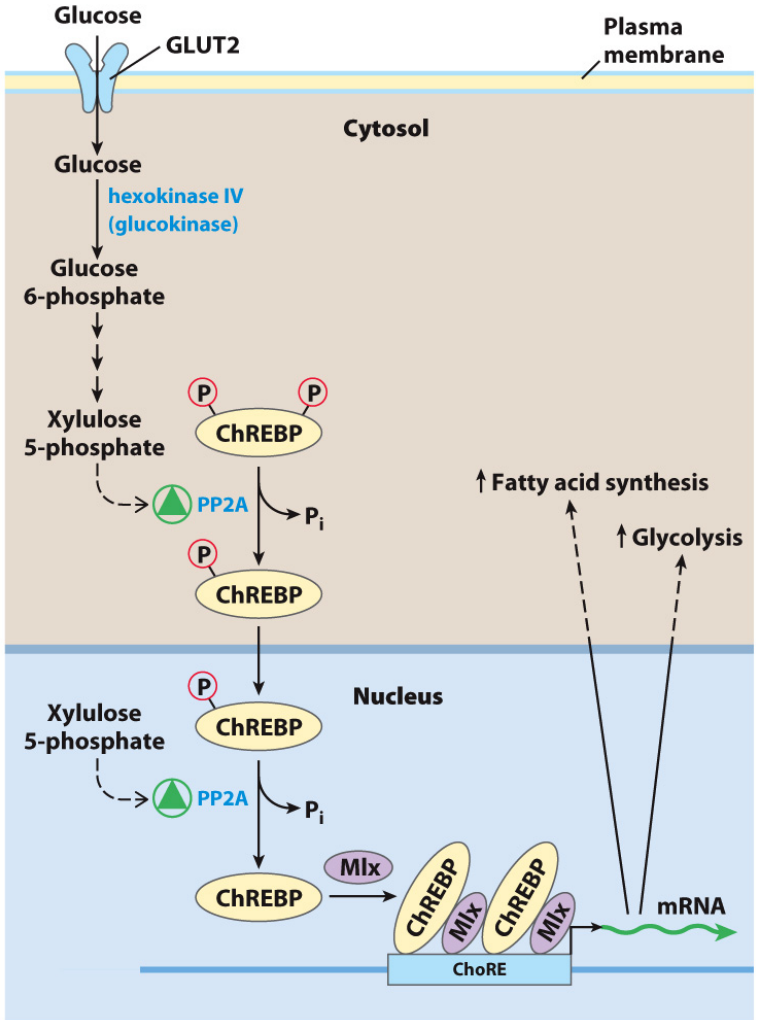
The Amount of Many Metabolic Enzymes Is Controlled by Transcription

TABLE 15-5 Some of the Many Genes Regulated by Insulin

Change in gene expression	Role in glucose metabolism
Increased expression Hexokinase II Hexokinase IV Phosphofructokinase-1 (PFK-1) PFK-2/FBPase-2 Pyruvate kinase	Essential for glycolysis, which consumes glucose for energy
Glucose 6-phosphate dehydrogenase 6-Phosphogluconate dehydrogenase Malic enzyme	Produce NADPH, which is essential for conversion of glucose to lipids
ATP-citrate lyase Pyruvate dehydrogenase	Produce acetyl-CoA, which is essential for conversion of glucose to lipids
Acetyl-CoA carboxylase Fatty acid synthase complex Stearoyl-CoA dehydrogenase Acyl-CoA–glycerol transferases	Essential for conversion of glucose to lipids
Decreased expression PEP carboxykinase Glucose 6-phosphatase (catalytic subunit)	Essential for glucose production by gluconeogenesis

Carbohydrate responsive element binding protein (ChREBP) activates transcription in response to glucose



Glycogen is an energy source stored mainly in the liver and muscle

- ~ 10% of liver weight!

  - if this much glc is dissolved in the cytosol of a hepatocyte it would constitute 0.4 M (osmotic problems)
  (by contrast glycogen is only 0.01 μM)

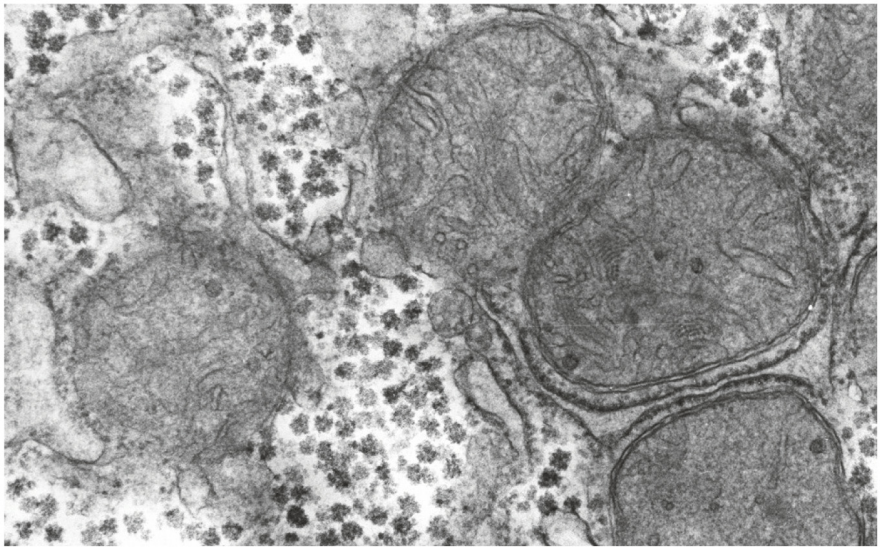


Figure 15-26
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- Stored in granules

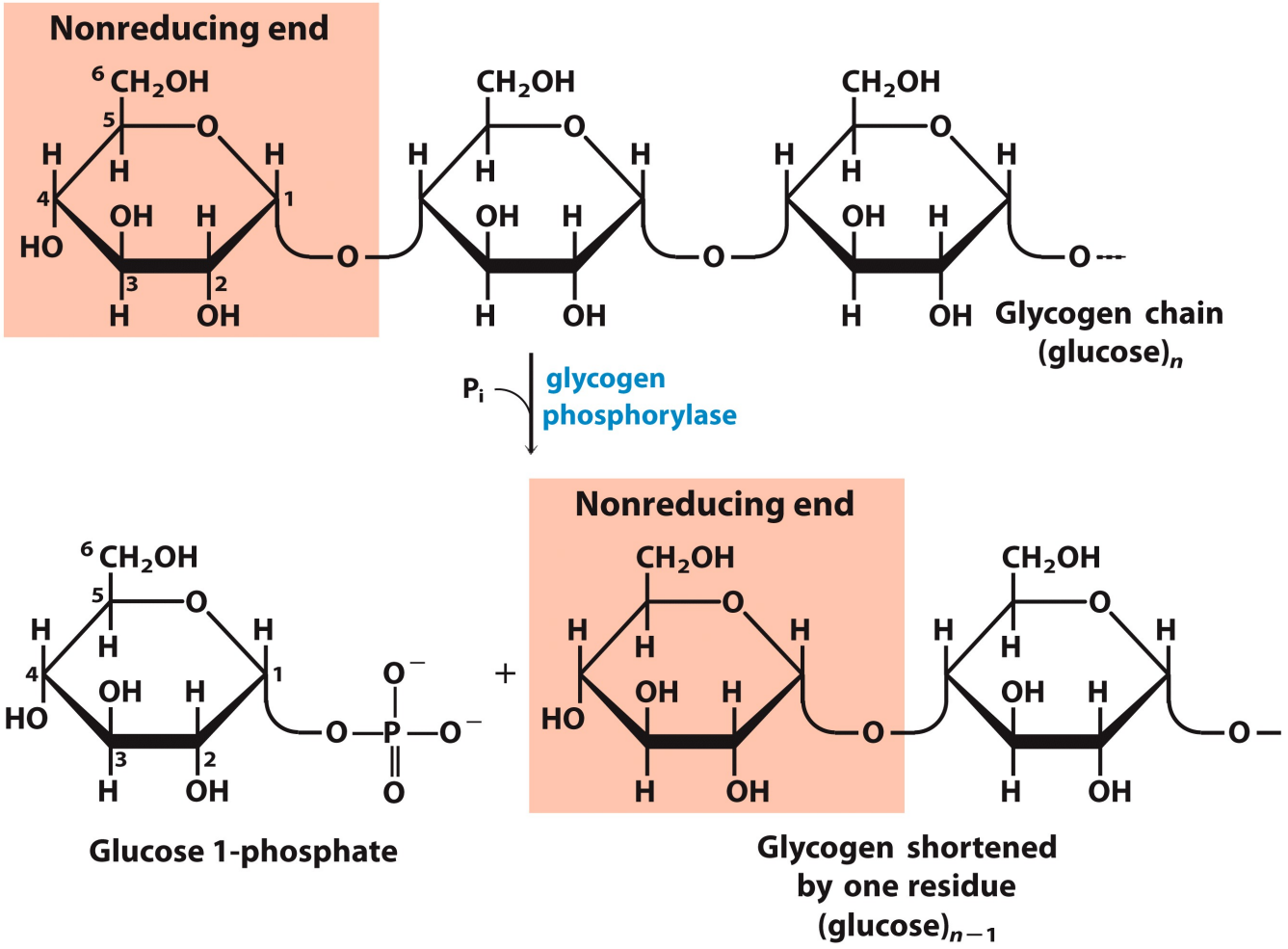
  - complex aggregates of glycogen and enzymes that synthesize and digest it (as well as enzymes that control these processes)

- Muscle glycogen is used up in less than 1 hour during vigorous exercise
- Liver glycogen is used up in 12 – 24 hours (reservoir for glc when it is not available in the diet)

Glycogenolysis

- Glycogenolysis is the breakdown of glycogen into glucose subunits
- The outer branches of glycogen are broken down first by the action of three enzymes
- *Glycogen phosphorylase*, *debranching enzyme* and *phosphoglucomutase*

Glucose residues are removed from glycogen by glycogen phosphorylase



Repetitive – removal of successive glc until the 4th glc from a branch point

Dealing with Branch Points in Glycogen

- Glycogen phosphorylase works on non-reducing ends until it reaches four residues from an (α1→ 6) branch point

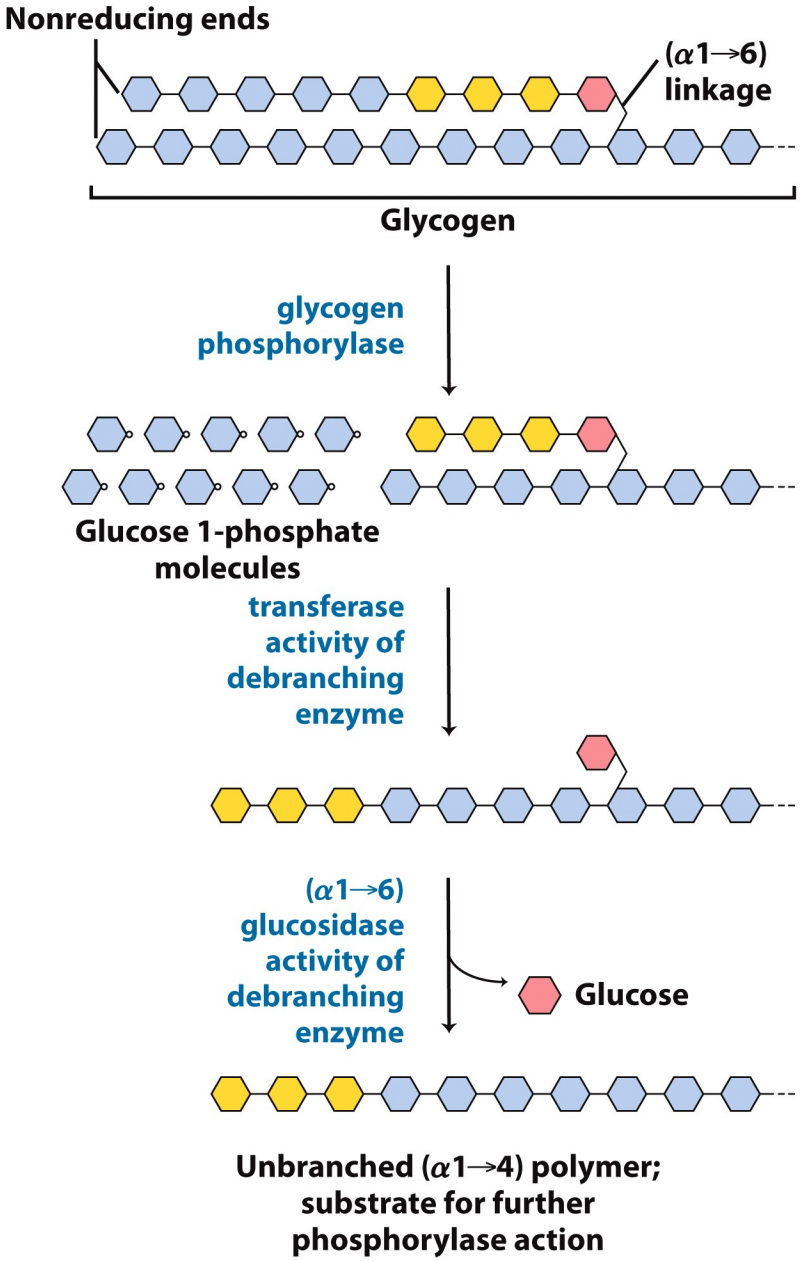
  Recall: *Phosphorolysis* reaction (attack by P_i, cellular degradation) is different from *hydrolysis* reaction (attack by H_2O; intestinal degradation)

- Debranching enzyme catalyzes two successive reactions:

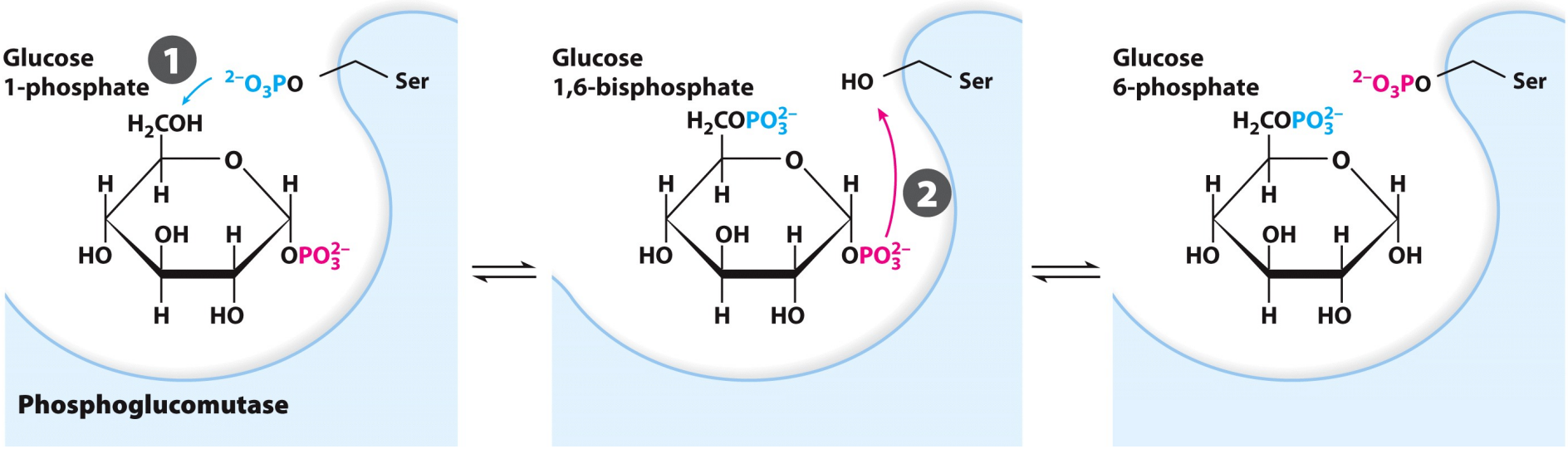
1. Transfers a block of three residues to the non-reducing end of the chain
2. Cleaves the single remaining (α1→6)–linked glc

- Glycogen phosphorylase resumes

Dealing with Branch Points in Glycogen

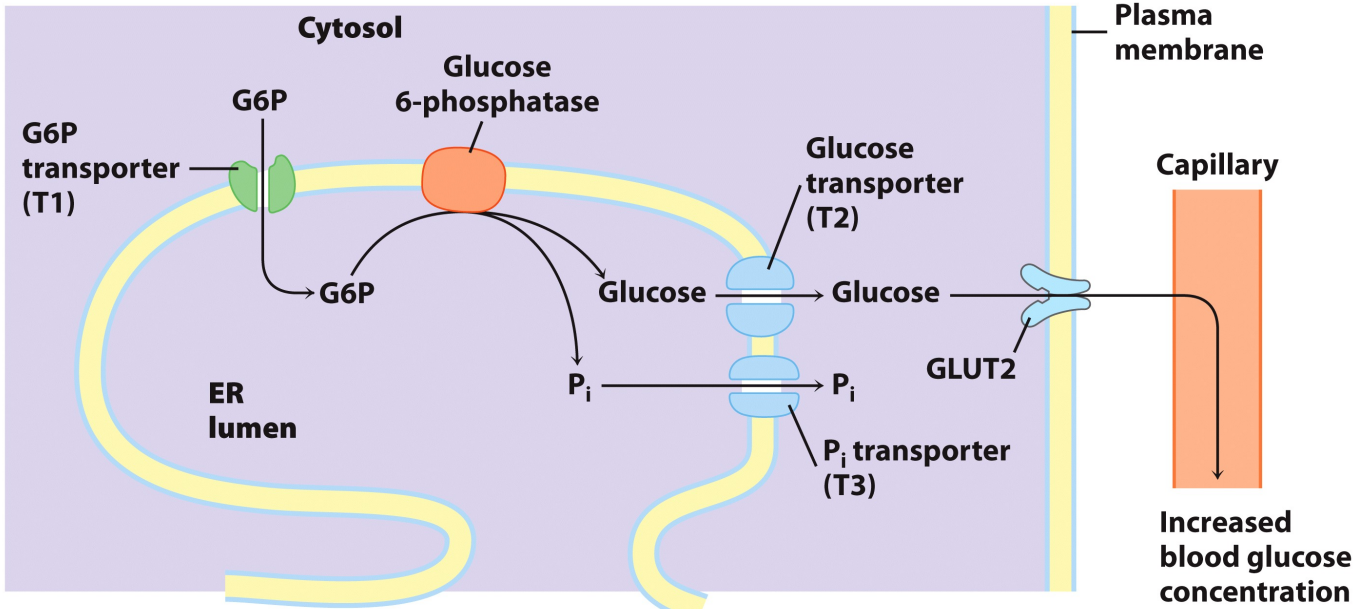


Glucose-1-phosphate must be isomerized to glucose-6-phosphate for metabolism



- In muscle: glc-6-p enters glycolysis and serves as energy source for muscle contraction
- In liver: releases glc into blood when $[glc]_{blood}$ drops (requires the enzyme *glucose 6-phosphatase*)

Glucose-6-phosphate is dephosphorylated in the liver for transport out of the liver



- Enzyme is only found in liver and kidney
- Active site inside the ER (separation of this function from glycolysis; otherwise it would abort glycolysis!)
- Other tissues cannot convert glc-6-P from glycogen breakdown to glc ➔ cannot contribute to $[glc]_{blood}$

Glycogen Synthesis from Glucose Occurs in Multiple Steps

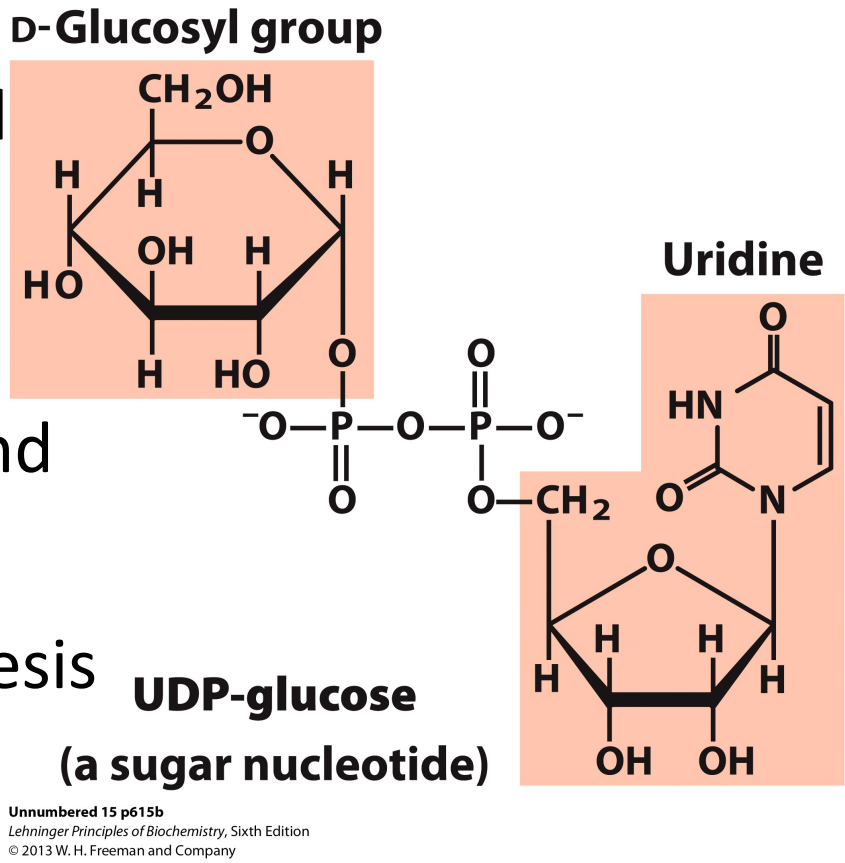
- Synthesis of glycogen requires more enzymes and metabolic intermediates than glycogen degradation.

- Blood glucose must be:
  - phosphorylated
  - labeled with UDP
  - added to glycogen

Multiple steps allow for multiple points in regulation.

Glycogenesis

- **Sugar nucleotides:** anomeric C of a sugar is activated by the attachment of a nucleo-tide with a phosphate ester bond
- Substrates for polymerization of monosaccharides
- Intermediates in aminohexose and deoxyhexose biosyntheses
- Intermediates in vitamin C synthesis



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- UDP-glucose is the substrate of glycogen synthase

Suitability of sugar nucleotides for biosynthetic reactions

1. Metabolically irreversible formation

   - NTP + hexose 1-P → sugar nucleotide + PP_i $\Delta G'^{o}$ (small +ve)
   - PP_i is rapidly hydrolyzed by pyrophosphatase (-19.2kJ/mol)
     → $\Delta G'$ for the reaction is favorable

   - rapid removal of PP_i pulls the synthetic reaction forward

2. Increase in catalytic activity due to free energy of binding

   - nucleotide part of the molecule has many groups that undergo noncovalent interactions

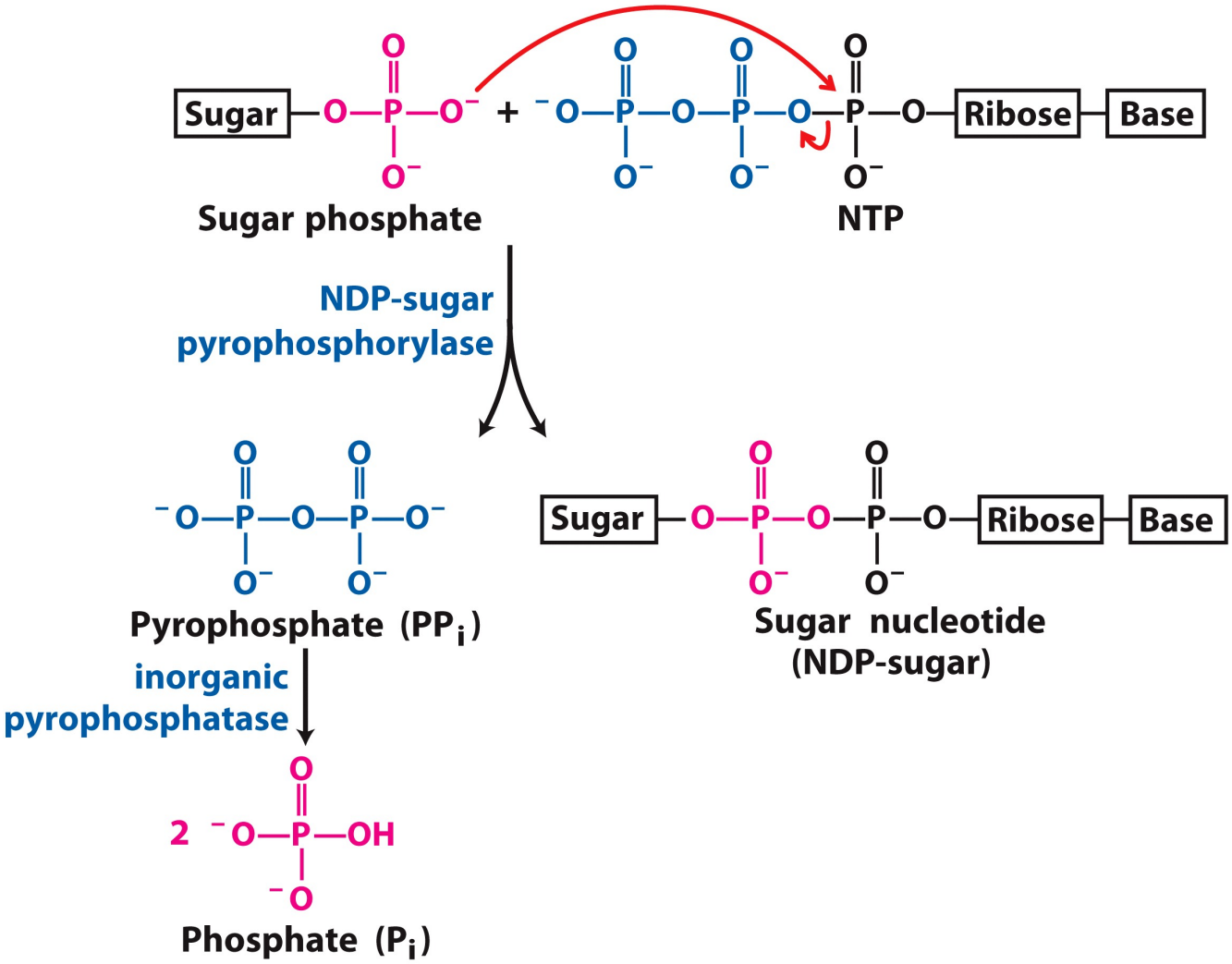
3. Excellent leaving group

   - thus activates the sugar C it is attached to to facilitate nucleophilic attack

4. The "tag" separates the hexoses in a different pool

   - keeps hexose phosphates for one purpose (glycogen synthesis) separate from hexose phosphates for another purpose (glycolysis)

Formation of sugar nucleotides is favorable



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

Glycogen is synthesized by glycogen synthase

- All tissues, but prominent in liver and muscles
- To initiate glycogen synthesis, glc-6-p is converted to glc-1-p (***phosphoglucomutase***)
- Glc-1-p is converted to UDP-glc by ***UDP-glc pyrophosphorylase***
- ***Glycogen synthase*** mediates the transfer of glc from UDP-glc to a nonreducing end of glycogen

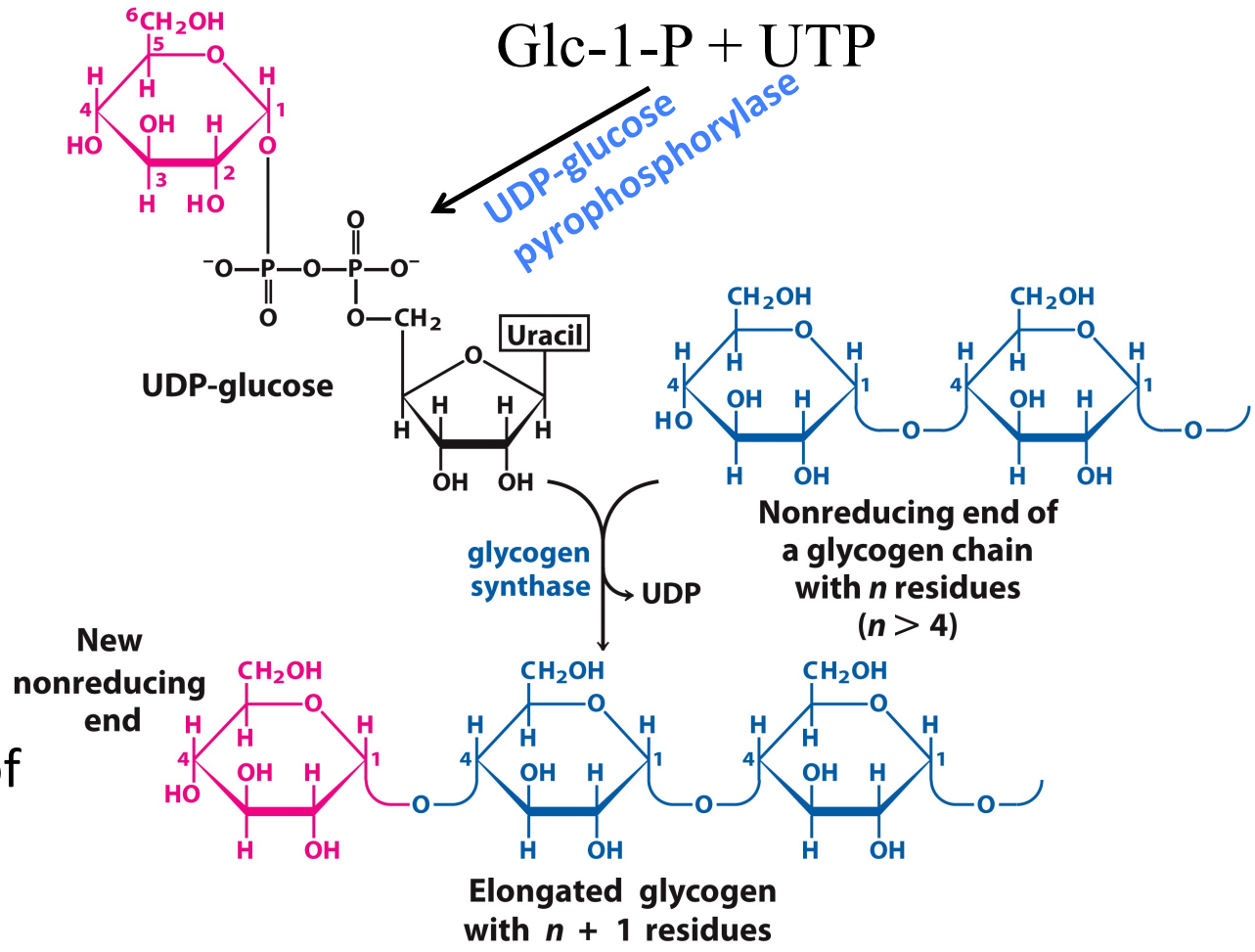


Figure 15-32
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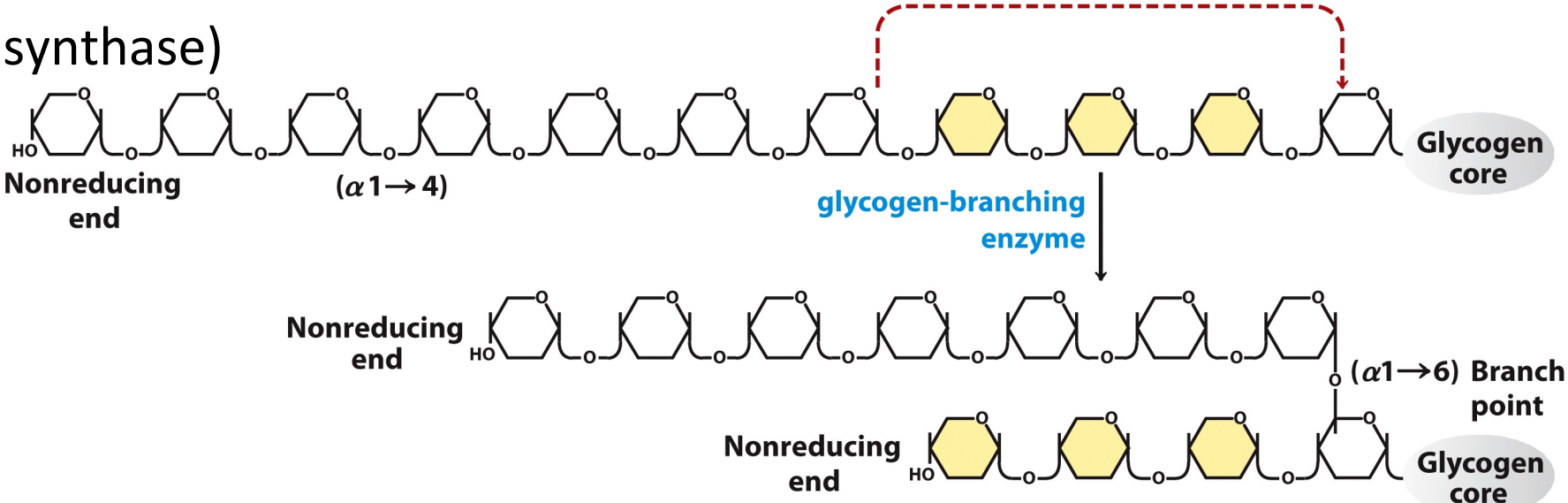
Synthesis of branches in glycogen

- Glycogen synthase **cannot** make ($\alpha 1 \rightarrow 6$) branches
- Formed by ***glycogen branching enzyme***
- Catalyzes the transfer of a terminal fragment of 6 or 7 glc from nonreducing end of a glycogen branch to the C-6 hydroxyl group of a glc residue at a more interior position
- More glc residues can be added by glycogen sythase
- Branching makes the molecule more soluble and increases the number of nonreducing ends (more access for phosphorylase and synthase)



Glycogenin starts a new glycogen chain

- Glycogen synthase needs a preformed ($\alpha 1 \rightarrow 4$) polyglucose having at least 4 residues to function
- ***Glycogenin*** is the enzyme that produces new chains AND the primer on which new chains are produced
- Two activities of glycogenin: transferase activity and chain-extending activities
- Glycogen synthase takes over after the addition of up to 8 glc
- Glycogenin remains buried in the interior of the glycogen molecule attached to the only reducing end

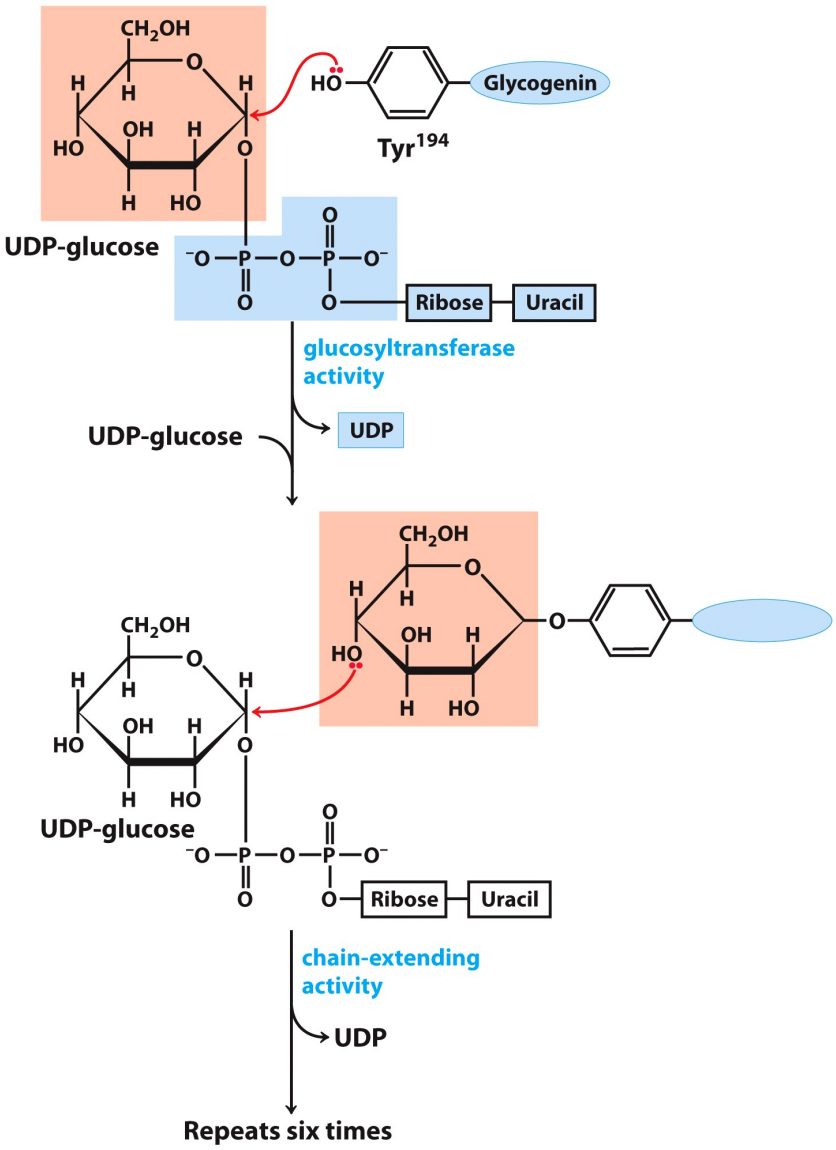


Figure 15-35a
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General structure of a glycogen particle

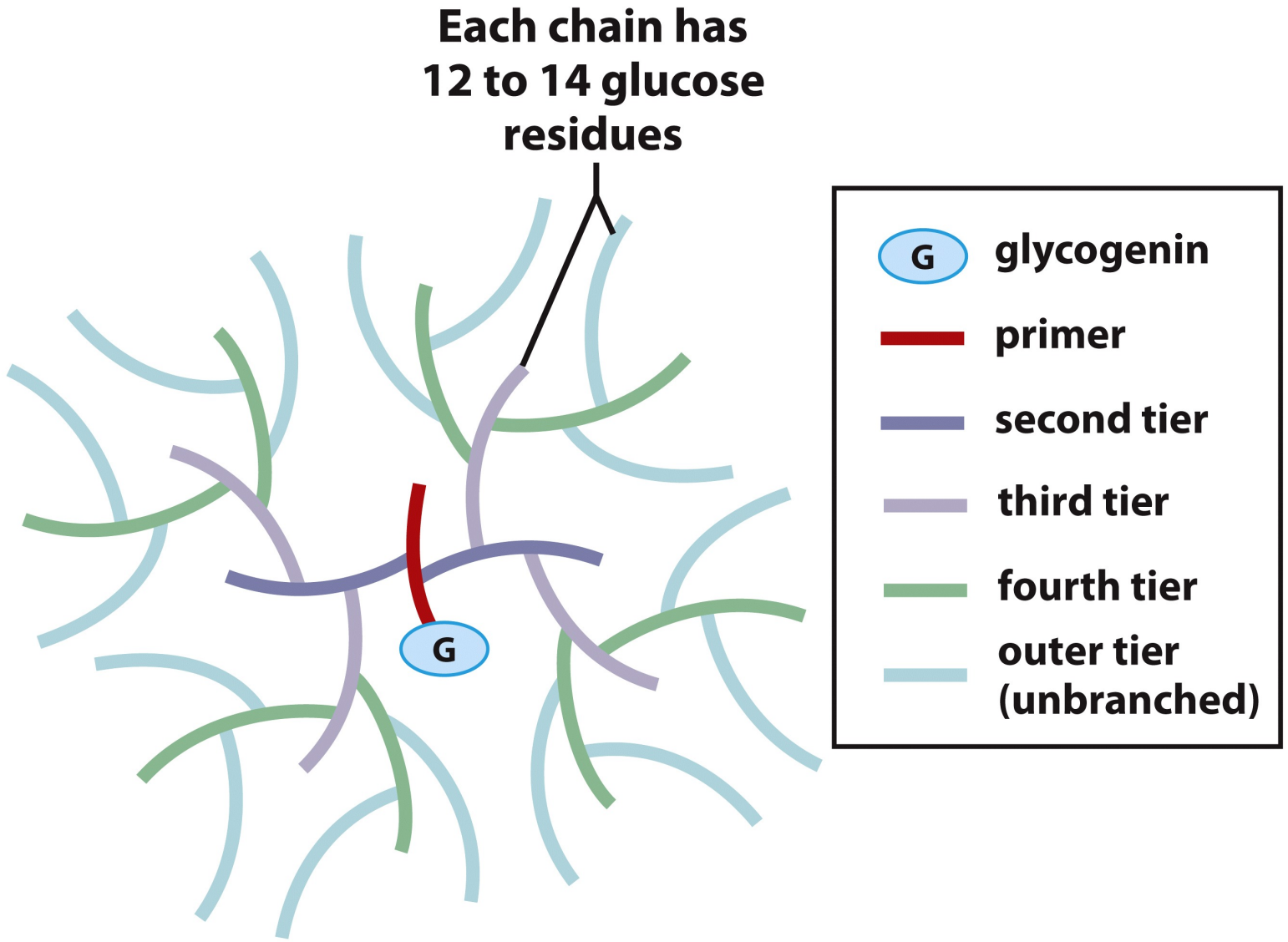

Figure 15-35b
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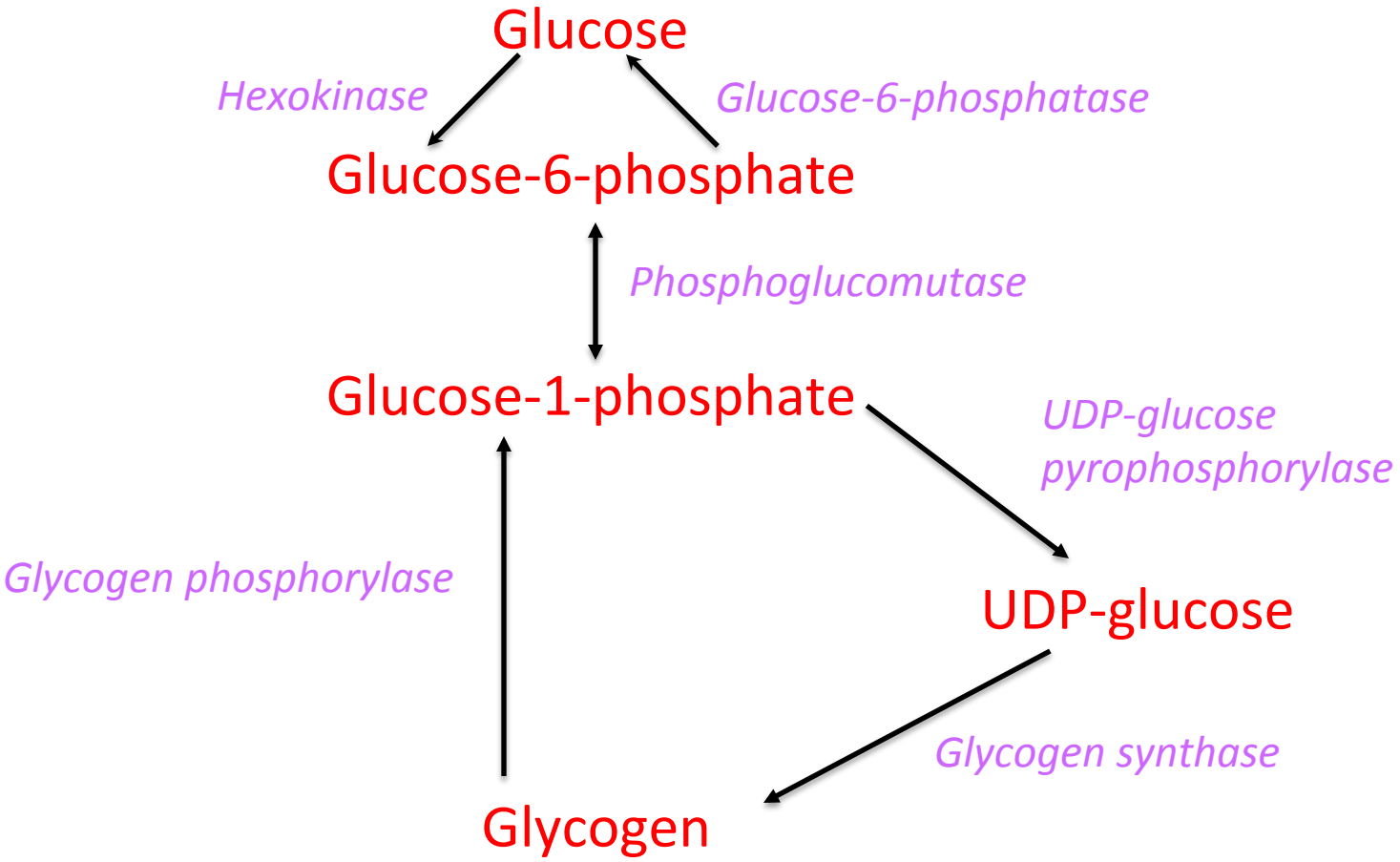
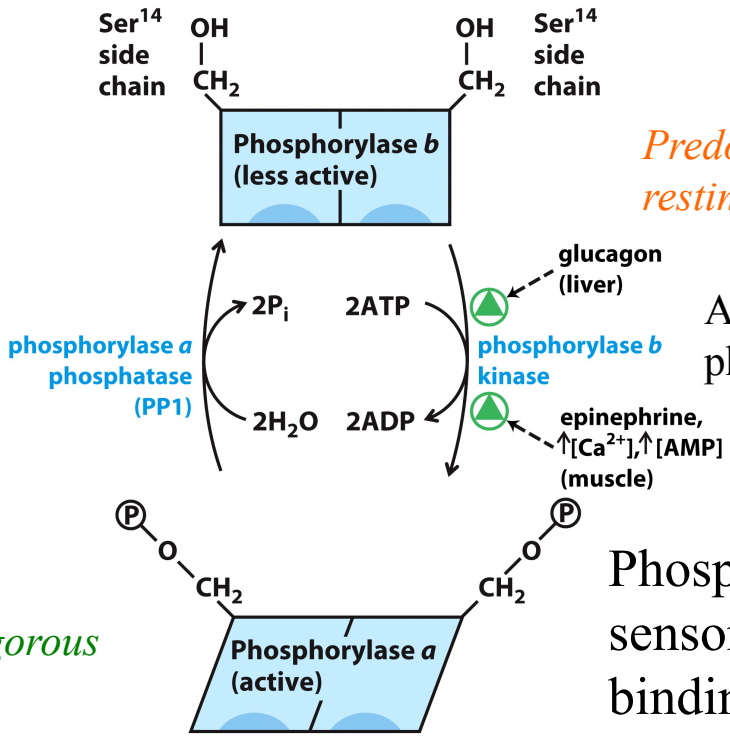
Integration of Glycogen Synthesis and Degradation



Like Glycolysis and Gluconeogenesis, regulation occurs at irreversible points in the pathway

Control of Glycogen Breakdown

- Glucagon/Epinephrine signaling pathway
  - Starts phosphorylation cascade via cAMP
  - activates glycogen phosphorylase
- Glycogen phosphorylase cleaves glucose residues off glycogen, generating glucose-1-phosphate



Phosphorylase works as glucose sensor in the liver (allosteric binding of glc exposes the phosphates for degradation)

Figure 15-36
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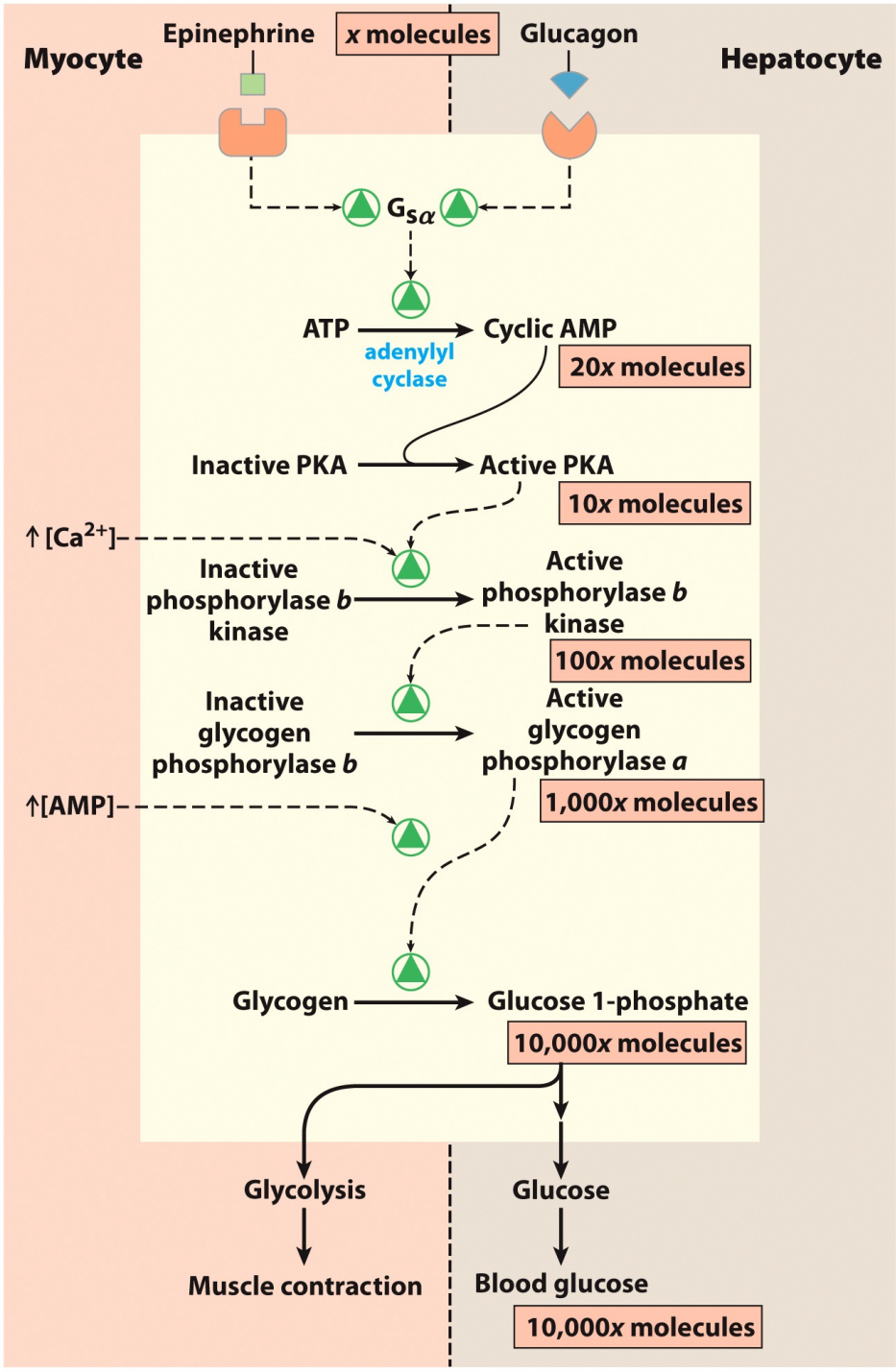
Epinephrine and glucagon stimulate breakdown of glycogen

- Ca^{2+} is the signal for muscle contraction, it activates phosphorylase *b* kinase

- AMP accumulates in vigorously-active muscle; it also activates glycogen phosphorylase allosterically, speeding up the release of glc-1-p from glycogen



Control of Glycogen Synthesis

- Insulin-signaling pathway
  - increases glucose import into muscle
  - stimulates the activity of muscle hexokinase
  - activates the enzyme glycogen synthase
  - stimulates the activity of phosphorylase *a* phosphatase

- Increased hexokinase activity enables activation of glucose
- Glycogen synthase makes glycogen for energy storage
- Phosphorylase *a* phosphatase induces the inhibition of glycogenolysis by dephosphorylating phosphorylase *a*

Glycogen synthase is controlled by phosphorylation

- Glycogen synthase *a* is dephosphorylated (active)
- Deactivated by phosphorylation by **GSK3**
- GSK3 cannot phosphorylate until **CKII** has first phosphorylated on a nearby residue (**priming step**)
- PP1 dephosphorylates glycogen synthase *b* in the liver
- Glc-6-P is an allosteric activator of glycogen synthase because it binds the *b* isoform and makes it a better substrate for dephosphorylation
- Glycogen synthase is a glc-6-p sensor

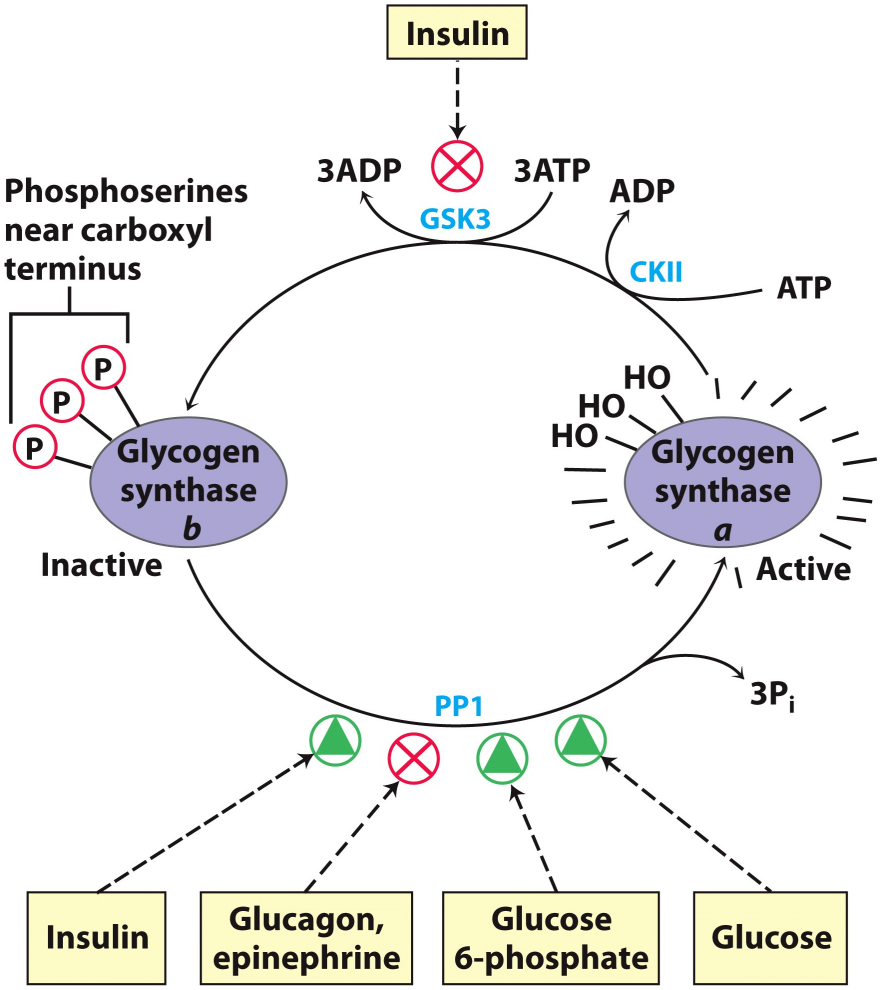


Figure 15-39
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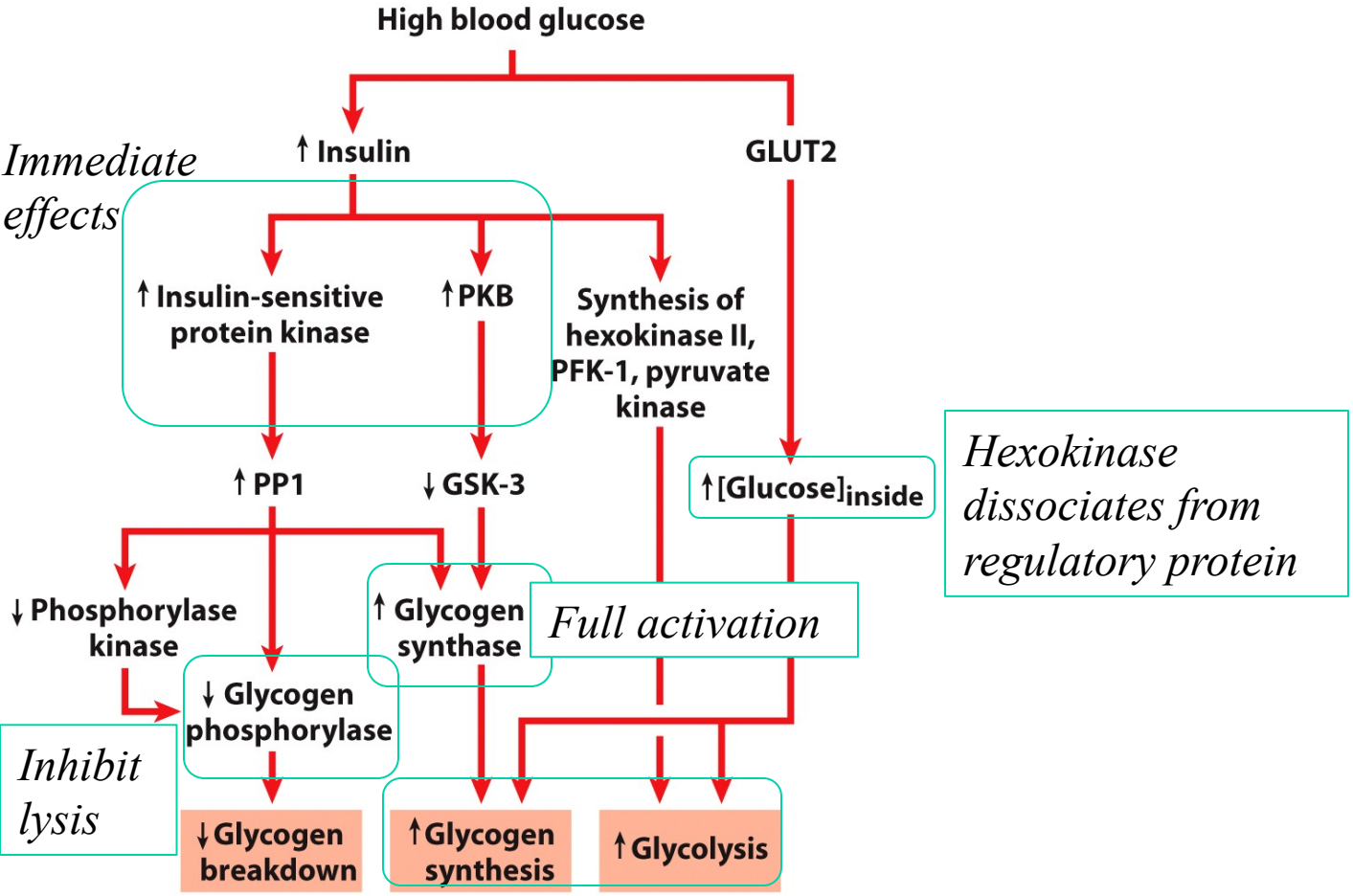
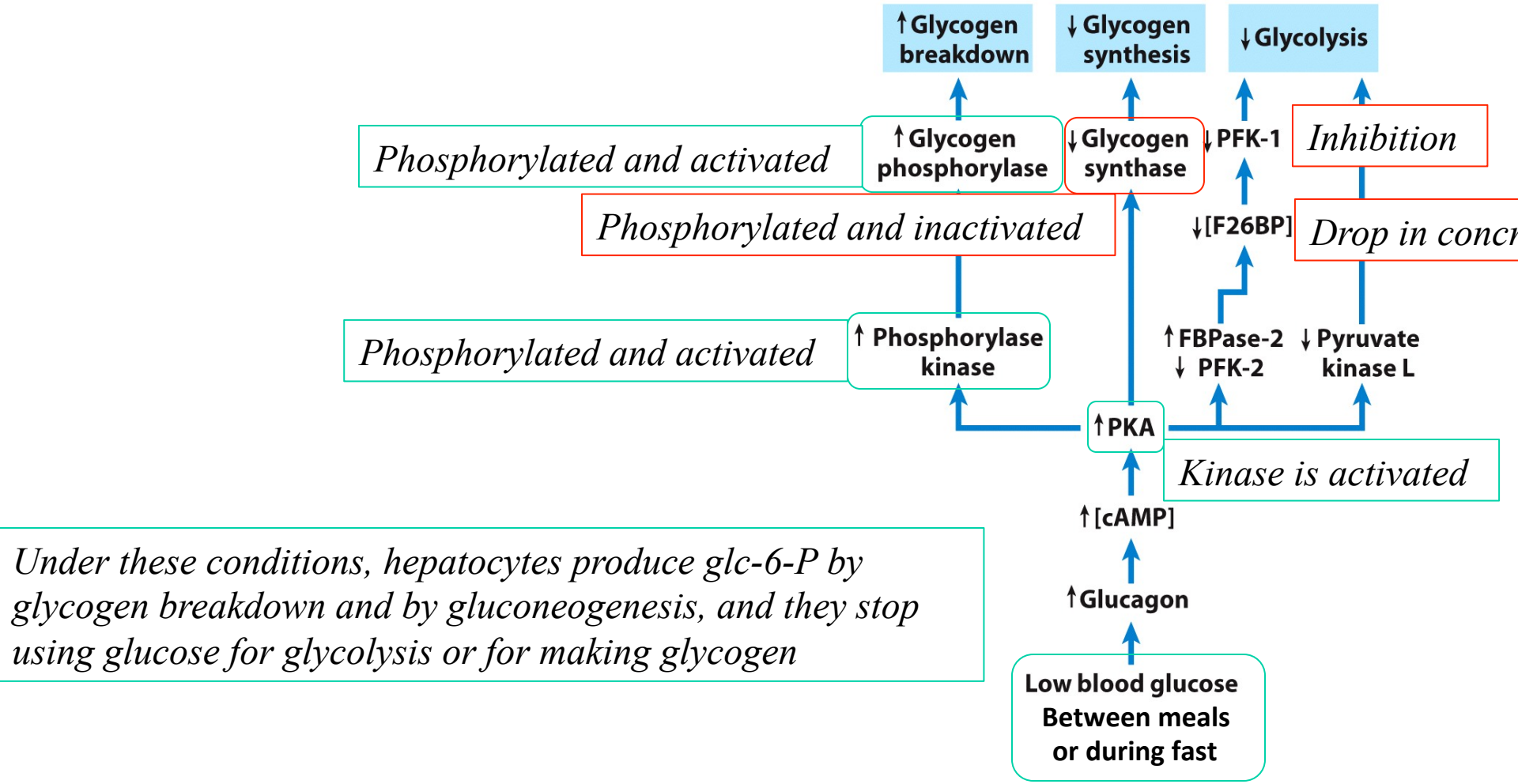
Control of Carbohydrate Metabolism in the Liver



Under these conditions, hepatocytes use excess glc in blood to synthesize glycogen

Control of Carbohydrate Metabolism in the Liver



Under these conditions, hepatocytes produce glc-6-P by glycogen breakdown and by gluconeogenesis, and they stop using glucose for glycolysis or for making glycogen

Control of Carbohydrate Metabolism in the Liver vs. the Muscle

- Muscles are different from liver:

1. Use their stored glycogen for their own needs
2. Very large changes in demand for ATP (from rest to exercise)
3. No gluconeogenesis machinery
4. Insulin induces sequestered GLUT4 to be moved to PM

- In muscles, PKA doesn't phosphorylate pyruvate kinase ➔ glycolysis is not turned off when [cAMP] is high

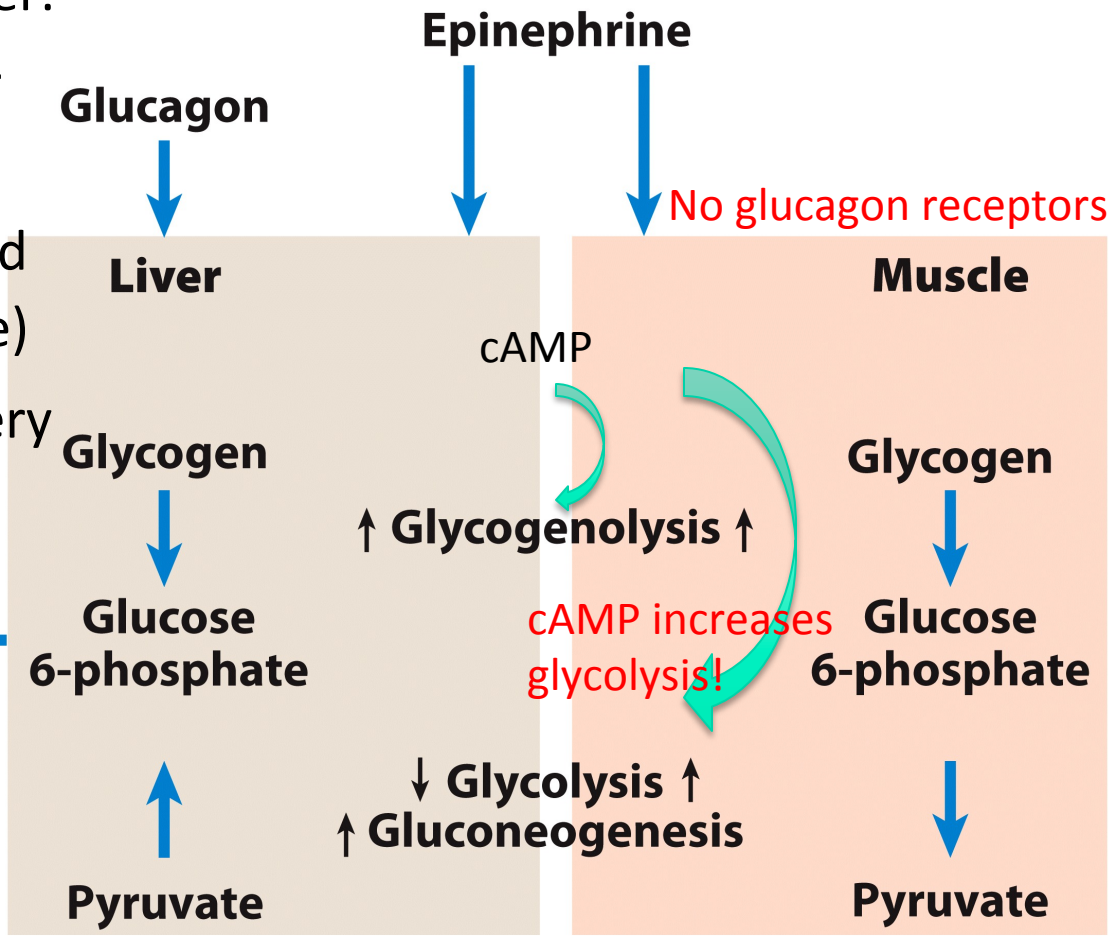


Figure 15-44
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- Bear in mind: it is not the whole story!
- Hormonal signals such as insulin and changes in diet are very important in fat metabolism

Question 4 (Take home exam)
Due: NEXT WEEK (jstiban@birzeit.edu)

- **Please solve questions:**

1. **1 (intracellular metabolite concentrations)**
2. **2 (equilibrium of metabolic reactions)**
3. **11 (enzyme defects in carbohydrate metabolism)**
4. **12 (insufficient insulin in diabetic person)**

For written answers, I prefer to have them typed in Word. I can accept the assignment in one file sent to my email. For answers that require solving mathematically, you can either type them or write them down and scan them.