Glykogenmetabolism

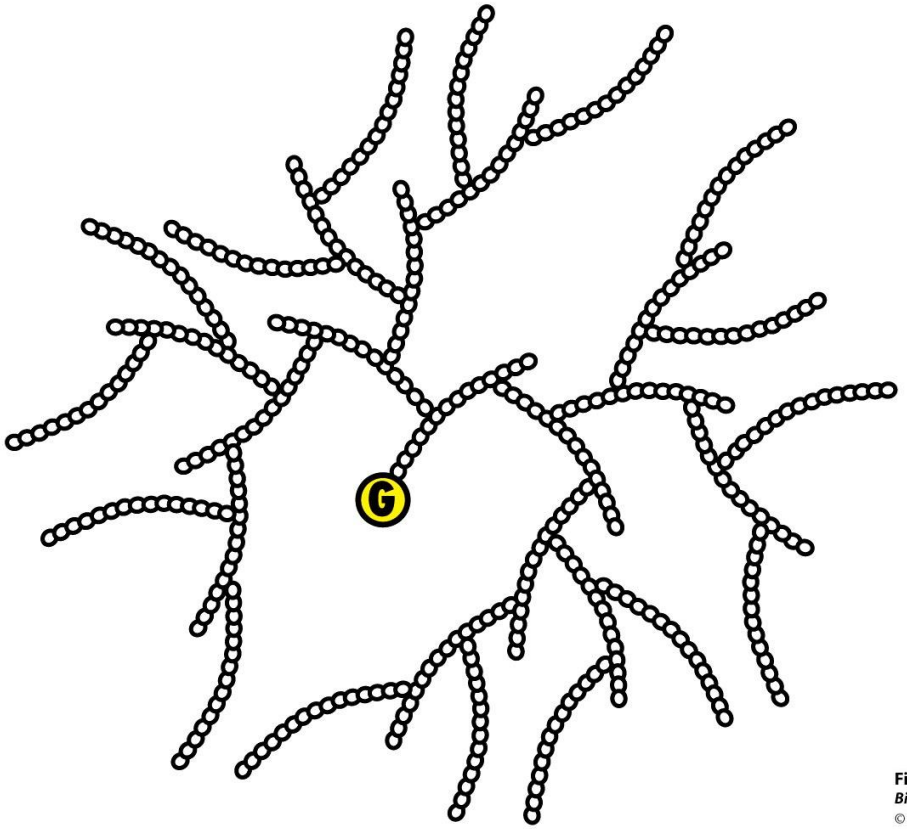


Figure 21-16
Biochemistry, Sixth Edition

LPG001

Martin Lidell

Glykogenmetabolism

– föreläsningsupplägg

- **Glykogen – en lagringsform av glukos**
- **Glykogens funktioner**
- **Hur sker nedbrytningen av glykogen?**
- **Hur bildas glykogen?**
- **Hur regleras glykogenmetabolismen?**

Gerty and Carl Cori

The Nobel Prize in Physiology or Medicine 1947

"for their discovery of the course of the catalytic conversion of glycogen"

Triglycerider en effektivare form av energilagring – *varför har vi då glykogen?*

Tabell 9.1 Kroppens bränsleförråd.

	Man 70 kg (L 175 cm) BMI ≈ 23		
	kg	**kJ**	**%**
Fettvävens TG	12	452 400	83
Protein (främst i muskulatur)	5	83 500	15
Muskelglykogen*	*0,3* (–0,8)	5 010	0,9
Leverglykogen*	(0,07–) *0,1*	1 670	0,3
Extracell. glukos	0,02	334	<0,1
		543 MJ	
Uppskattat dagligt energi-behov (i genomsnitt under hela svälten)		8,4 MJ	
Energin räcker i så fall		65 dygn	

Del av Tabell 9.1 i ”Om kroppens omsättning av kolhydrat, fett och alkohol”, Anders Eklund, Studentlitteratur, 2004

Triglycerider – en reducerad och vattenfri form av energiupplagring

1 gram fett innehåller ca 6.75 ggr mer energi än hydrerad glykogen
(1 g glykogen binder normalt 2 g vatten)

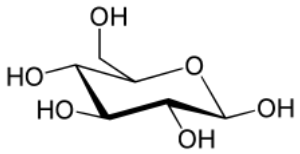
Varför behöver vi glykogen?

Hjärnan behöver glukos även mellan måltider

Muskel kan använda glukos som energikälla vid arbete; även anaerobt
(fettsyror kan ej användas vid anaerobt arbete)

Glukos kan ej bildas från fettsyror

Kroppen behöver ett lager av glukos!



Glukos

– en essentiell energikälla

TABLE 27.1 Energy Metabolism in Major Vertebrate Organs

Organ	Energy Reservoir	Preferred Substrate	Energy Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (strenuous exercise)	None	Glucose from glycogen	Lactate
Heart muscle	Glycogen	Fatty acids	None
Adipose tissue	Triacylglycerol	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerol	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

Table 27.1 in ”Biochemistry, 4th ed”, Garrett and Grisham, Brooks/Cole, 2010

Problem:

Glukos kan inte lagras eftersom molekylen är osmotiskt aktiv.
Höga koncentrationer av glukos skulle förstöra den osmotiska balansen i en cell och orsaka cellskador/celldöd.

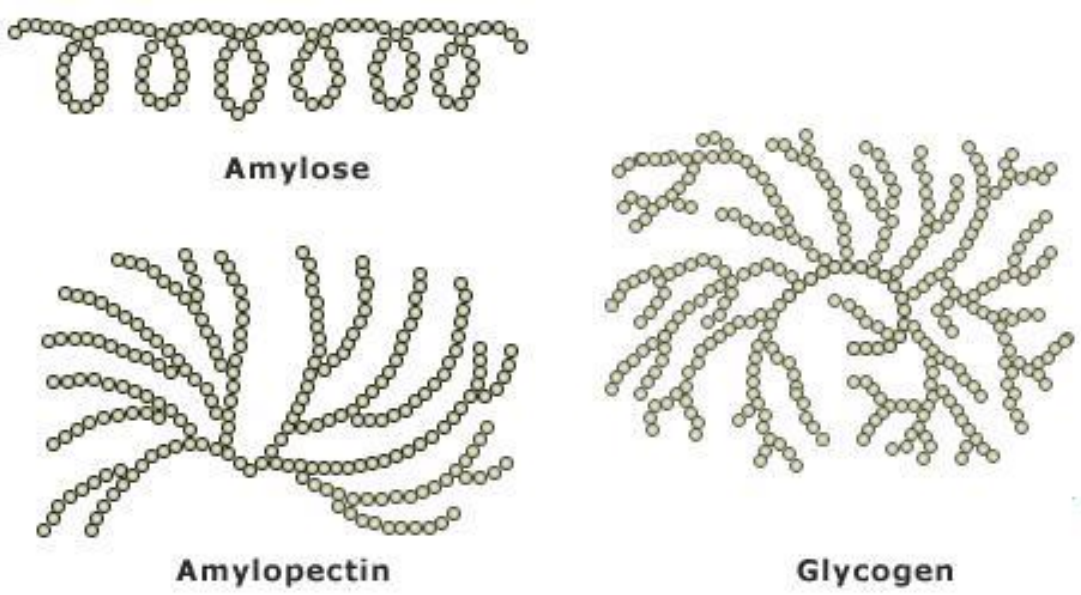
Hur kan en tillräcklig mängd glukos lagras utan att orsaka cellskador?

Lösning:

Glukos lagras som icke-osmotiskt aktiv polymer

- Glykogen (djur)
- Stärkelse; amylos och amylopektin (växter)

Polymererna kan ses som lättmobiliserade lagringsformer av glukos, vilken kan frisättas när energi behövs



Glykogen

– en väldigt stor och grenad polymer av "glukosenheter"

Vi kan lagra upp till ca 450 g glykogen; ungefär 1/3 i levern och resterande del främst i skelett-muskulaturen.

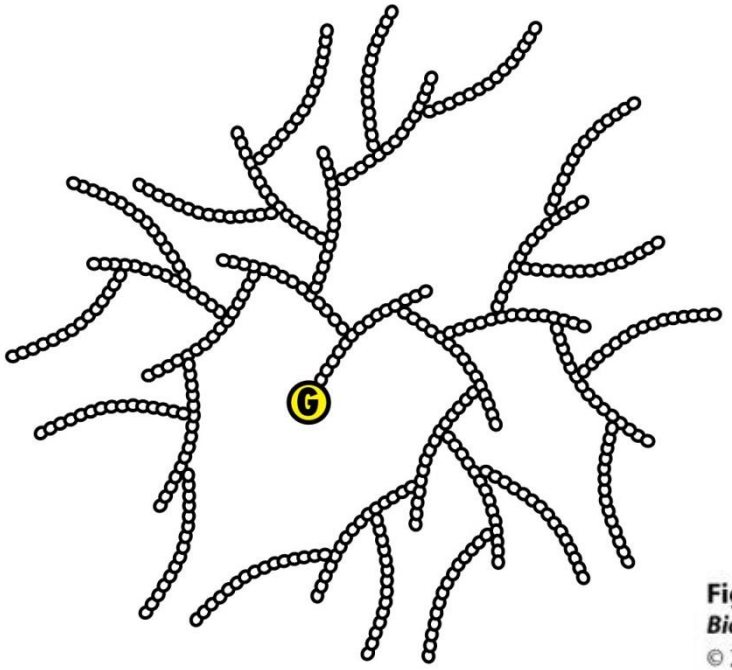


Figure 21-16
Biochemistry, Sixth Edition

Stukturen är optimerad för att lagra/frigöra energi snabbt

Glykogenet tillgodoser behovet av glukos på kort sikt

Glykogenmetabolismen styrs av allostera effektorer och hormoner

Two types of glycosidic bonds in glycogen

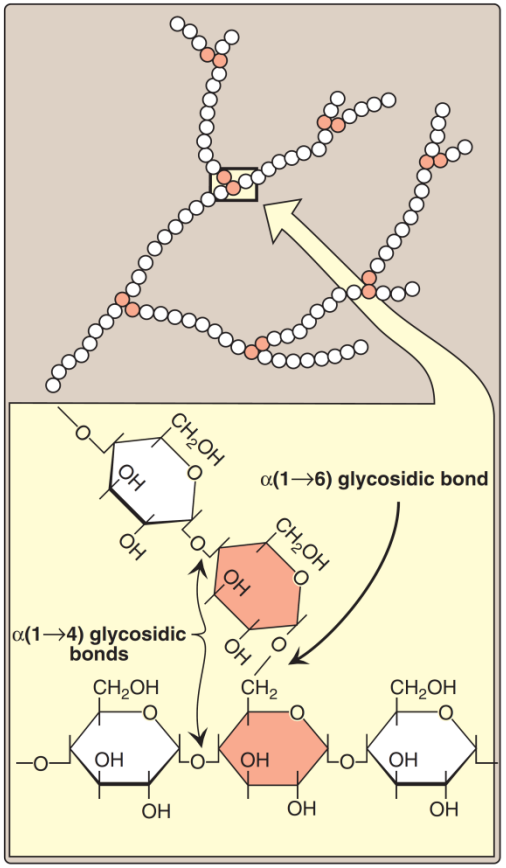


Figure 11.3 in Biochemistry 5th ed. / Harvey and Ferrier
Lippincott Williams & Wilkins, 2011

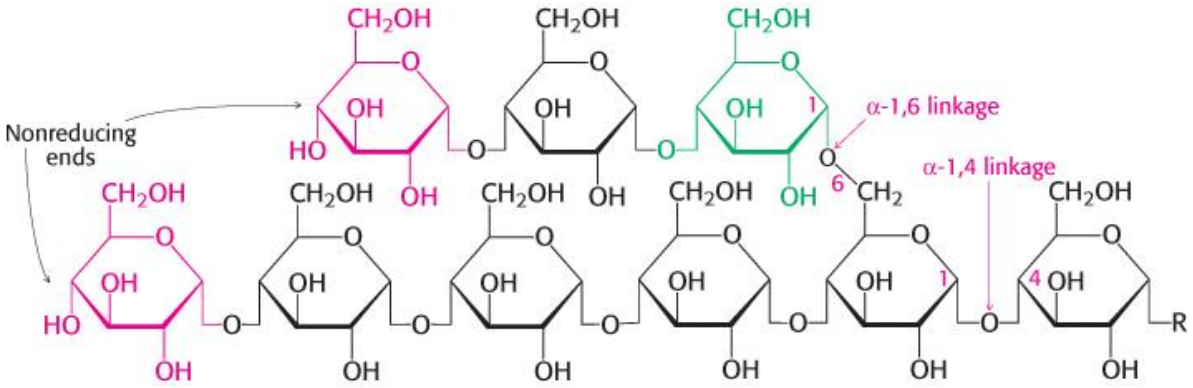
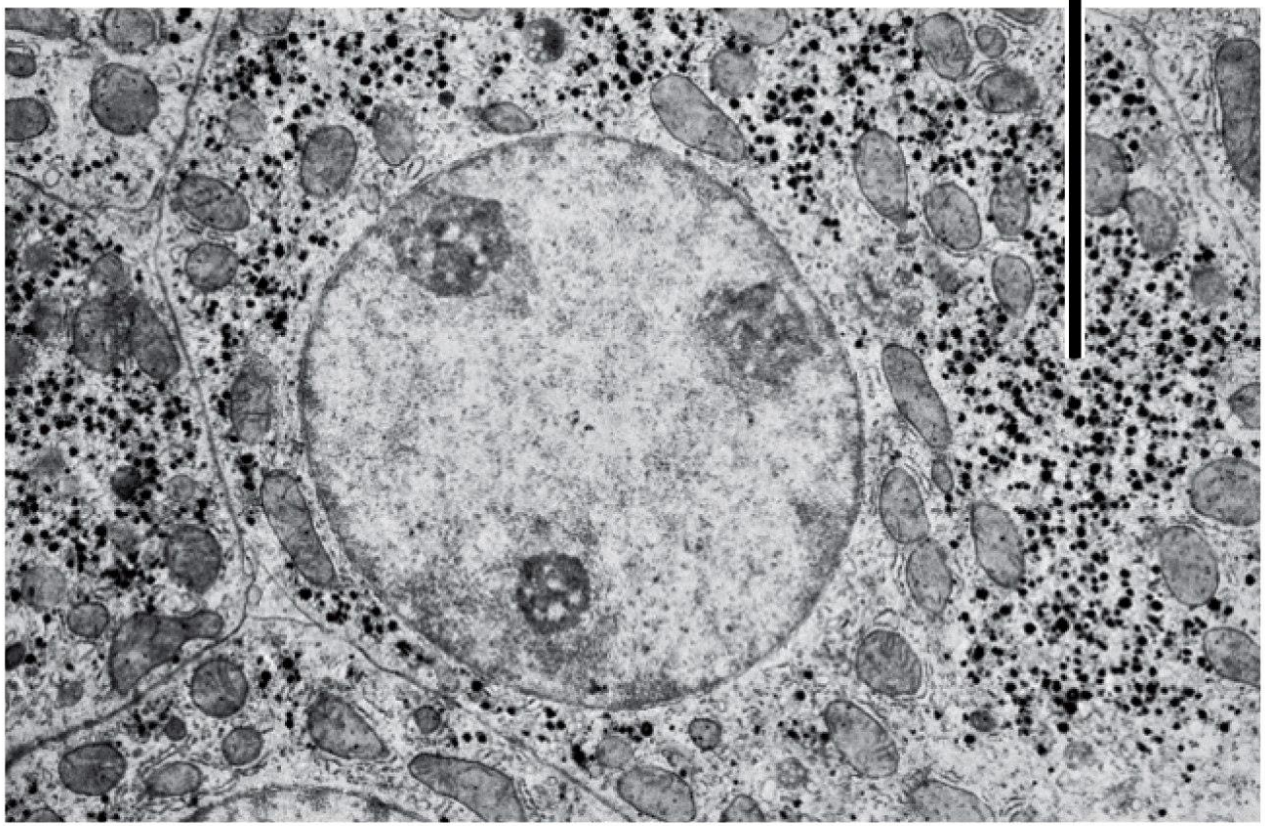


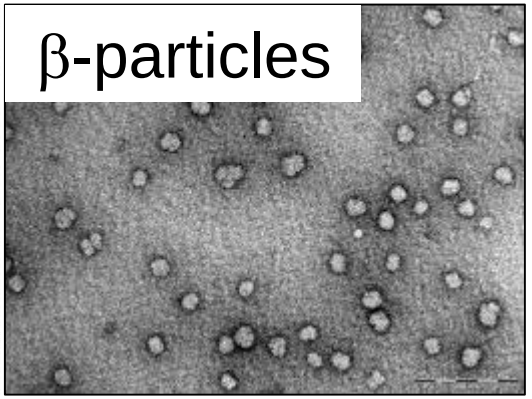
Figure 21.2
Biochemistry, 8th ed, Berg et al.
2015 W.H. Freeman and Company

α-1,4-glycosidic linkages in linear parts

α-1,6-glycosidic linkages at branching points

Glycogen granules





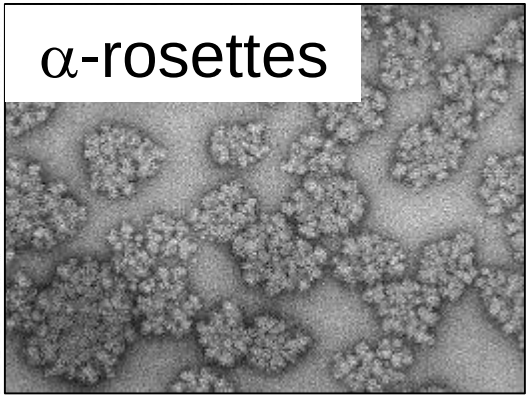


Figure 21-2
Biochemistry, Sixth Edition

The elementary particle of glycogen is sometimes called the β-particle. The particle is about 21 nm in diameter, consists of up to 55000 glucose residues with about 2000 nonreducing ends. 20-40 β-particles can cluster together to form α-rosettes.

Different functions of glycogen in liver and muscle

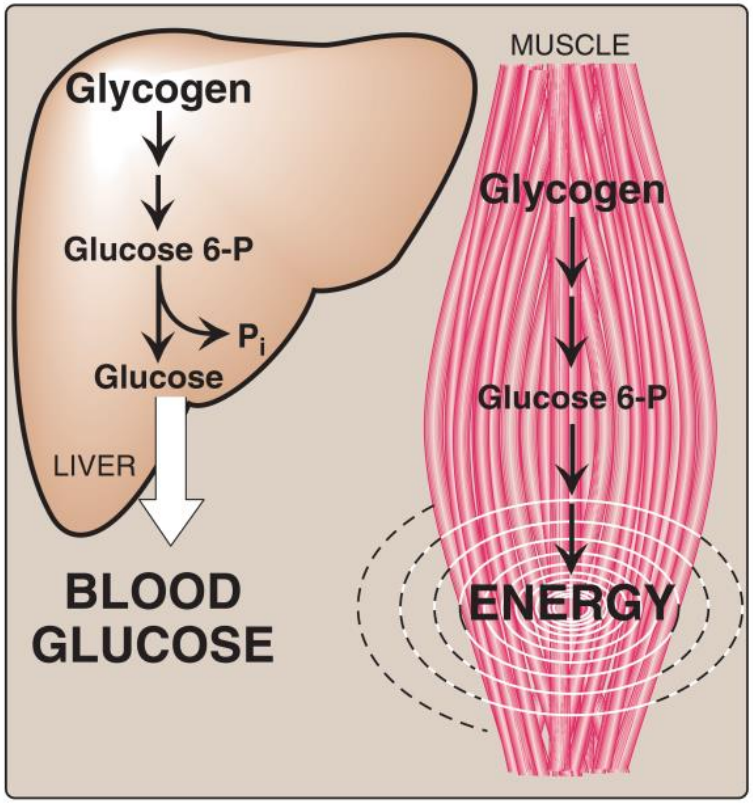


Figure 11.2 in Biochemistry 5th ed. / Harvey and Ferrier
Lippincott Williams & Wilkins, 2011

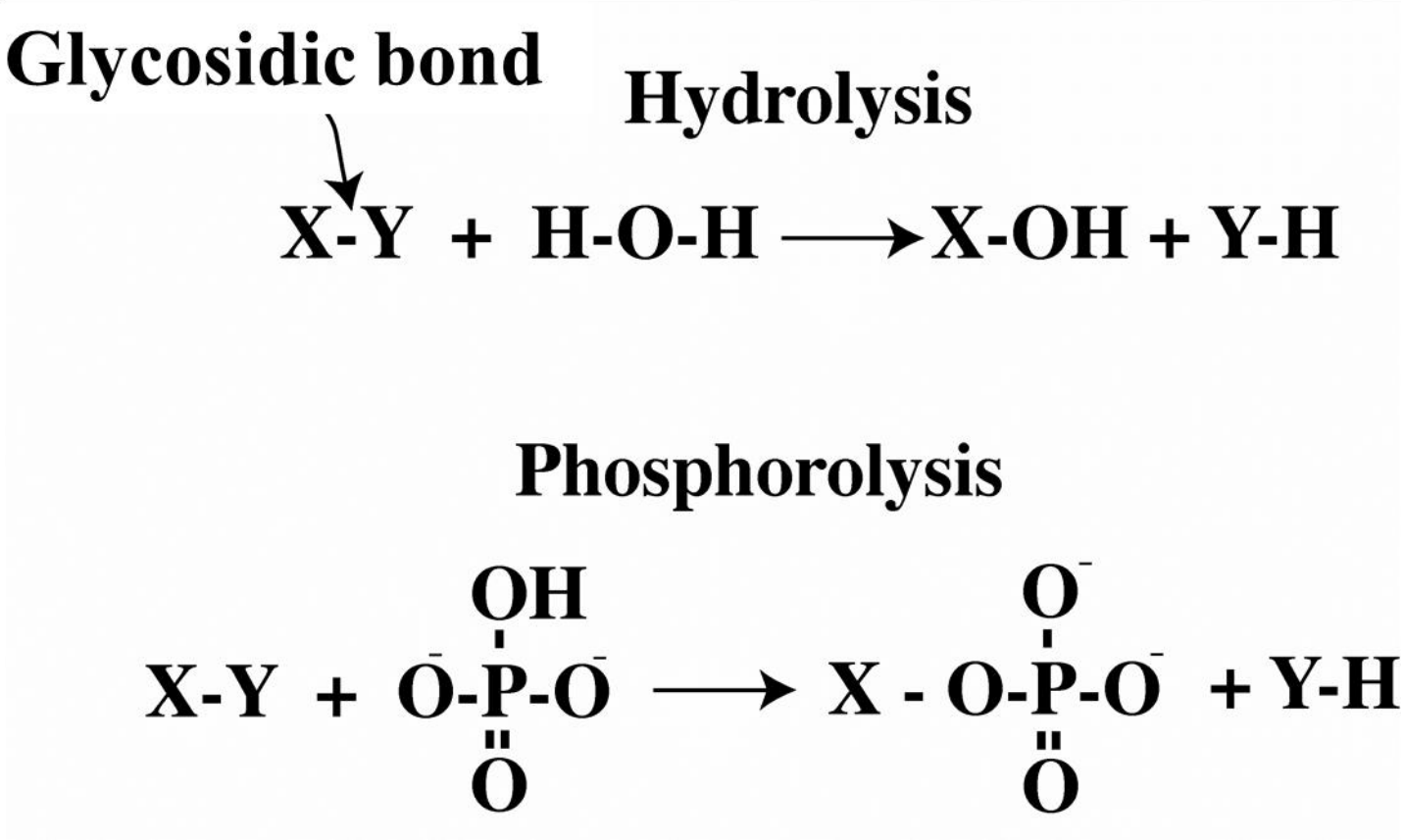
Liver glycogen serves, above all, in the maintenance of the blood glucose level between meals. The glycogen content in the liver is very variable

Muscle glycogen serves as an energy reserve for the muscle itself. It is not involved in the maintenance of blood glucose, since muscles do not possess glucose-6-phosphatase and cannot release glucose into blood.

The three steps in glycogen degradation (glycogenolysis)

1. release of glucose 1-phosphate from glycogen
2. remodeling of the glycogen substrate to permit further degradation
3. conversion of glucose 1-phosphate into glucose 6-phosphate for further metabolism

Polysaccharides can be degraded by hydrolysis or phosphorolysis

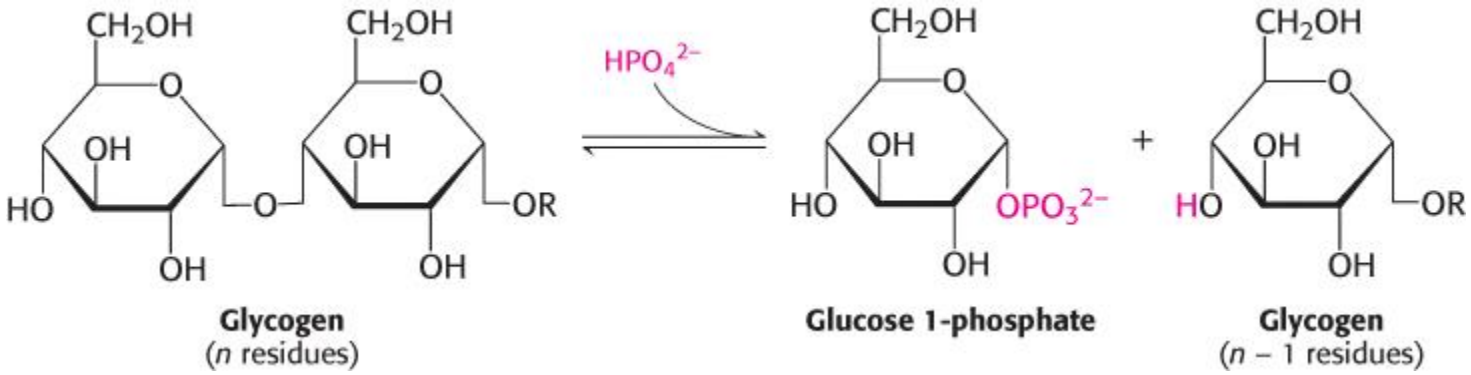


Glycogen phosphorylase
– *the key enzyme in glycogen degradation*

Cleaves its substrate by the addition of orthophosphate (P_i) to yield *glucose 1-phosphate*

Cleavage of a bond by the addition of orthophosphate is referred to as *phosphorolysis*

Allosteric enzyme whose activity is further regulated by reversible covalent modification



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Glycogen phosphorylase acting alone degrades glycogen to a limited extent

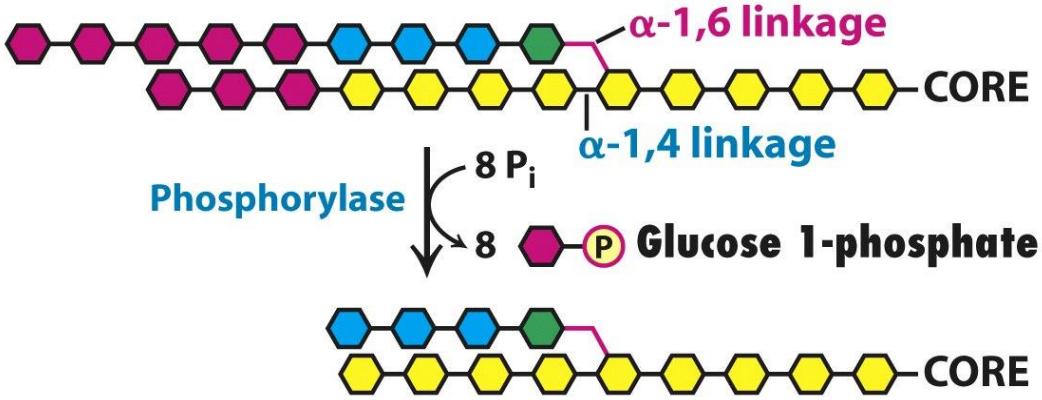


Figure 21-4
Biochemistry, Sixth Edition

Glycogen phosphorylase cannot cleave the α-1,6-glycosidic bonds at branch points

Stops cleaving α-1,4-glycosidic linkages four residues away from a branch point

Approximately 1 in 12 residues is branched; cleavage by the phosphorylase alone would stop after the release of eight glucose molecules per branch

A debranching enzyme is needed for the complete degradation of glycogen

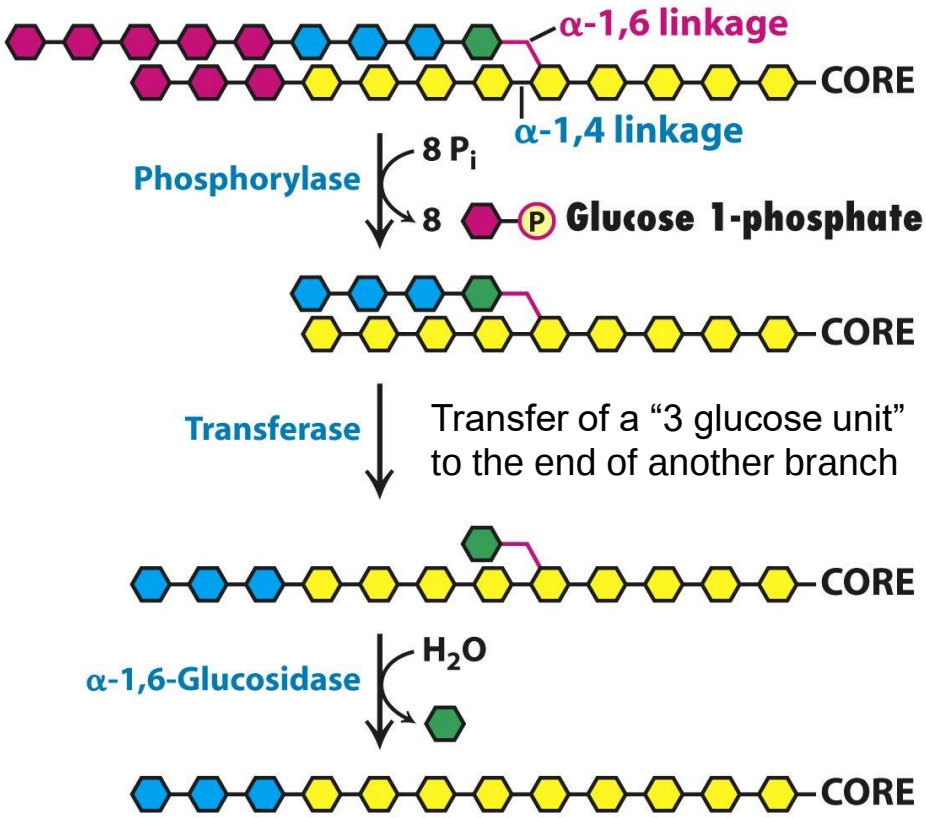
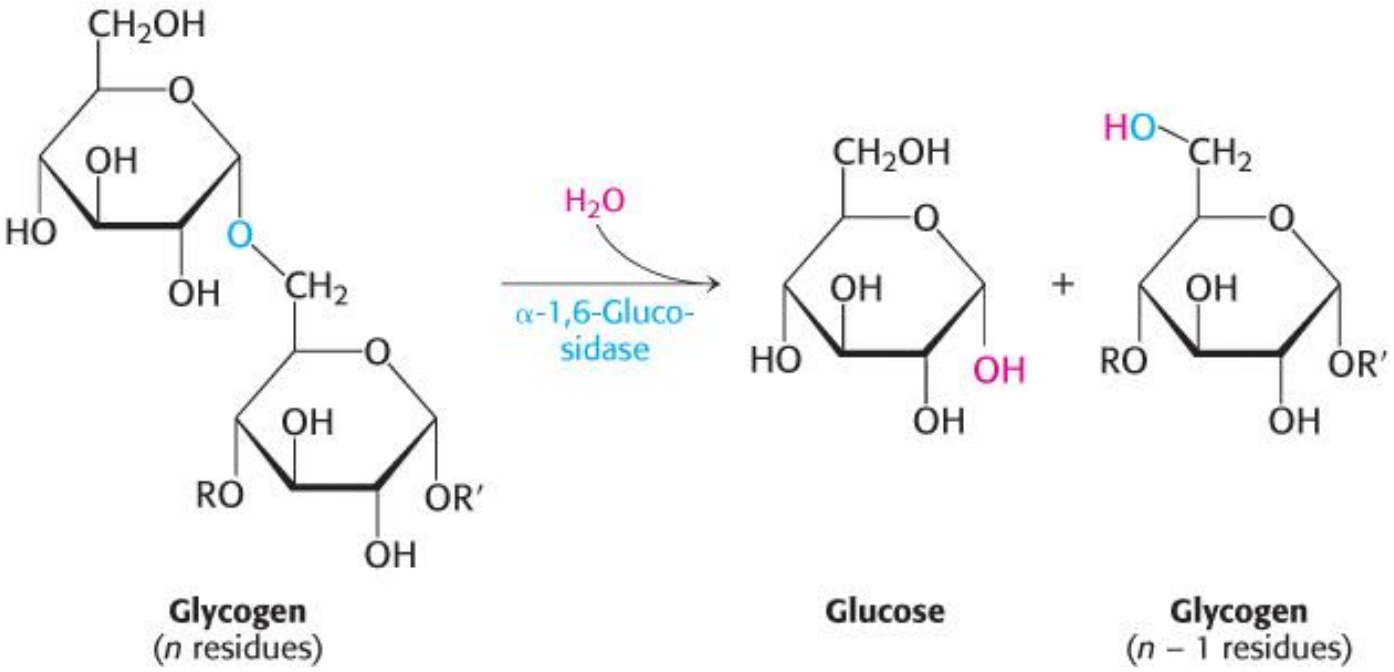


Figure 21-4
Biochemistry, Sixth Edition

One protein with two enzymatic activities; transferase and α-1,6-glucosidase

The α-1,6-linkage is hydrolyzed to give glucose and glycogen shortened by one residue



Phosphoglucomutase

converts glucose 1-phosphate into glucose 6-phosphate

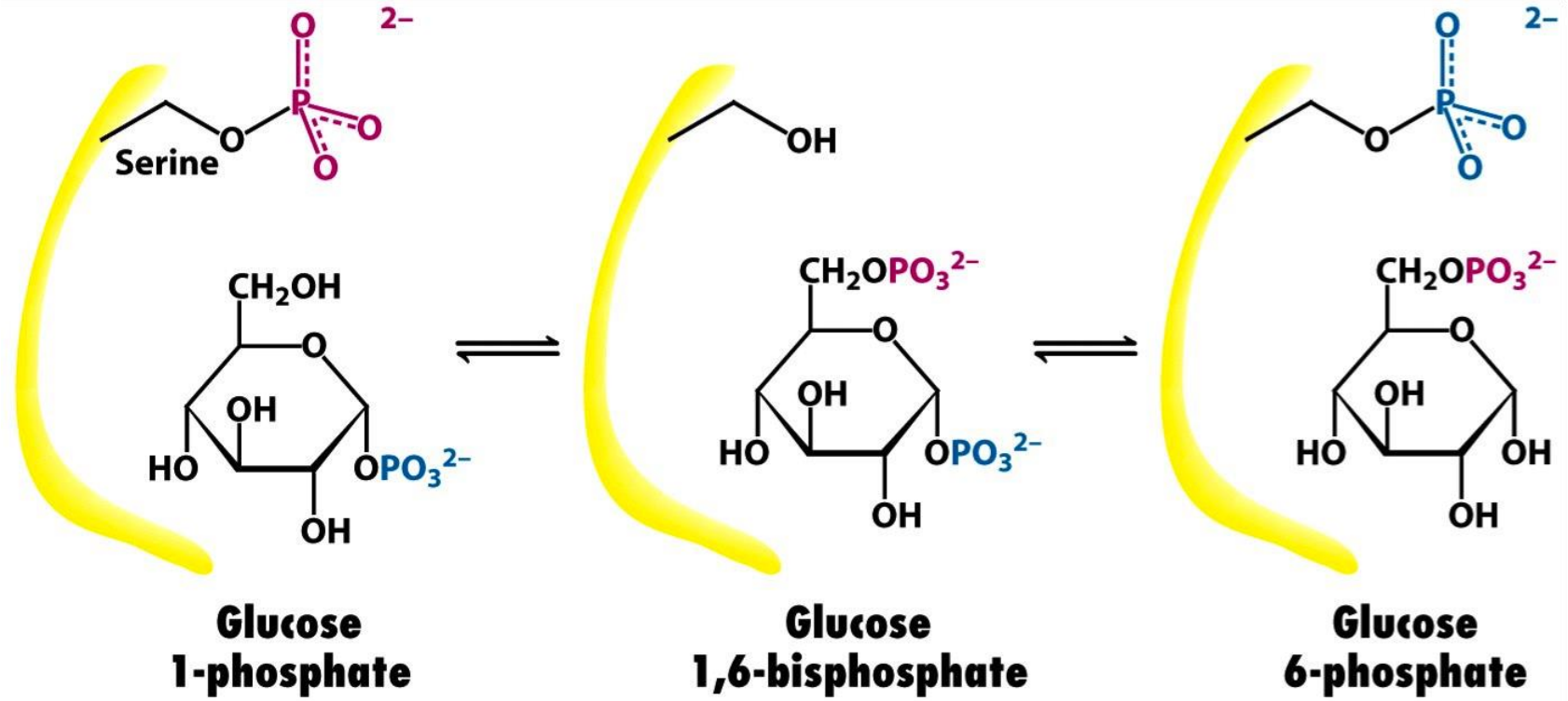


Figure 21-5
Biochemistry, Sixth Edition

Reversible reactions

Glucose 6-phosphate can be converted into glucose in the liver

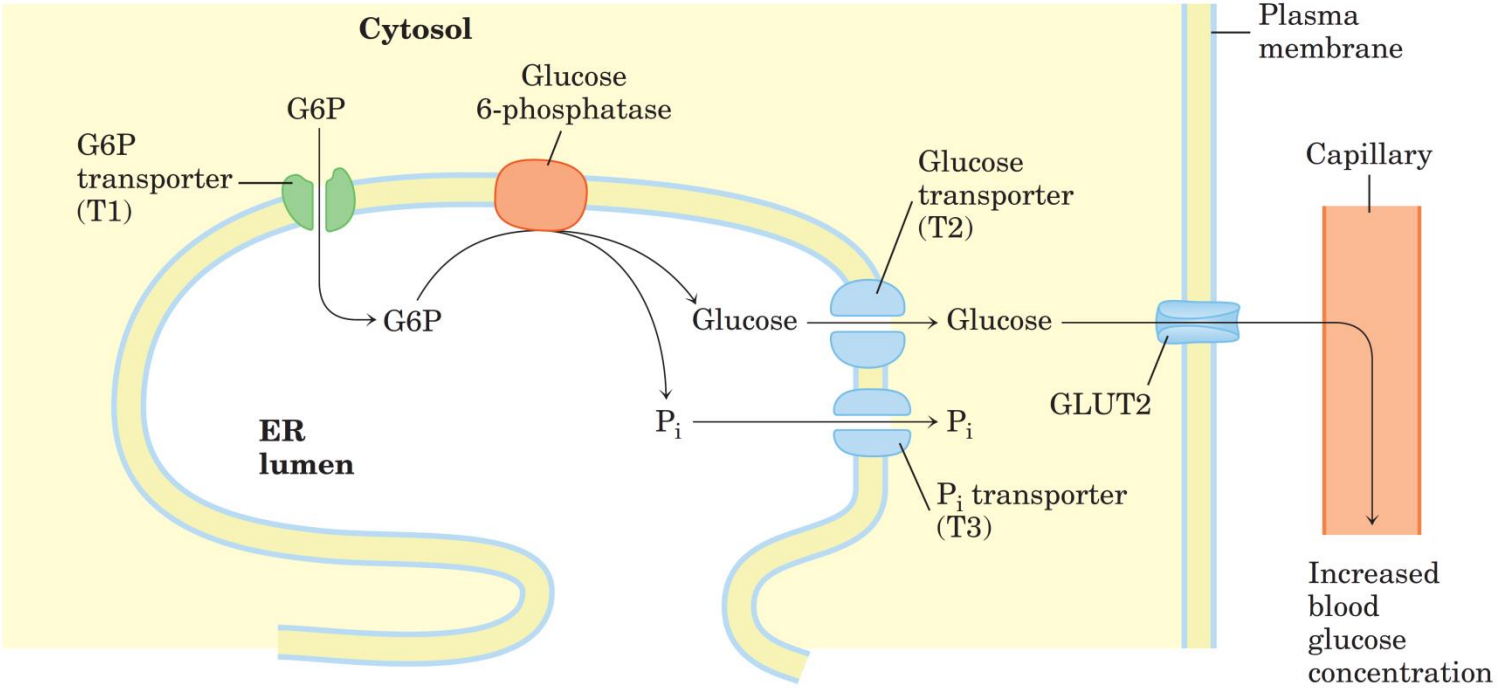


Figure 15-6 in "Lehninger principles of biochemistry, 4th ed", Nelson and Cox, W.H. Freeman, 2005

The glucose 6-phosphatase is present only in the liver and kidney

<u>Phosphatases</u>; group of enzymes that removes phosphate groups from their substrates

Metabolism of glucose-6-phosphate

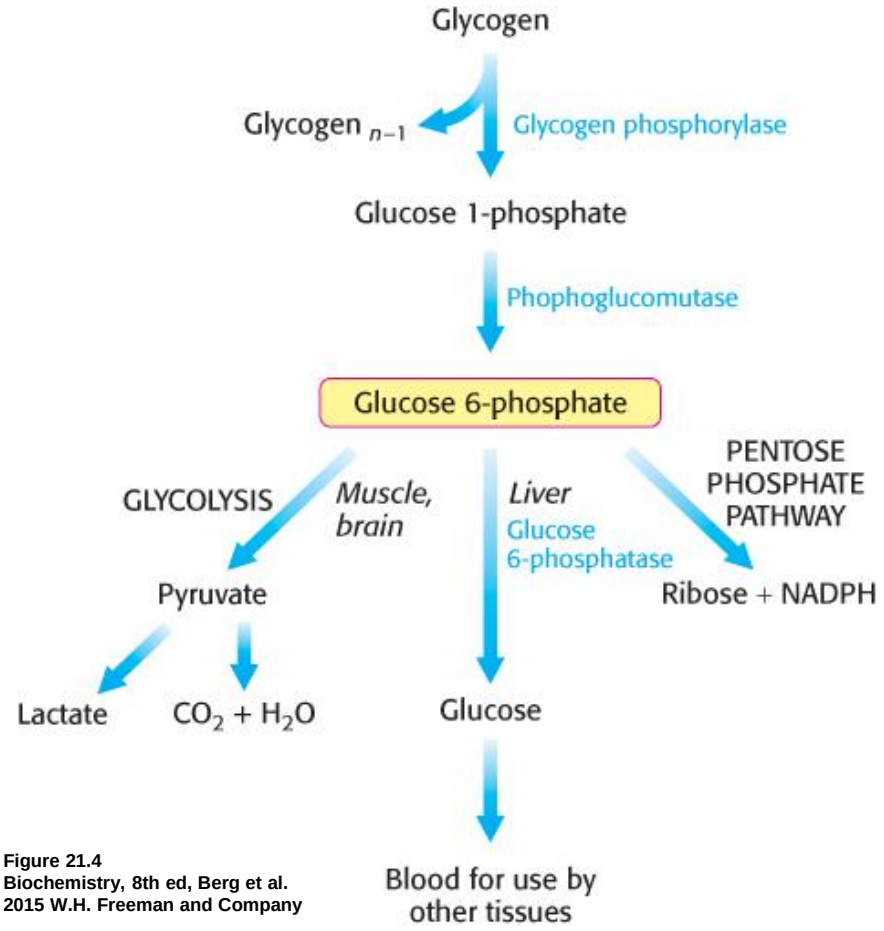


Figure 21.4
Biochemistry, 8th ed, Berg et al.
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1. <u>fuel</u> for anaerobic or aerobic metabolism (muscle)
2. converted to <u>glucose</u> and released into the blood (liver)
3. processed into <u>NADPH and/or ribose-5-phosphate</u> (many tissues)

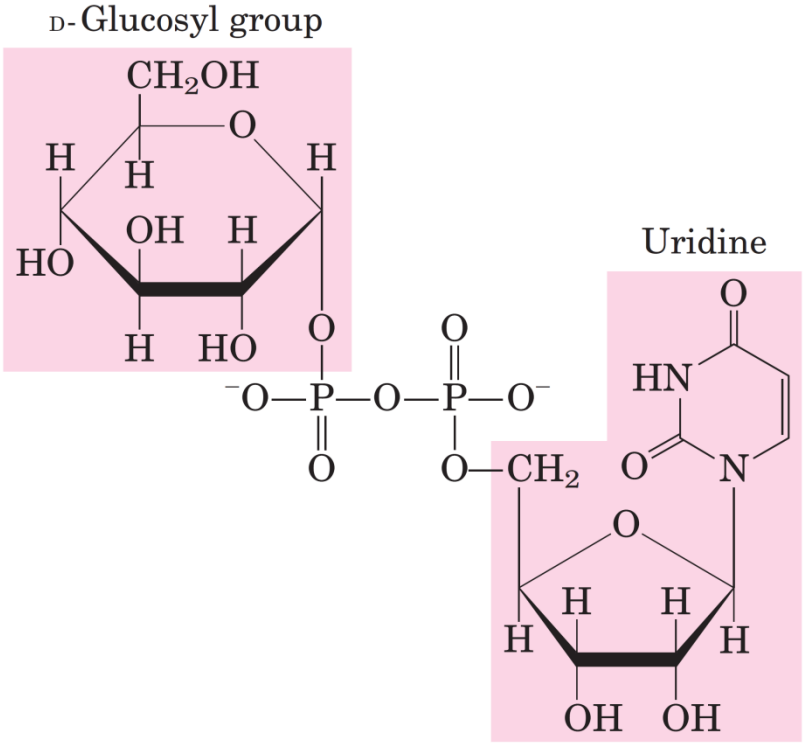
The four steps in glycogen synthesis

1. Activation of glucose to UDP-glucose
2. Initiation; synthesis of glycogen primer
3. Elongation of the glycogen chain
4. Formation of branches

Takes place in the cytosol of cells

UDP-Glucose

– an activated form of glucose



"Lehninger principles of biochemistry, 4th ed", Nelson and Cox, W.H. Freeman, 2005

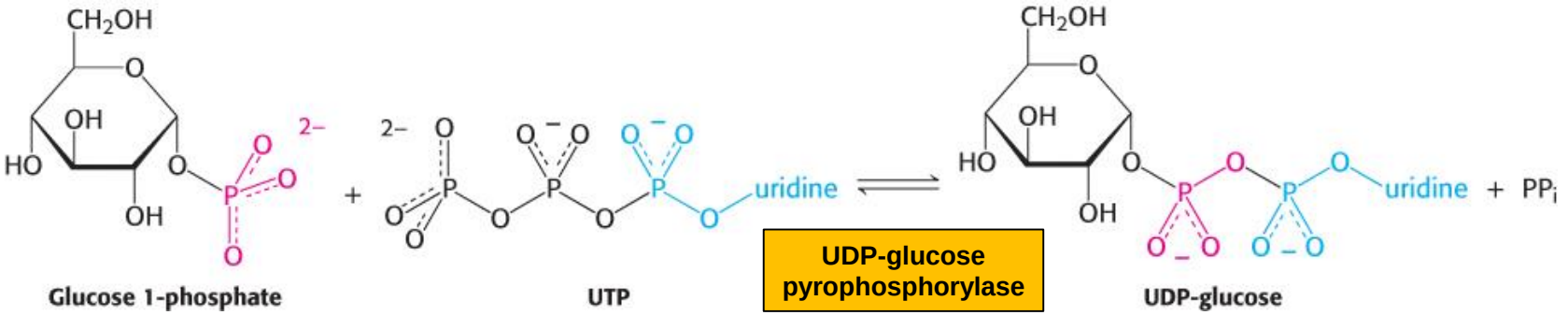
Acts as glucose donor in the biosynthesis of glycogen

UDP-Glucose

Synthesized from glucose 1-phosphate (made from glucose 6-phosphate by phosphoglucomutase) and uridine triphosphate (UTP)

Catalyzed by UDP-glucose pyrophosphorylase

The reaction is readily reversible as it is not energetically favorable



Biochemistry, 8th ed, Berg et al.
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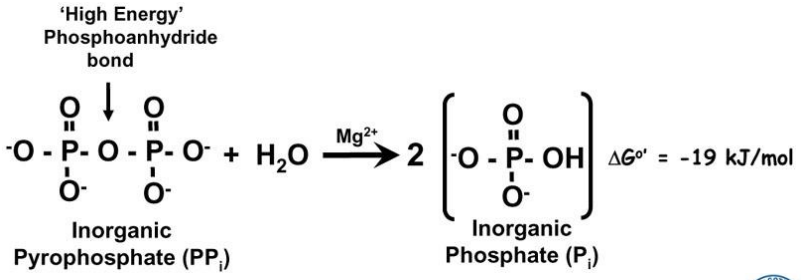
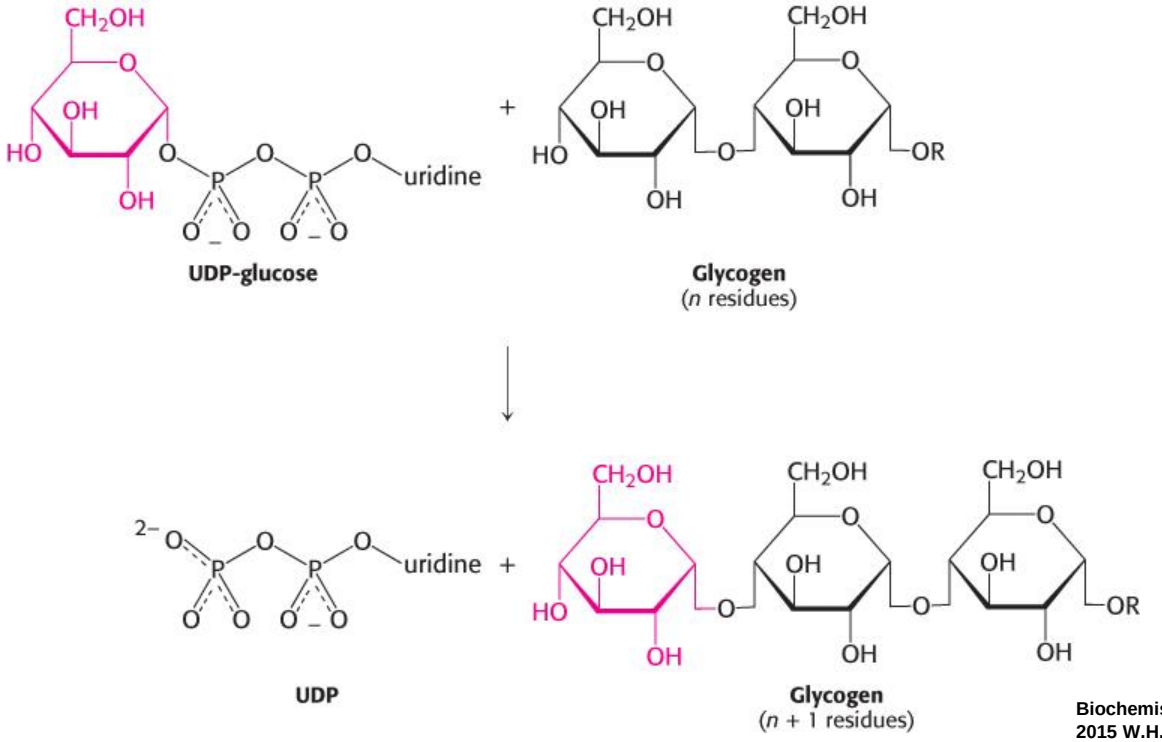
The reaction is driven by the hydrolysis of pyrophosphate (catalyzed by inorganic pyrophosphatase)



Glycogen synthase
– *the key enzyme in glycogen synthesis*

Adds new glucosyl units to the nonreducing end of glycogen



Biochemistry, 8th ed, Berg et al.
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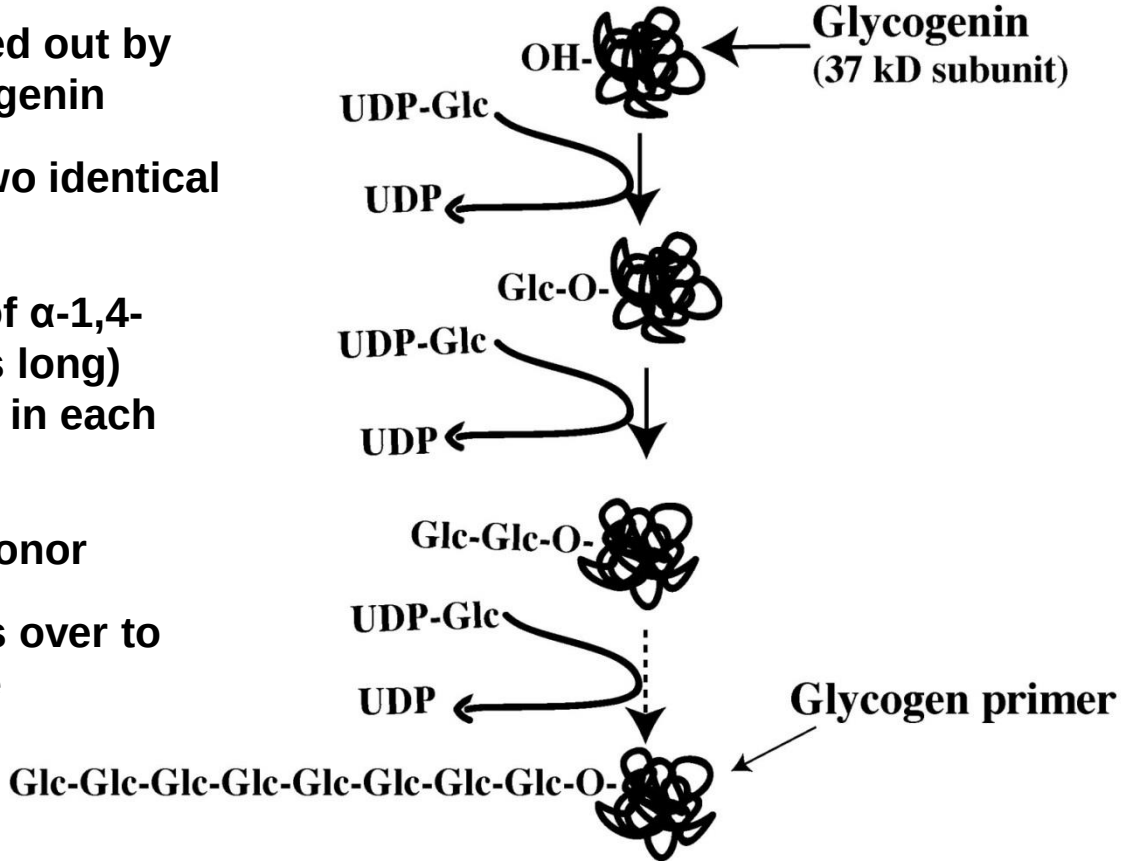
An α-1,4-glycosidic linkage is formed

Problem:

Glucosyl units can only be added to a chain already containing at least four residues!

Initiation of glycogen synthesis
– formation of the glycogen primer

- **Glycogen synthesis requires a primer**
- **This priming function is carried out by the glycosyltransferase glycogenin**
- **Glycogenin is composed of two identical subunits**
- **Autocatalyzes the formation of α-1,4-glucose polymers (10-20 units long) attached to a tyrosine residue in each subunit of the glycogenin**
- **UDP-glucose is the glucose donor**
- **Glycogen synthase then takes over to extend the glycogen molecule**



A branching enzyme forms the α-1,6-glycosidic linkages

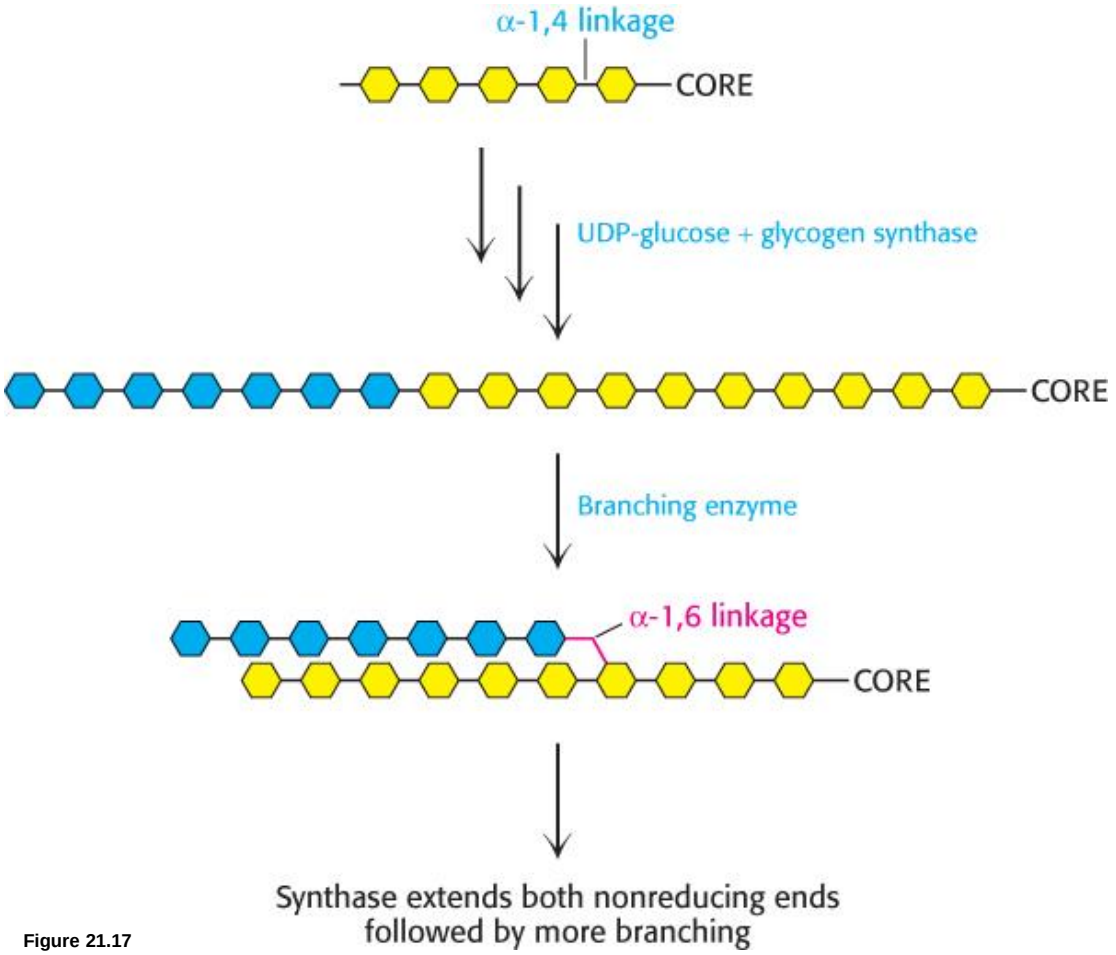


Figure 21.17
Biochemistry, 8th ed, Berg et al.
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A branch is created by the breaking of an α-1,4-glycosidic linkage and the formation of an α-1,6-glycosidic linkage.

A block of residues, typically 7 in number, is transferred to a more interior site.

The *branching enzyme* that catalyzes this reaction requires that the block of 7 or so residues must include the nonreducing terminus, and must come from a chain at least 11 residues long. In addition, the new branch point must be at least 4 residues away from a preexisting one.

Summary of glycogen synthesis

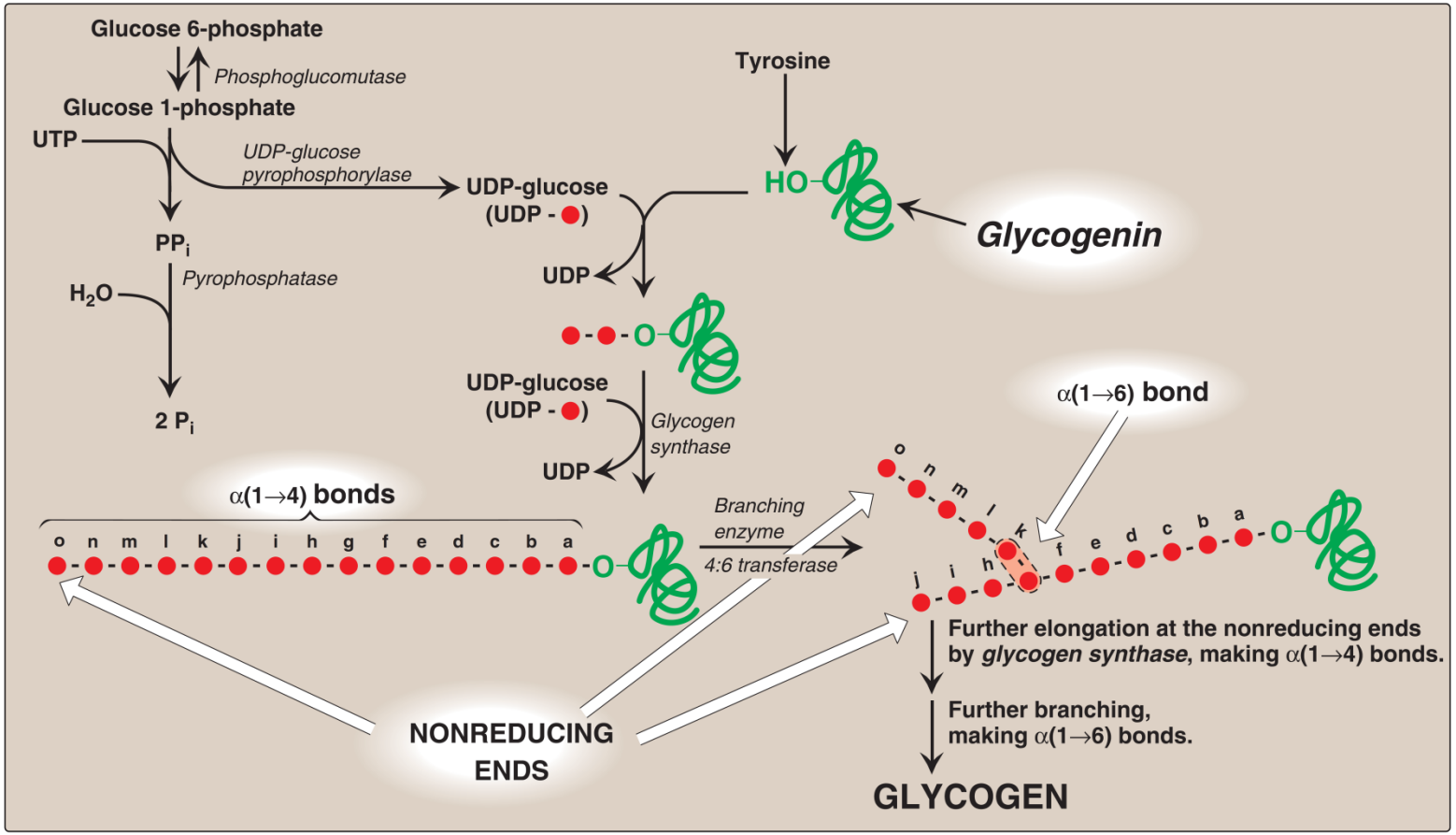


Figure 11.5 in Biochemistry 5th ed. / Harvey and Ferrier
Lippincott Williams & Wilkins, 2011

Glycogen metabolism is controlled by multiple mechanisms

– glycogen phosphorylase and glycogen synthase are key enzymes

<u>Allosteric regulation</u>

allosteric effectors (allosteric modulators) such as glucose, glucose-6-phosphate, AMP, and ATP binds to the enzymes thereby affecting their enzymatic activity

<u>Reversible phosphorylation</u>

hormones such as glucagon, epinephrine, and insulin triggers intracellular signaling cascades leading to phosphorylation or dephosphorylation of the enzymes thereby affecting their enzymatic activity

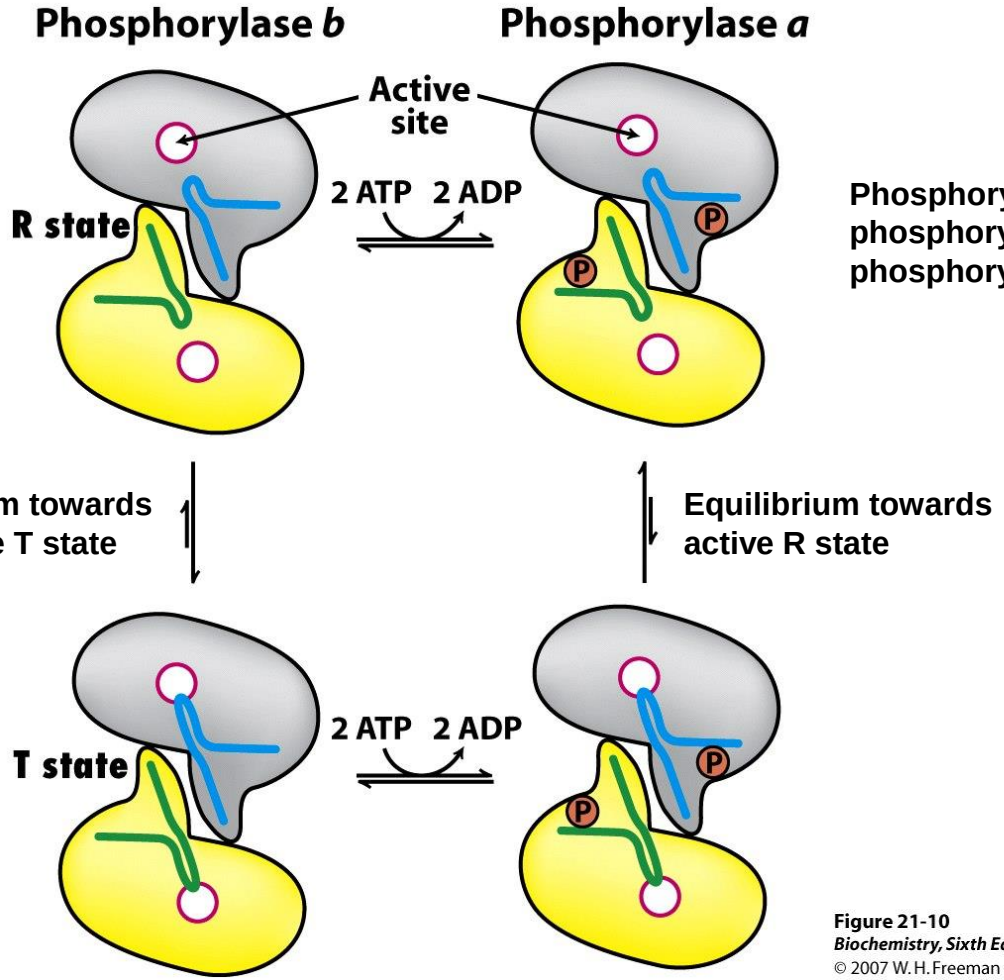
<u>Purpose:</u>

To regulate glycogen metabolism in response to energetic status

Regulation of glycogen degradation

– *glycogen phosphorylase is the control point*

Allosteric effectors affects the equilibrium between the R and T states



Phosphorylation converts phosphorylase *b* to phosphorylase *a*

Figure 21-10
Biochemistry, Sixth Edition

Regulation of glycogen degradation

– glycogen phosphorylase is the control point

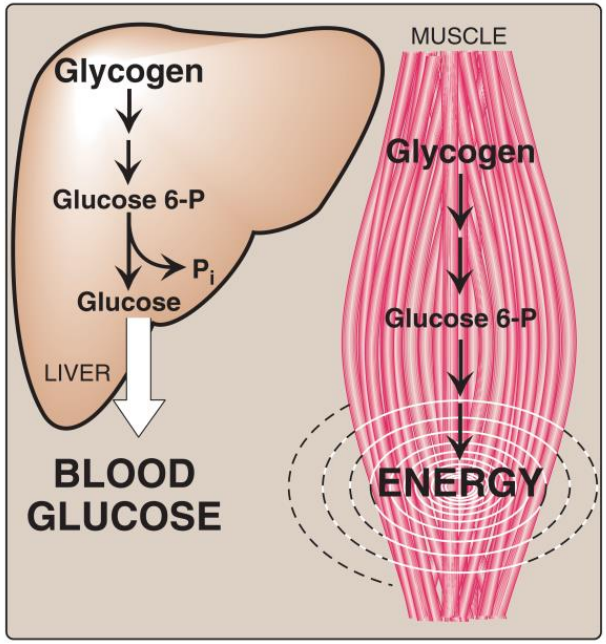


Figure 11.2 in Biochemistry 5th ed. / Harvey and Ferrier Lippincott Williams & Wilkins, 2011

Glycogen plays a different role in liver and muscle

Humans have two isozymes of glycogen phosphorylase; one in the liver and one in muscle and other tissues

The isozymes are affected differently by allosteric effectors

Allosteric regulation of liver glycogen phosphorylase

Purpose of glycogen degradation in the liver; export glucose to other tissues when the blood-glucose level is low

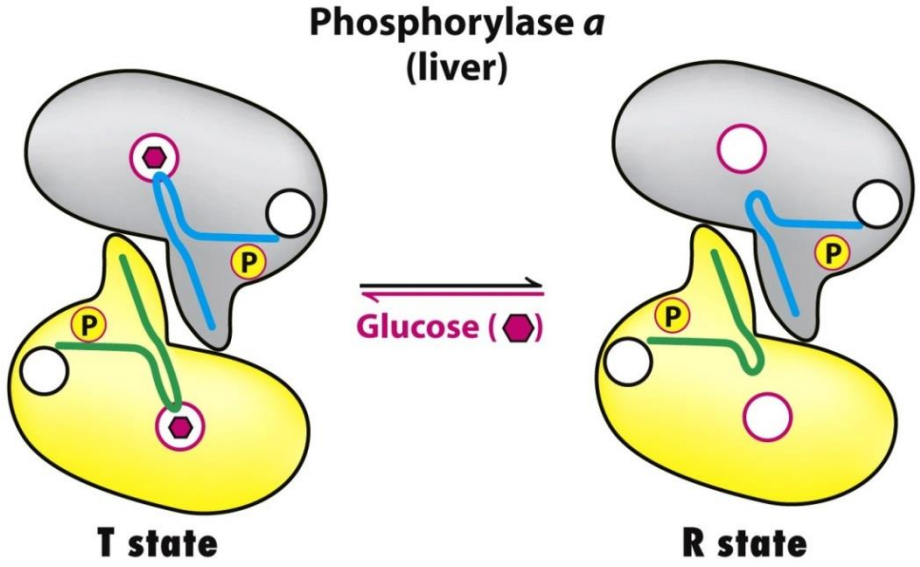


Figure 21-12
Biochemistry, Sixth Edition

The enzyme can be seen as a glucose sensor

If glucose is not sensed ⟶ produce glucose (enzyme active)

If glucose is sensed ⟶ do not produce glucose (enzyme inactive)

Allosteric regulation of muscle glycogen phosphorylase

Purpose of glycogen degradation in the muscle; supply the muscle itself with energy for muscle contraction

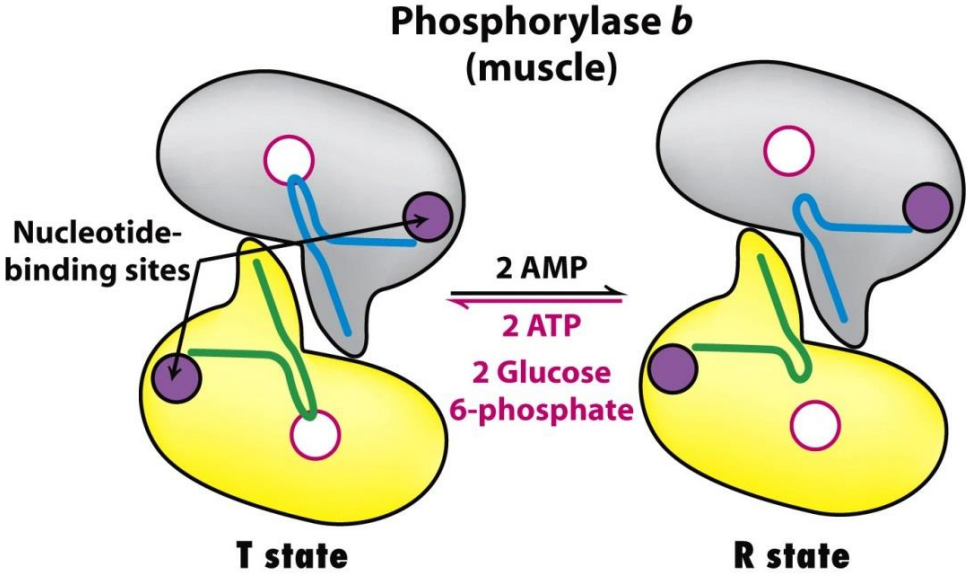


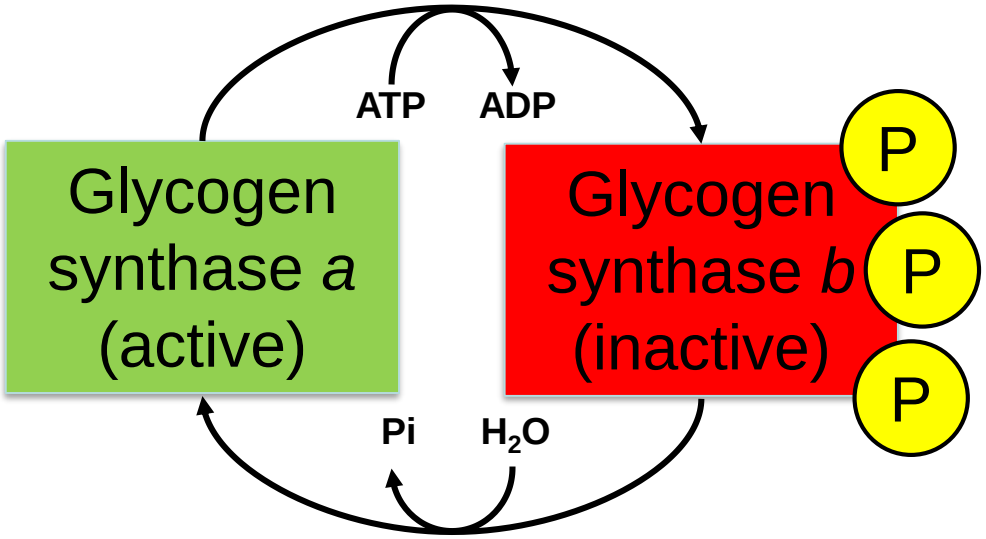
Figure 21-11
Biochemistry, Sixth Edition

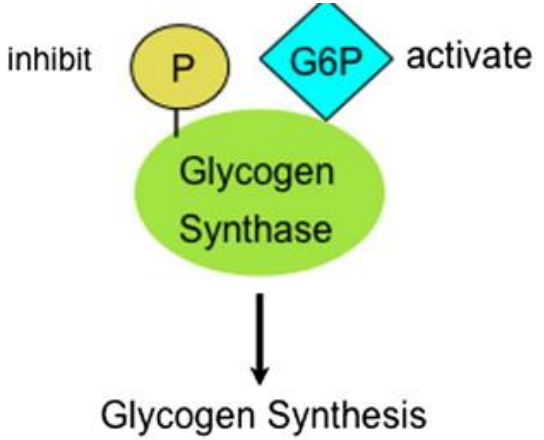
The enzyme can be seen as an energy sensor

If AMP (a sign of low energy status) is sensed ⟶ produce glucose-6-phosphate

If ATP and/or glucose-6-phosphate (signs of sufficient energy status) is sensed ⟶ do not produce glucose-6-phosphate

The regulation of glycogen synthase





Adapted from Bouskila *et al.* (2010) *Cell Metab*, **12**:456-466

The enzyme can be seen as a glucose-6-phosphate sensor

If G6P is sensed ⟶ produce glycogen

If G6P is not sensed ⟶ do not produce glycogen

Summary of allosteric regulation of glycogen metabolism

	Glycogen synthase	Glycogen phosphorylase
Glc-6-P	Activation	Inhibition in muscles
Glc		Inhibition in liver
AMP		Activation in muscles
ATP		Inhibition in muscles

Glycogen synthesis is stimulated by Glc-6-P

Glycogen degradation is stimulated by AMP in skeletal muscles, inhibited by ATP and Glc-6-P in skeletal muscles, and inhibited by Glc in the liver

Insulin, glukagon och adrenalin

– tre viktiga hormoner som påverkar metabola flöden

Insulin

- Utsöndras från pankreas beta-celler vid höga blodglukoskoncentrationer (efter måltid)
- Signalerar att glukos skall tas från blodbanan och omvandlas till energilagringsformer som glykogen och fett

Glukagon

- Utsöndras från pankreas alfa-celler vid låga blodglukoskoncentrationer (fasta); påverkar huvudsakligen levern
- Signalerar att blodglukoskoncentrationen måste höjas via glykogennedbrytning och glukoneogenes

Adrenalin

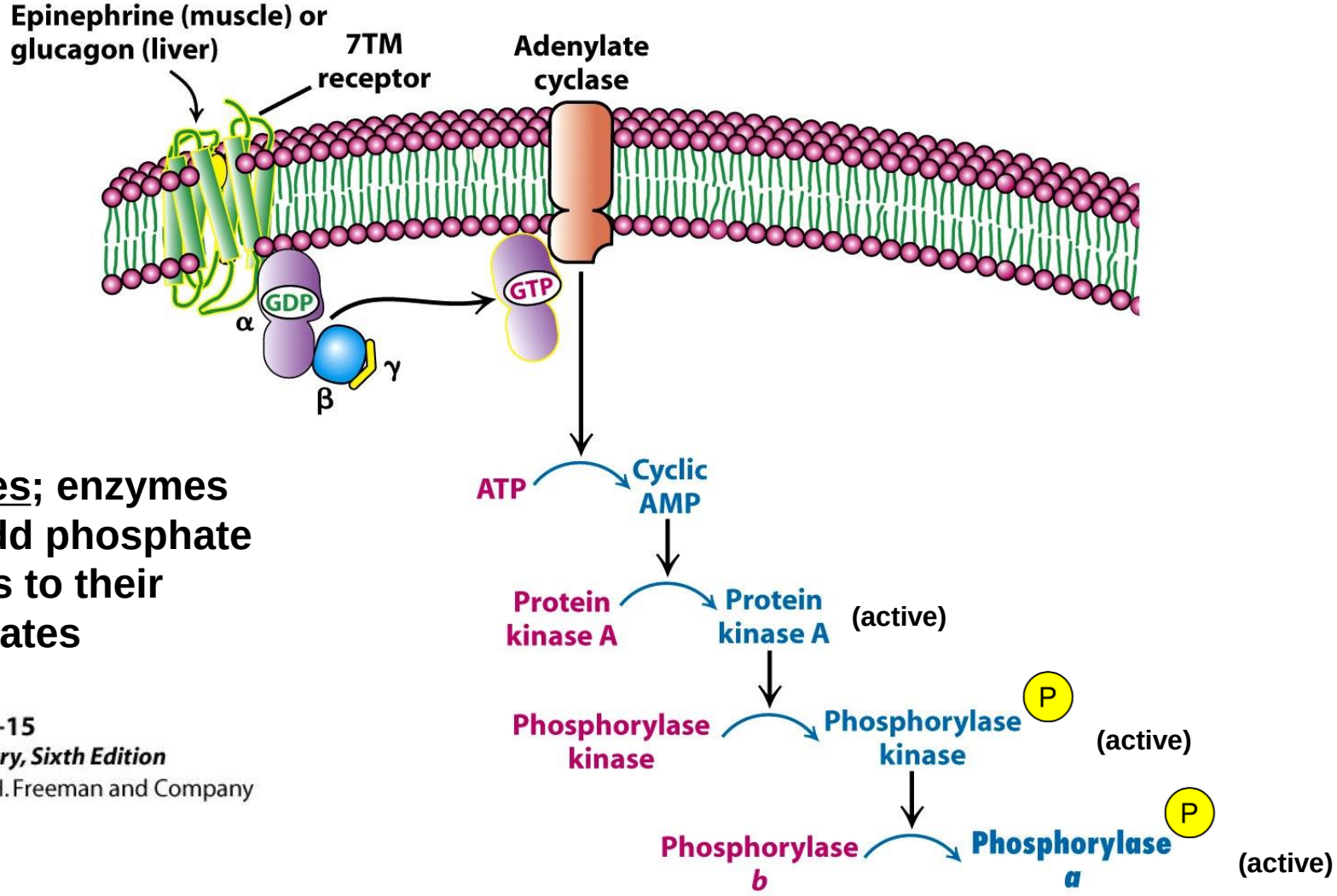
- Utsöndras från binjurarna vid stress
- Signalerar att energi för muskelarbete behövs; blodglukoskoncentrationen höjs via glykogennedbrytning och cirkulerande fettsyror ökar till följd av lipolys i fettcellerna

Overview of hormonal regulation of glycogen metabolism

- **Glycogen synthesis is favoured by insulin signalling (signals the fed state)**
- **Glycogen degradation is favoured by glucagon (signals the starved state) and epinephrine signalling (signals that energy is needed for muscle work)**

The hormones induce intracellular signalling pathways affecting the phosphorylation states of the key enzymes in glycogen metabolism, glycogen phosphorylase and glycogen synthase, thereby modulating their enzymatic activities.

Hormonal regulation of glycogen phosphorylase – *stimulation by glucagon och epinephrine*



<u>Kinases</u>; enzymes that add phosphate groups to their substrates

Figure 21-15
Biochemistry, Sixth Edition

Regulation of phosphorylase kinase
– *stimulation by Ca^{2+} and phosphorylation*

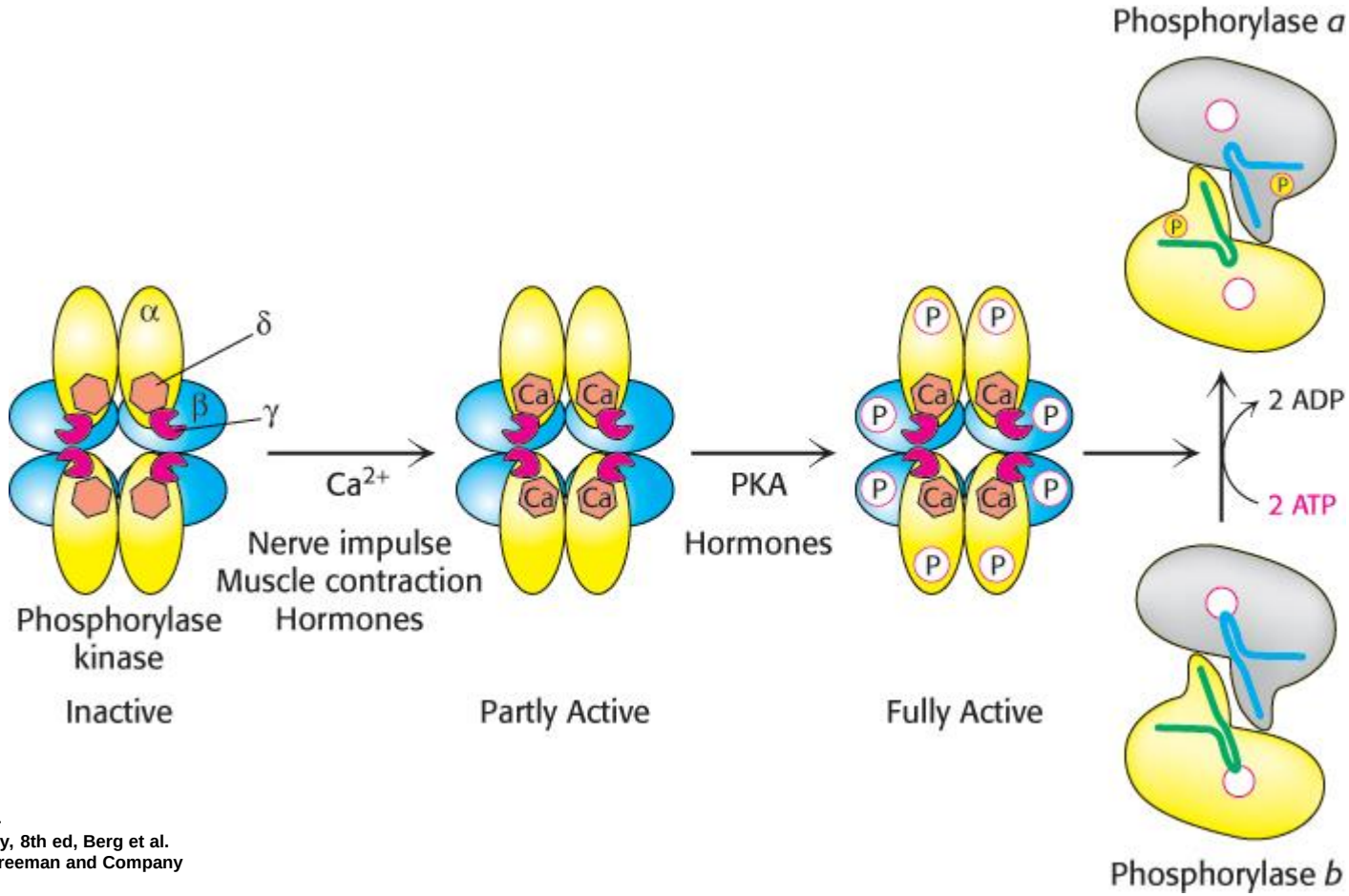
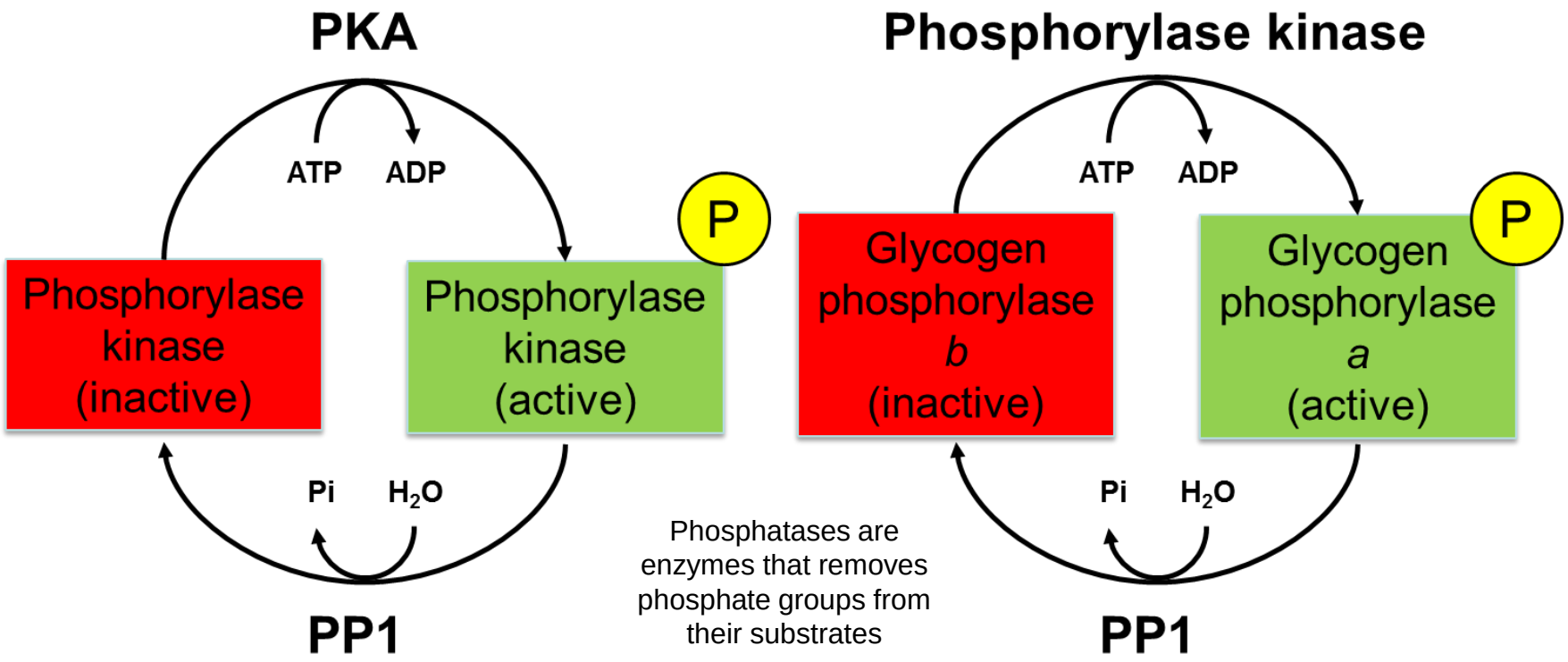


Figure 21.14
Biochemistry, 8th ed, Berg et al.

Protein phosphatase 1 (PP1)

– an important player in glycogen metabolism



Phosphatases are enzymes that removes phosphate groups from their substrates

PP1 inhibits glycogen degradation by dephosphorylating phosphorylase kinase and glycogen phosphorylase

Alternative names of PP1: glycogen-associated protein phosphatase-1, phosphoprotein phosphatase 1

Hormonal regulation of PP1 activity

- **<u>Glucagon and epinephrin</u> induced signalling <u>inhibits PP1</u>**
- **<u>Insulin</u> induced signalling <u>stimulates PP1</u>**

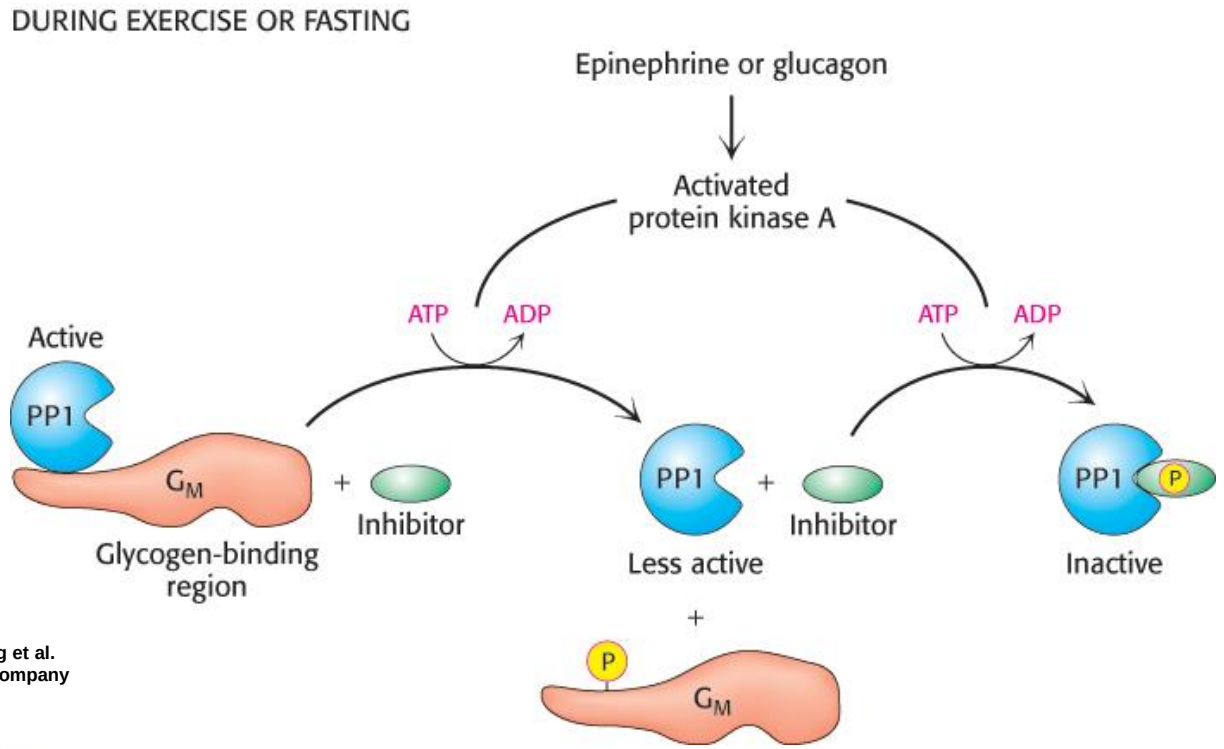


Figure 21.21
Biochemistry, 8th ed, Berg et al.
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Summary of the hormonal regulation of glycogen degradation

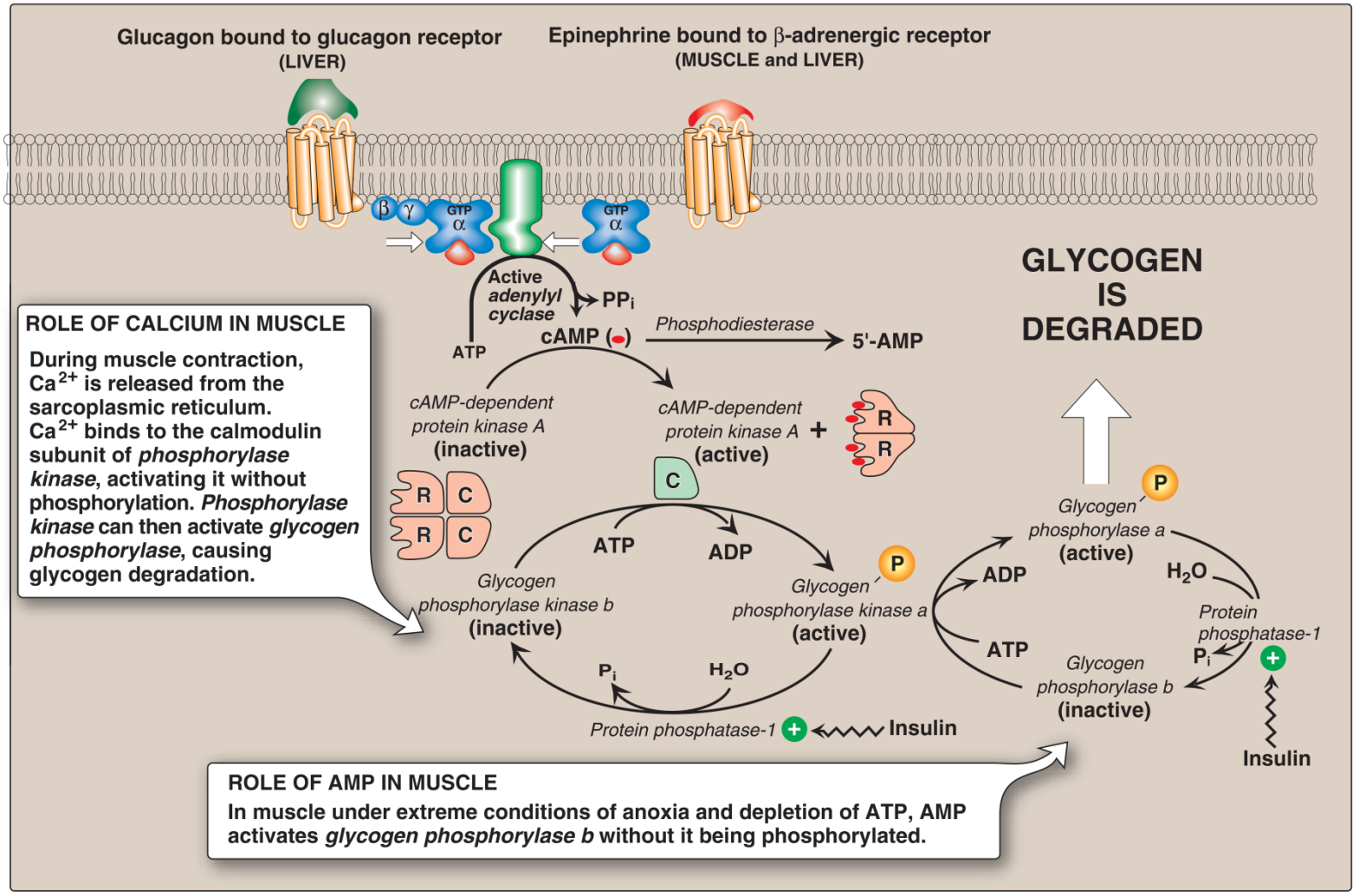


Figure 11.9 in Biochemistry 5th ed. / Harvey and Ferrier
Lippincott Williams & Wilkins, 2011

Hormonal regulation of glycogen synthase

– *inhibition by glucagon och epinephrine*

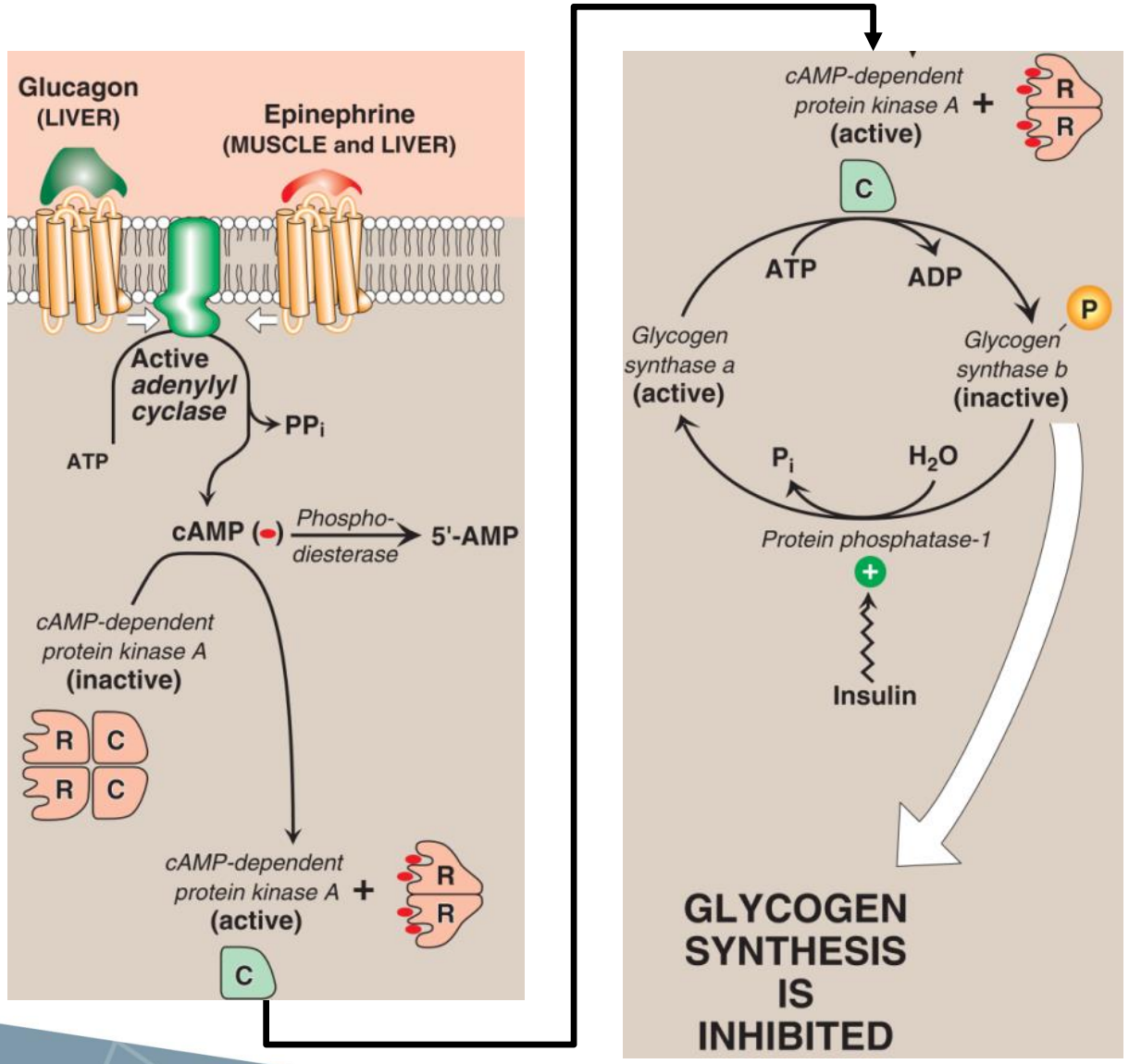


Figure 11.10 in Biochemistry 5th ed. / Harvey and Ferrier Lippincott Williams & Wilkins, 2011

Hormonal regulation of glycogen synthase – *stimulation by insulin*

Glycogen synthase kinase 3 (GSK3) also phosphorylates (and inhibits) glycogen synthase

Insulin signaling leads to phosphorylation and inactivation of GSK3

Insulin also activates PP1; activates glycogen synthase by dephosphorylation

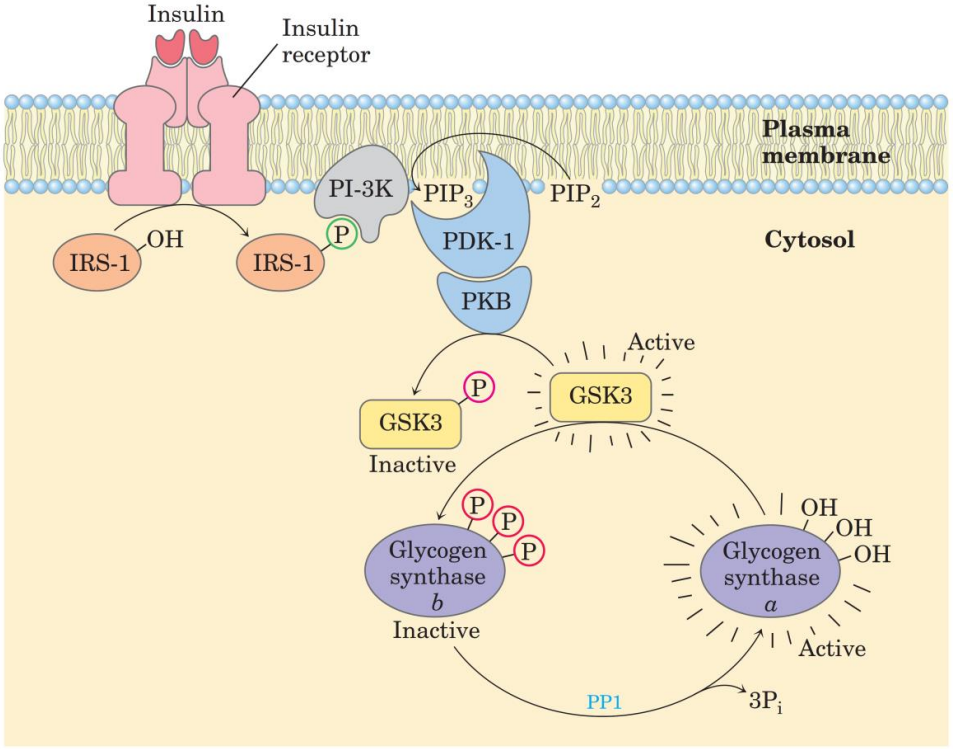
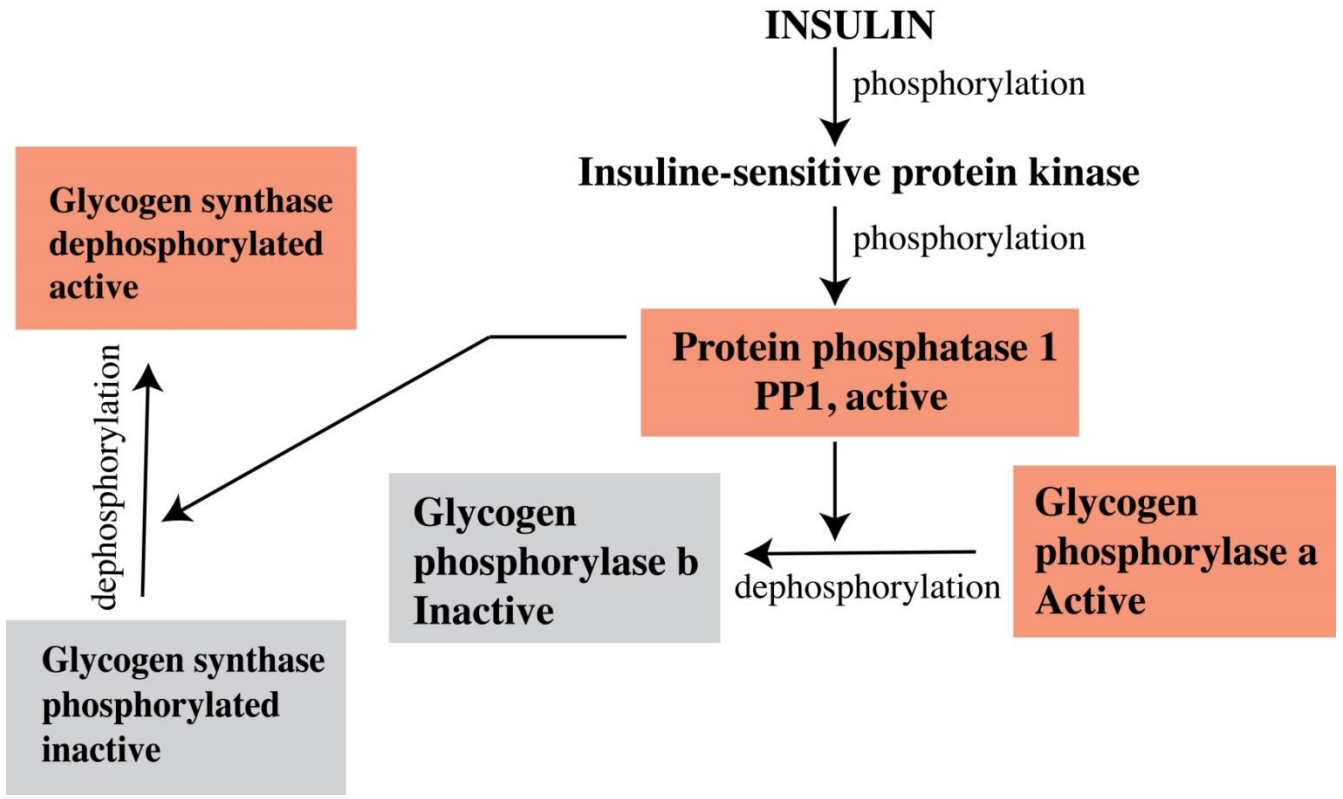


Figure 15-29 in "Lehninger principles of biochemistry, 4th ed", Nelson and Cox, W.H. Freeman, 2005

Insulin signalling favours glycogen synthesis

Insulin activates PP1 which results in activation (through dephosphorylation) of glycogen synthase and inactivation (through dephosphorylation) of glycogen phosphorylase.



Glucagon and epinephrine signalling favours glycogen degradation

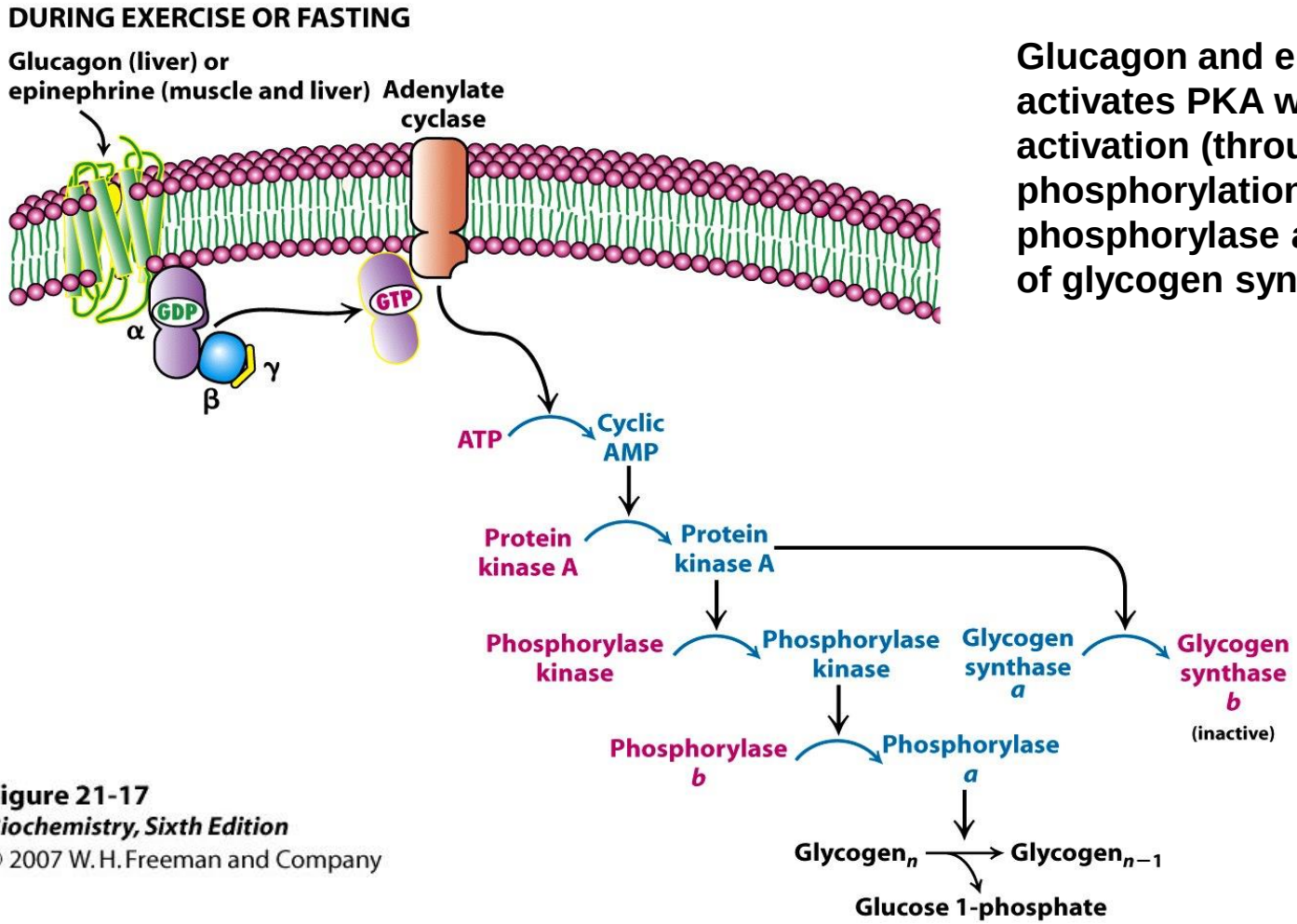


Figure 21-17
Biochemistry, Sixth Edition

Glucagon and epinephrine activates PKA which results in activation (through phosphorylation) of glycogen phosphorylase and inhibition of glycogen synthase.

Summary of the hormonal regulation of glycogen metabolism

	Glycogen synthase	Glycogen phosphorylase
Epinephrine (muscles and liver)	Inhibition	Activation
Glucagon (liver)	Inhibition	Activation
Insulin	Activation	Inhibition

Summary of the regulation of glycogen metabolism

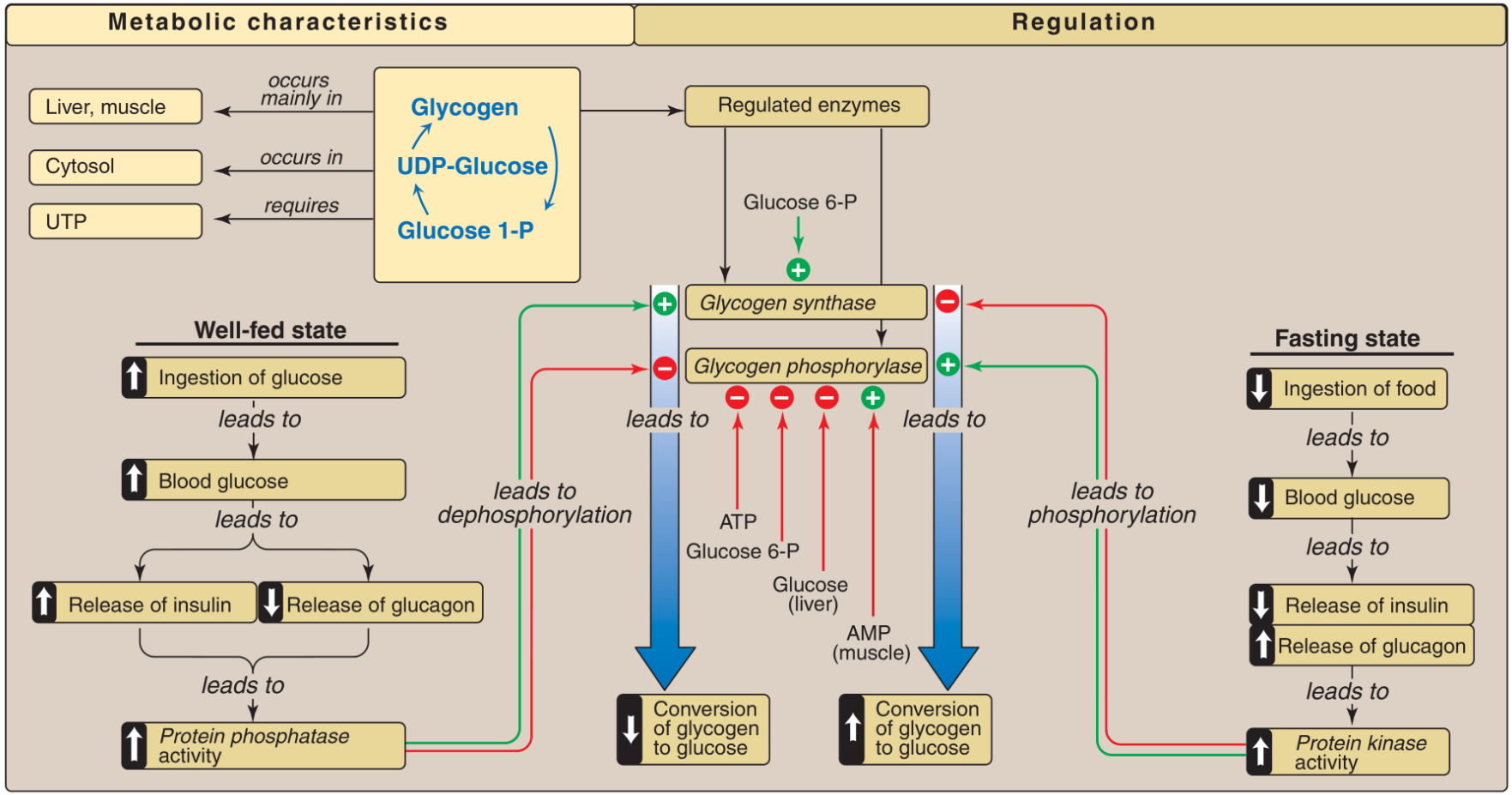


Figure 11.13 in Biochemistry 5th ed. / Harvey and Ferrier
Lippincott Williams & Wilkins, 2011

Enzymes involved glycogen metabolism

Glycogen synthesis

Hexokinase/glucokinase
Phosphoglucomutase
UDP-glucose pyrophosphorylase
Inorganic pyrophosphatase
Glycogenin
Glycogen synthase
Branching enzyme

Protein kinase A
Glycogen synthase kinase
Protein phosphatase 1

Glycogen degradation

Glycogen phosphorylase
Debranching enzyme
Phosphoglucomutase
Glucose-6-phosphatase

Protein kinase A
Phosphorylase kinase
Protein phosphatase 1

Summary of glycogen metabolism

- **Liver glycogen serves in the maintenance of the blood glucose**
- **Muscle glycogen serves as an energy reserve for the muscle itself**
- **Glycogen phosphorylase is the key enzyme in glycogen breakdown**
- **Glycogen synthase is the key enzyme in glycogen synthesis**
- **The activities of the key enzymes are regulated by allosteric effectors, and by reversible phosphorylation triggered by hormones**
- **Important hormones regulating glycogen metabolism are glucagon, epinephrine, and insulin**
- **Glucagon and epinephrine signalling favours glycogen degradation**
- **Insulin signalling favours glycogen synthesis**

Glykogenmetabolism

Läsanvisningar

Kapitel 21 i Biochemistry, 10th ed, Berg et al.
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