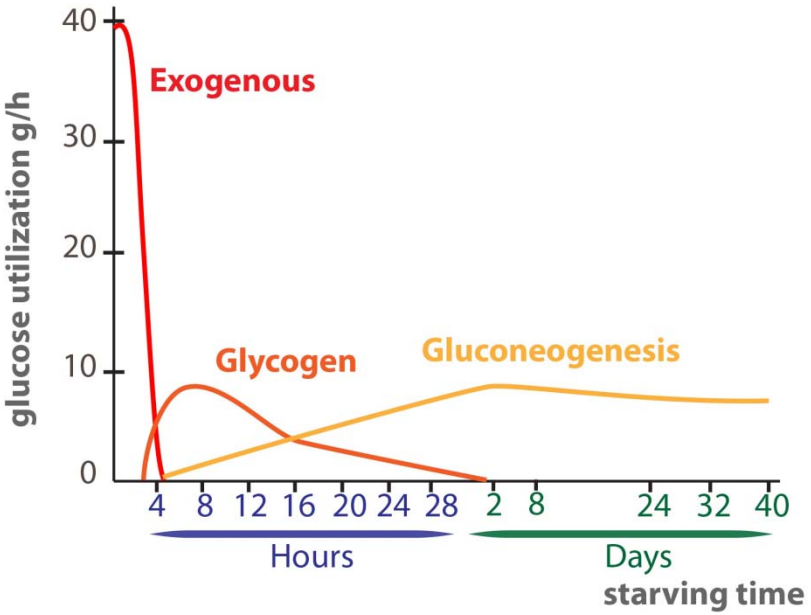
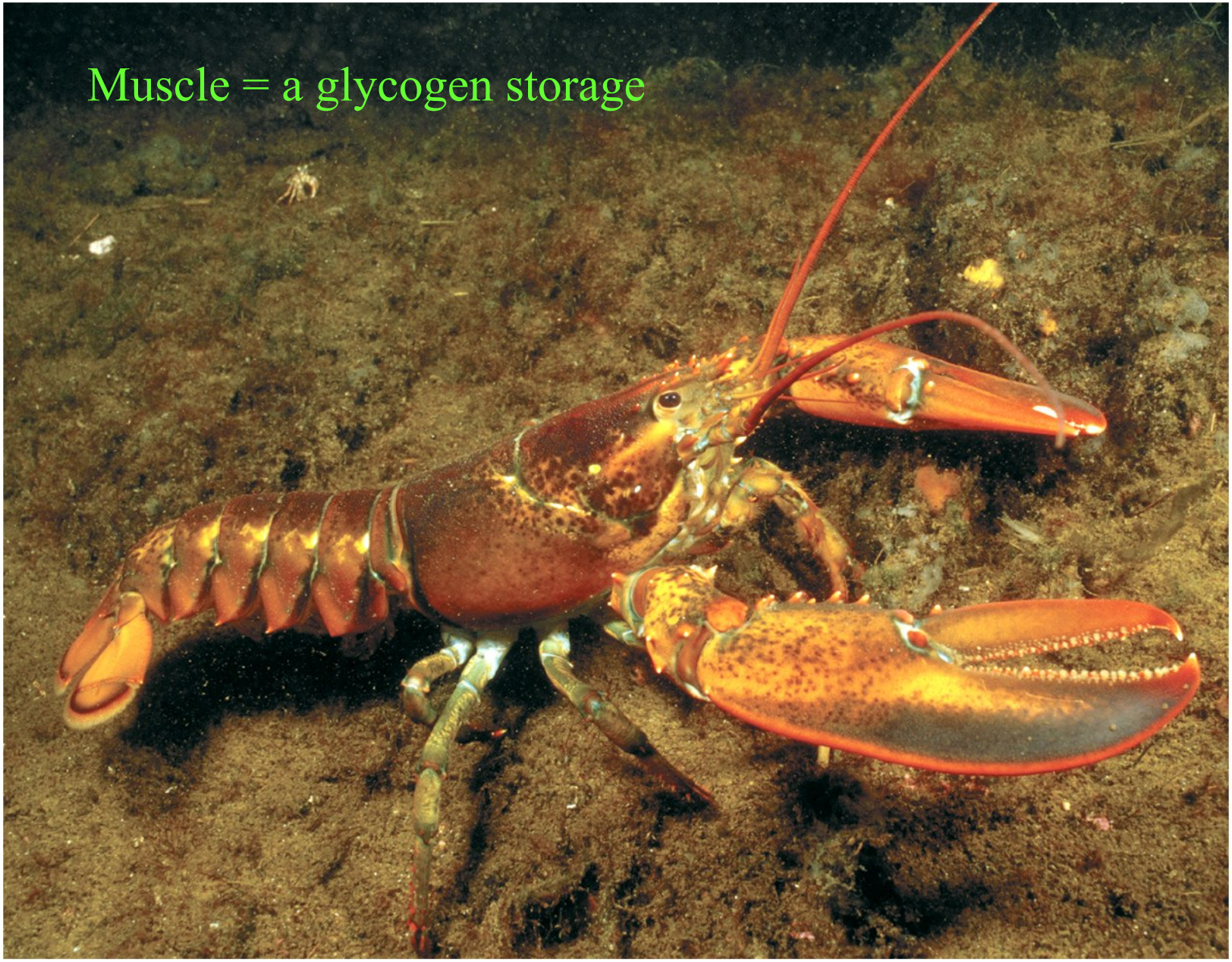
Chapter 3-I:
Glycogen Metabolism and Gluconeogenesis





Chapter 15 Opener Fundamentals of Biochemistry, 2/e

Glucose storage

Glycogen: animals, fungi, and bacteria
Starch: plants

Constant supply of glucose in animals: ~5 mM in blood
Maintenance of the concentration

Overview of glucose metabolism

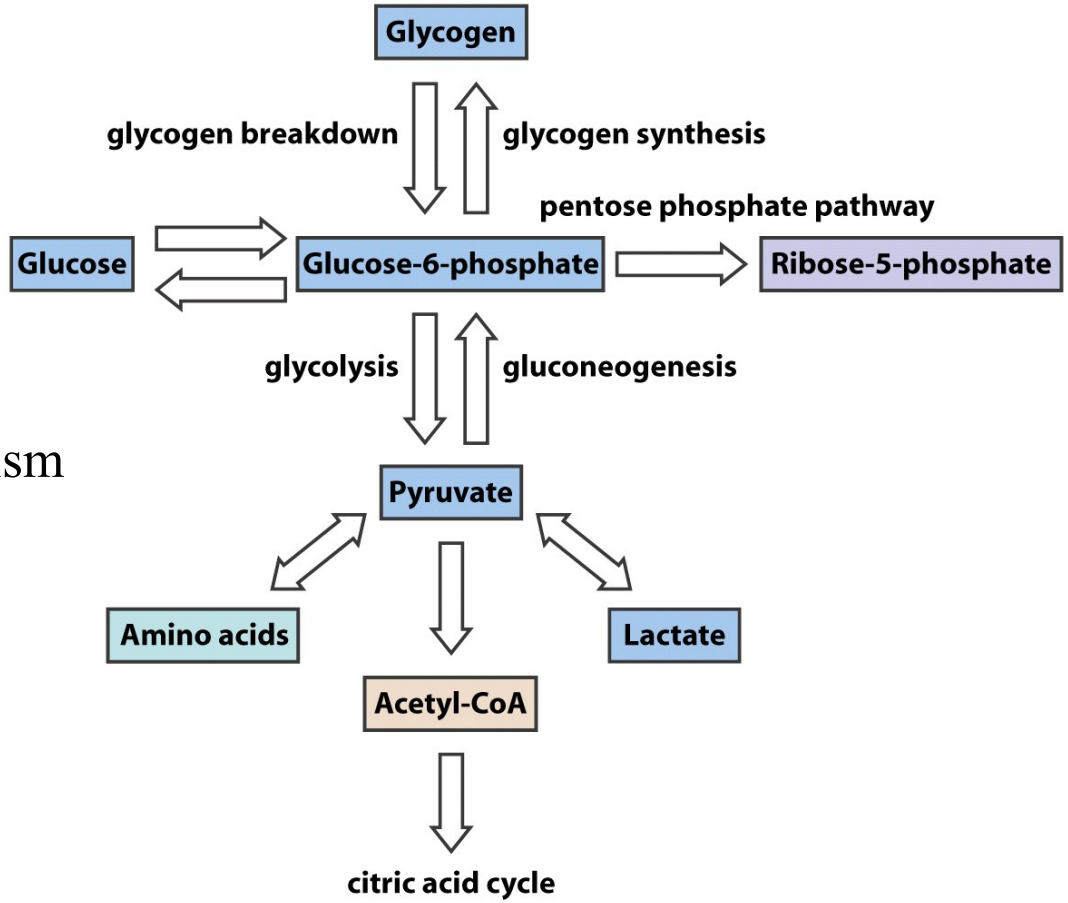


Figure 15-1 Fundamentals of Biochemistry, 2/e

Glycogen breakdown (glycogenolysis)

α(1-4)-linked D-glucose with α(1-6)-linked branches every 8-14 residues
Intracellular granules of 100~400 Å diameter
Abundant in muscle (up to 1-2%) and liver (up to 10%)
A complex with enzymes catalyzing synthesis and breakdown

- Glycogen phosphorylase
- Glycogen debranching enzyme
- phosphoglucomutase

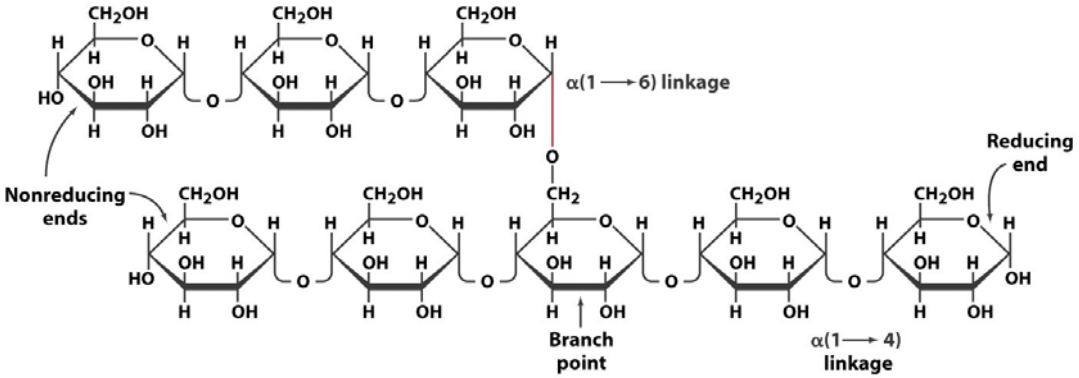


Figure 15-2a Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

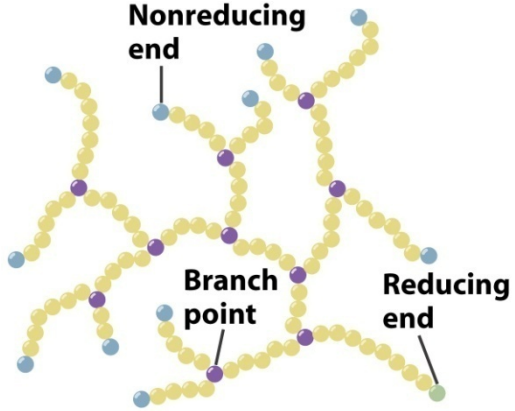


Figure 15-2b Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

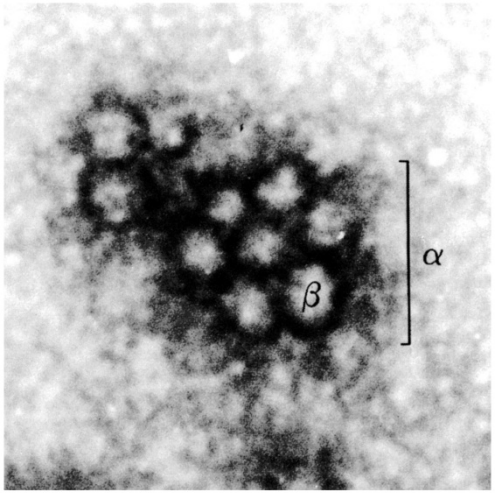


Figure 15-2c Fundamentals of Biochemistry, 2/e

Glycogen phosphorylase

Glycogen (n) + Pi ↔ glycogen (n-1) + G1P

Dimer of 97 kD subunits
Allosteric regulation
Inhibitors: ATP, G6P, glucose
Activator: AMP

Covalent modification (ser-14)
Phosphorylase a (phosphorylated)
Phosphorylase b (dephosphorylated)

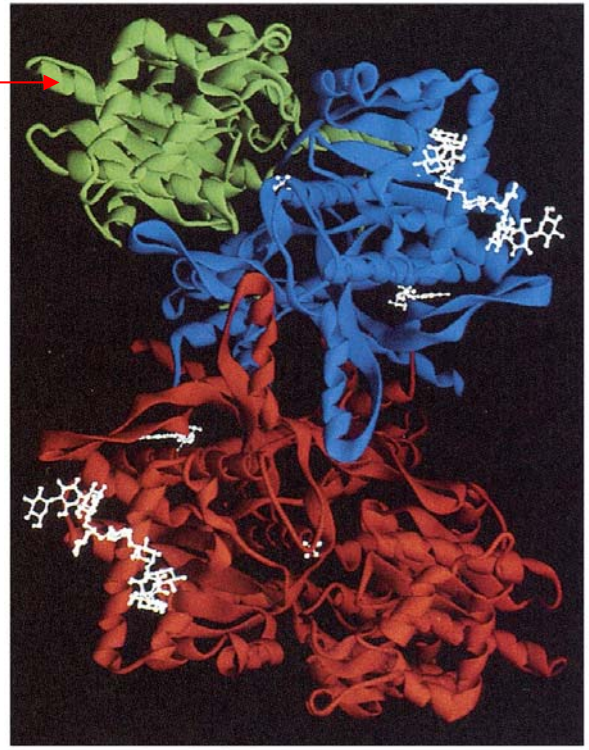


Figure 15-3a Fundamentals of Biochemistry, 2/e

Continuous feeding of substrate

Narrow crevice:
5 units away from a branching point

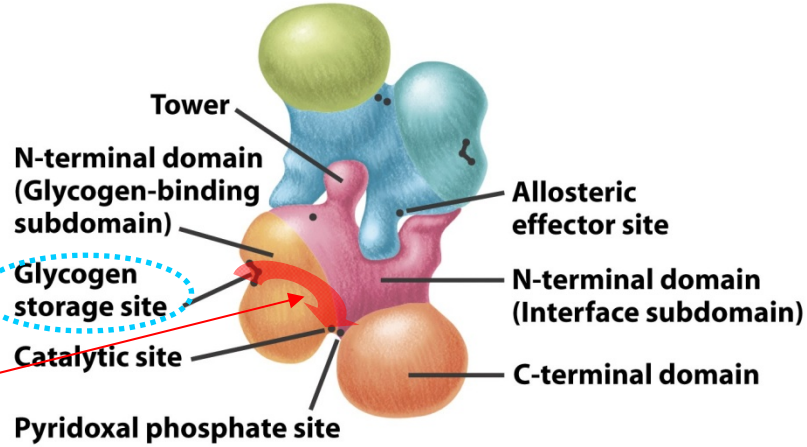
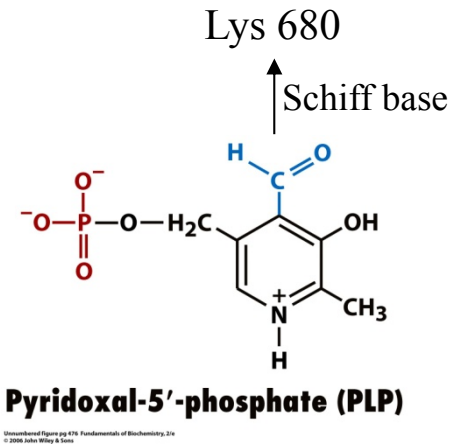
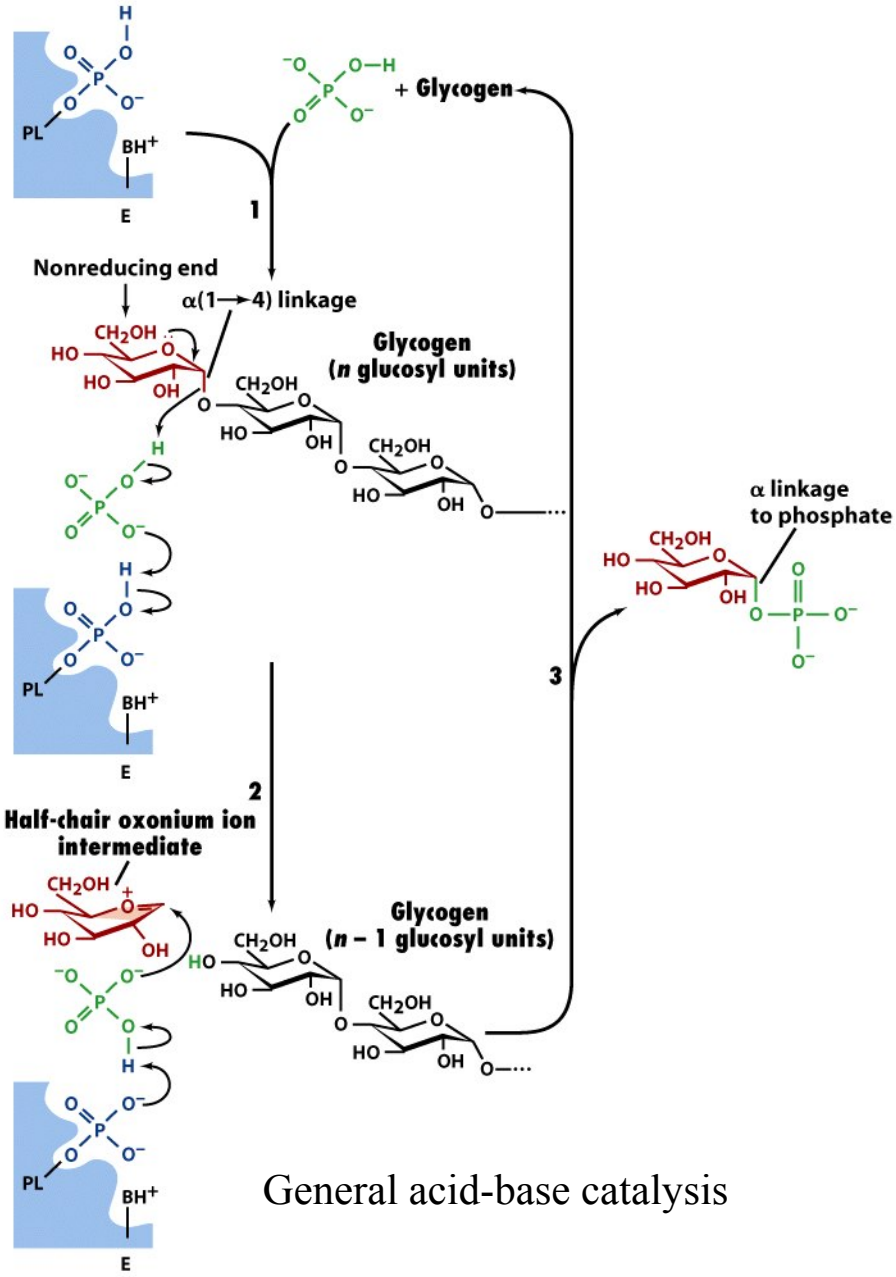


Figure 15-3b Fundamentals of Biochemistry, 2/e

The reaction mechanism of glycogen phosphorylase





General acid-base catalysis

Figure 15-4 Fundamentals of Biochemistry, 2/e

Glycogen debranching enzyme

Two separate active sites:

Transferase: α(1-4) transglycosylase

α(1-6) glucosidase

The maximal rate is slower than phosphorylase

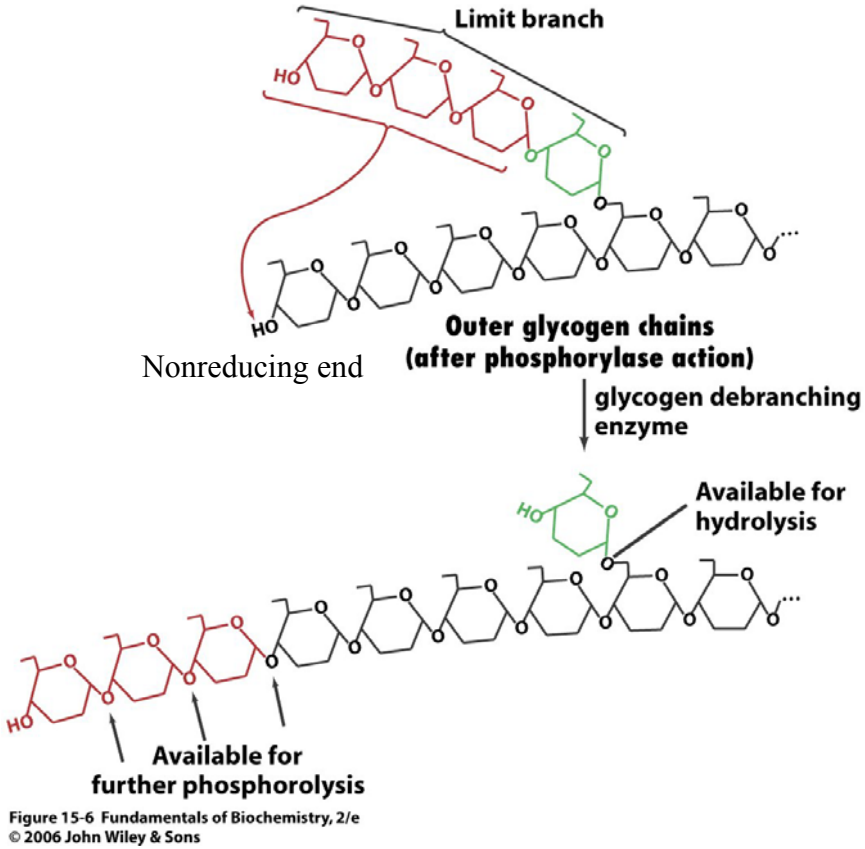


Figure 15-6 Fundamentals of Biochemistry, 2/e

Phosphoglucomutase

G1P to G6P via G1,6P

Hexokinase step is bypassed

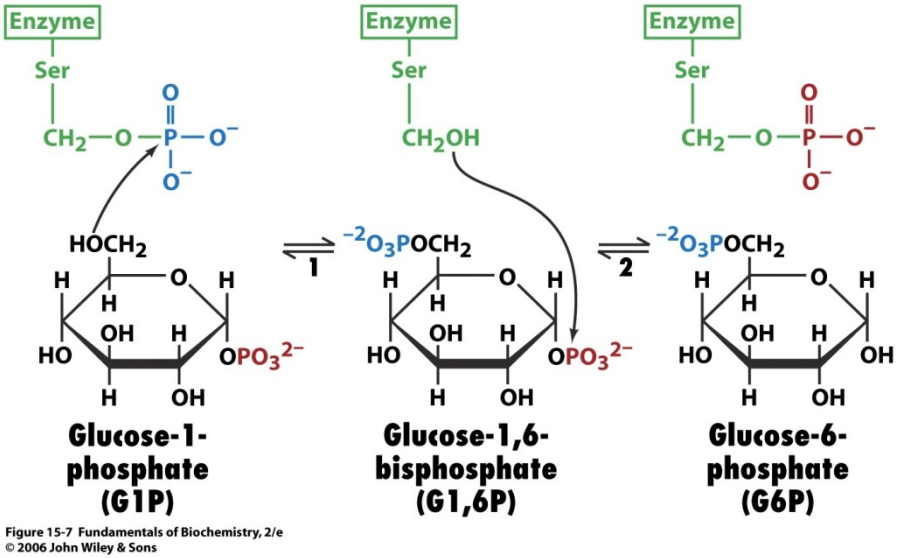


Figure 15-7 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

Glucose-6-phosphatase

G6P to Glucose

Liver enzyme in ER membrane

G6P is transported to ER and hydrolyzed

Leave liver via GLUT2

Type I glycogen storage disease: G6P process defect in liver

Hereditary Glycogen Storage Diseases

Type	Enzyme Deficiency	Tissue	Common Name	Glycogen Structure
I	Glucose-6-phosphatase	Liver	von Gierke's disease	Normal
II	α-1,4-Glucosidase	All lysosomes	Pompe's disease	Normal
III	Amylo-1,6-glucosidase (debranching enzyme)	All organs	Cori's disease	Outer chains missing or very short
IV	Amylo-(1,4→1,6)-transglycosylase (branching enzyme)	Liver, probably all organs	Andersen's disease	Very long unbranched chains
V	Glycogen phosphorylase	Muscle	McArdle's disease	Normal
VI	Glycogen phosphorylase	Liver	Hers' disease	Normal
VII	Phosphofructokinase	Muscle	Tarui's disease	Normal
VIII	Phosphorylase kinase	Liver	X-linked phosphorylase kinase deficiency	Normal
IX	Phosphorylase kinase	All organs		Normal
0	Glycogen synthase	Liver		Normal, deficient in quantity

Box 15-2 table 1 Fundamentals of Biochemistry, 2/e

Glycogen synthesis

UDP-glucose pyrophosphorylase
Glycogen synthase
Glycogen branching enzyme

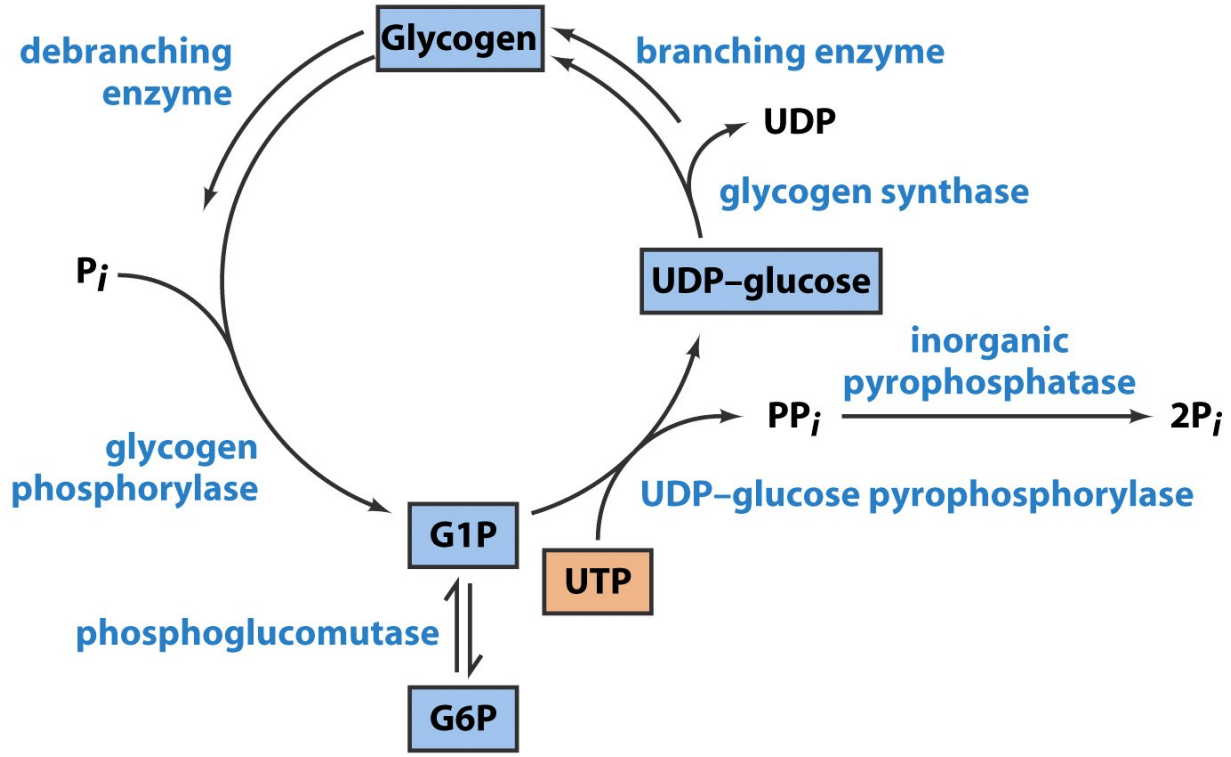


Figure 15-8 Fundamentals of Biochemistry, 2/e

A. UDP-glucose pyrophosphorylase

G1P + UTP ↔ UDPG + Ppi ~0

PPi + H2O → 2 Pi ~19.2

G1P + UTP → UDPG + 2 Pi ~19.2 ($\Delta G^{o'}$, KJ/mol)

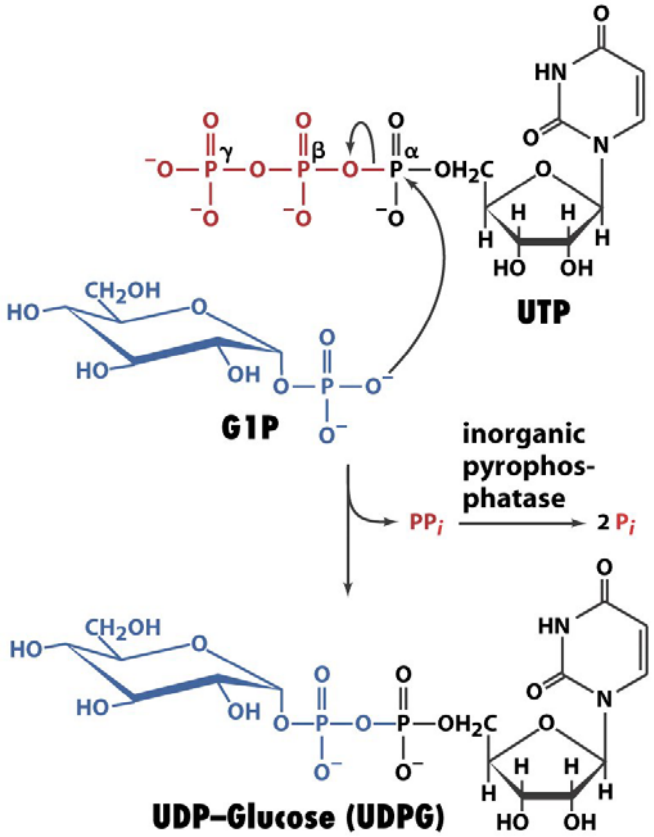


Figure 15-9 Fundamentals of Biochemistry, 2/e

B. Glycogen synthase

Catalyzes α(1-4) linkage to the existing glucan chain
UDPG + glycogen (n) → UDP + glycogen (n+1)
G1P + UTP → UDPG + 2 Pi

Glycogen (n) + G1P + UTP → glycogen (n+1) + UDP + 2 Pi

UDP + ATP ↔ UTP + ADP

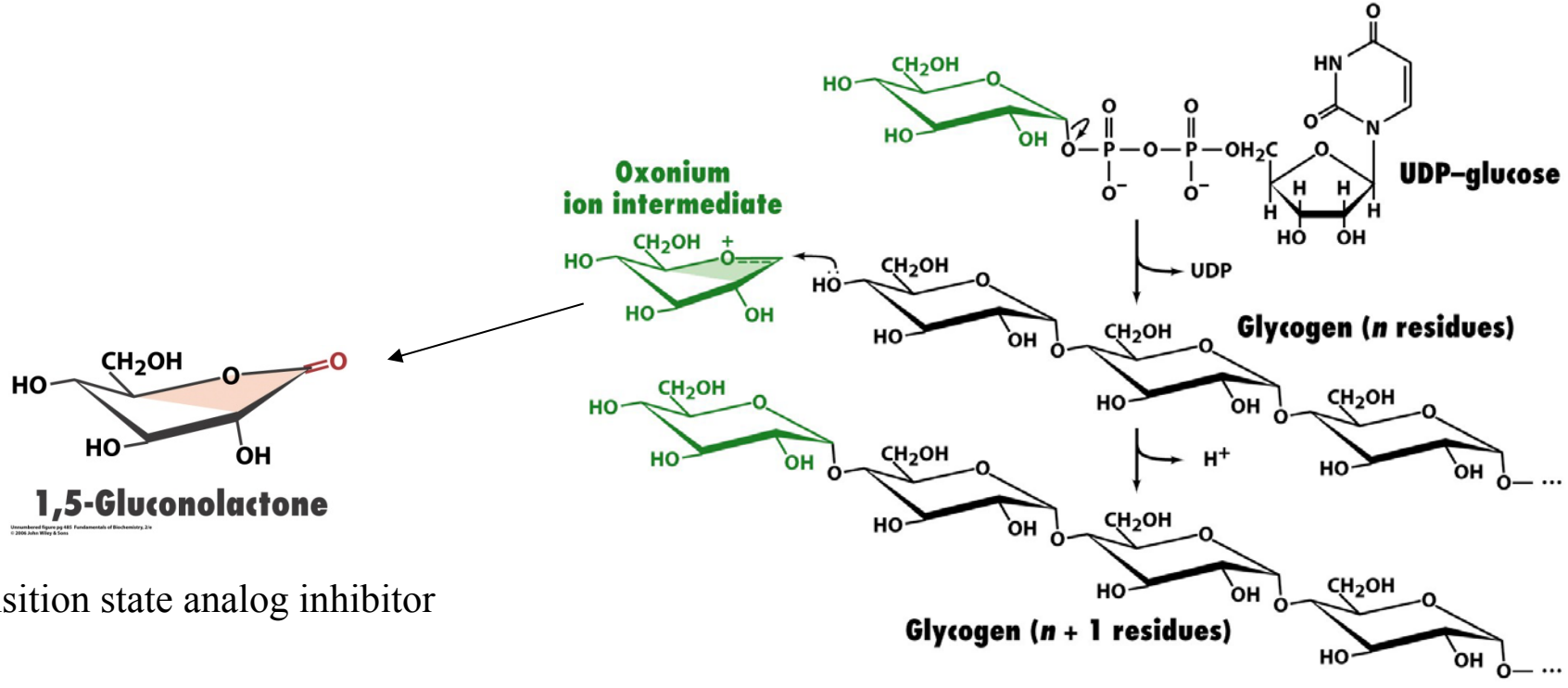


Figure 15-10 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

Transition state analog inhibitor

*Initiation of glycogen synthesis

Glycogenin: priming glycogen synthesis

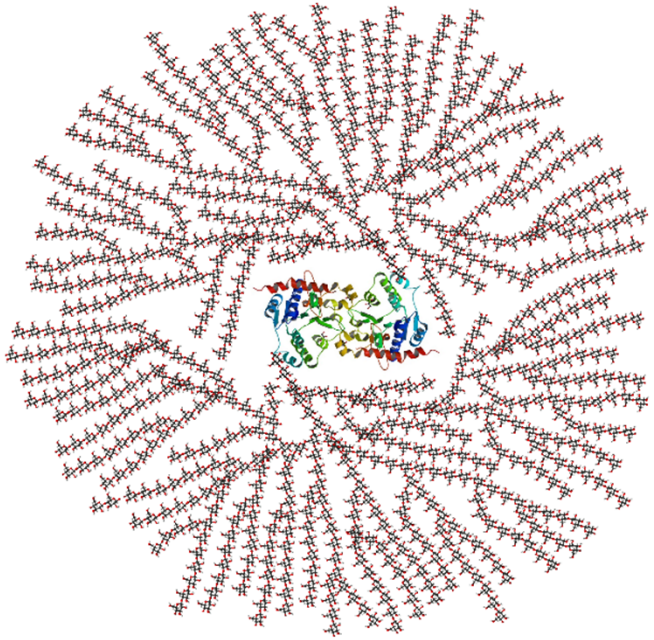
Glycosyltransferase

Attaches a glucose of UDPG to the Tyr194 and extends up to 7 additional residues

Glycogen synthase takes over the role

C. Glycogen branching enzyme

Amylo-(1,4 →1,6)-transglycosylase



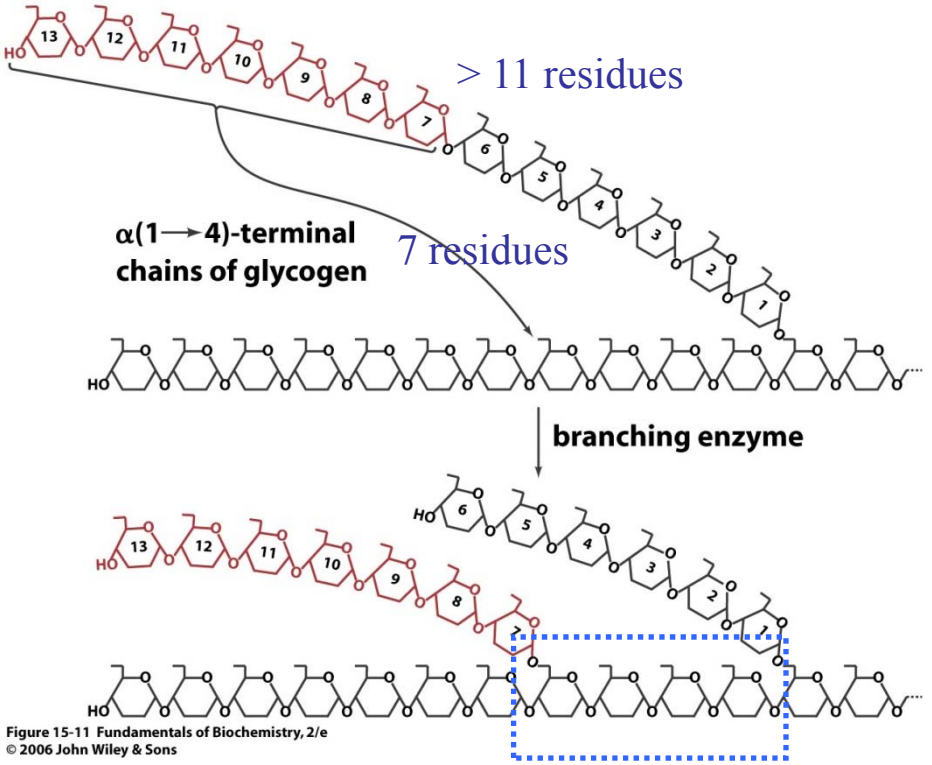


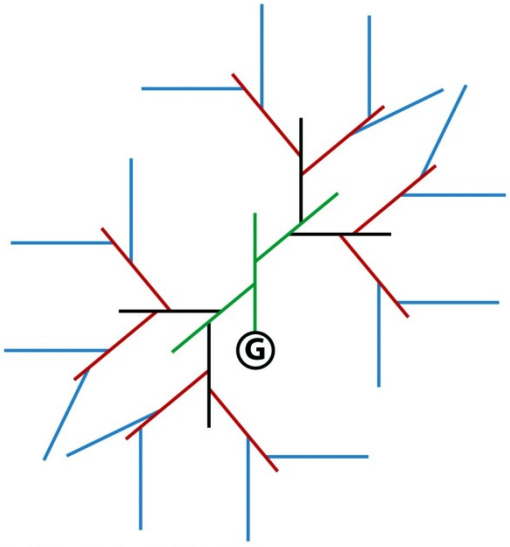
Figure 15-11 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

Optimizing glycogen structure

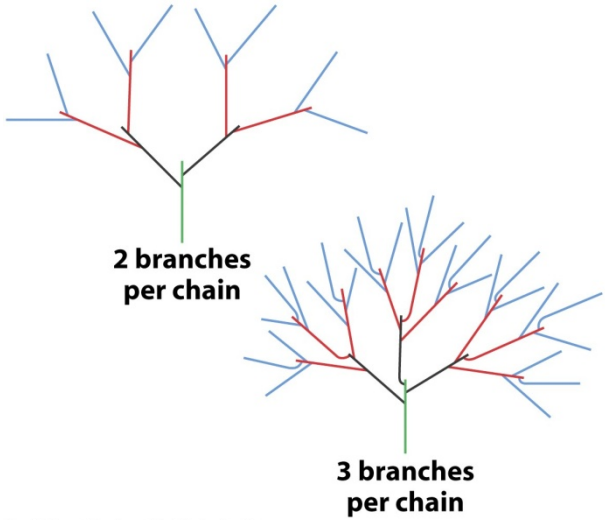
Branching & interval

The largest amount of glucose in the smallest possible volume

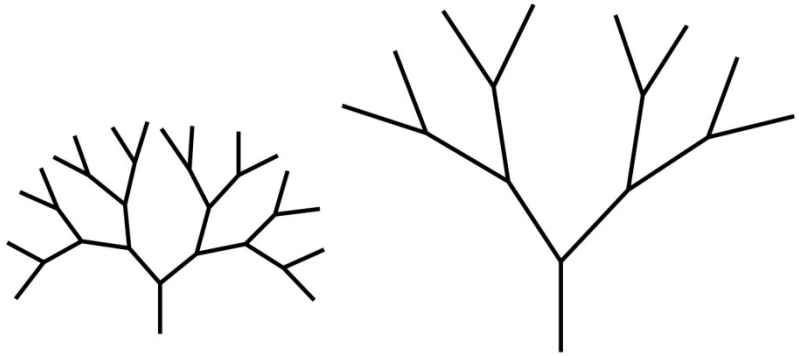
Branching frequency and length



Box 15-3 figure 1 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons



Box 15-3 figure 2 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons



Box 15-3 figure 3 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

Control of glycogen metabolism

Allosteric & covalent modification

A. Allosteric control of phosphorylase & synthase

Independent control of vf and vr
Effectors: ATP, G6P, AMP

Glycogen breakdown:
- High demand for ATP: low [ATP] & [G6P], high [AMP]
- Phosphorylase is stimulated
- Synthase is inhibited

Glycogen synthesis: When [ATP] & [G6P] are high

B. Covalent modification

Hormonal control
A set of kinases and phosphatases
Reverse regulation of phosphorylase and synthase

Synthase a: dephosphorylated form
- more active

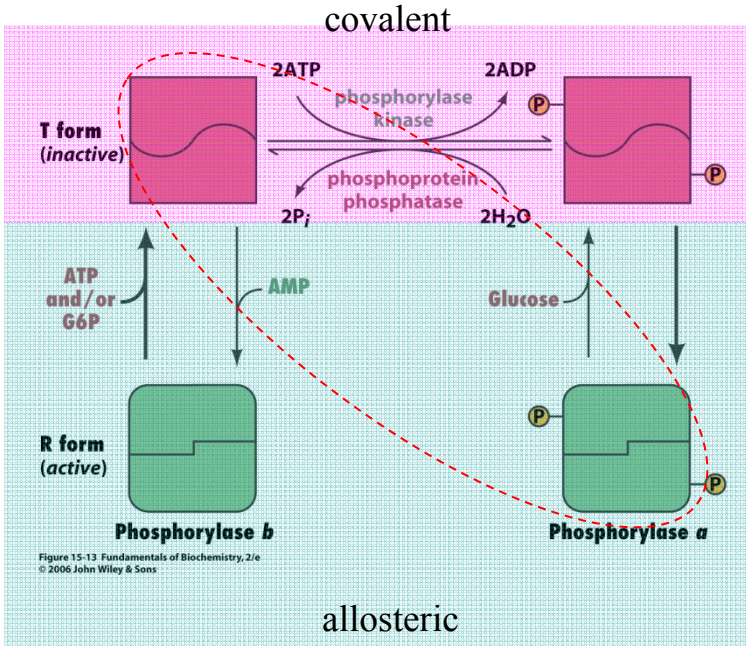
Synthase b: phosphorylated form
- less active
- activated by G6P

Covalent modification of glycogen phosphorylase

Phosphorylase a: phosphorylated, active (even without AMP stimulation)
Phosphorylase b: dephosphorylated, inactive

<u>3 involved enzymes</u>

Phosphorylase kinase
Protein kinase A (PKA)
Phosphoprotein phosphatase-1



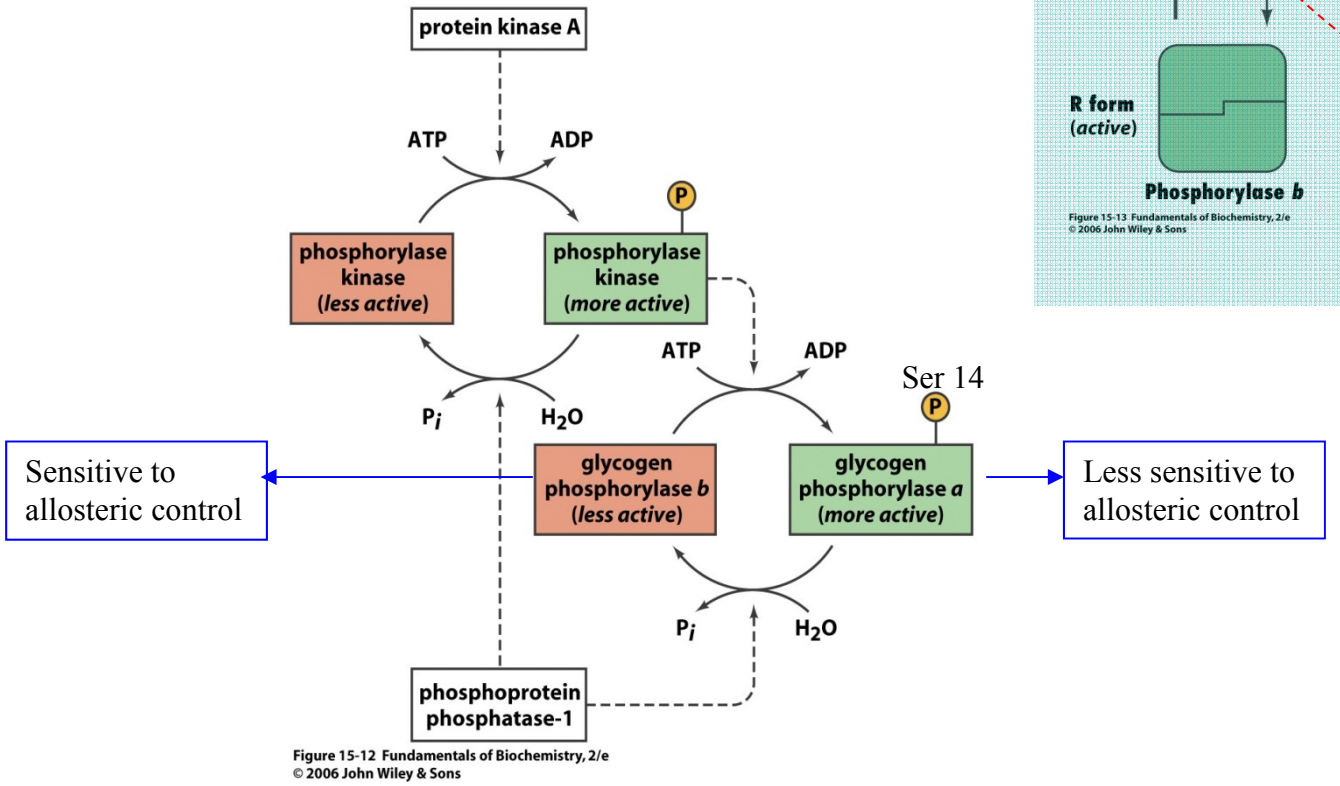


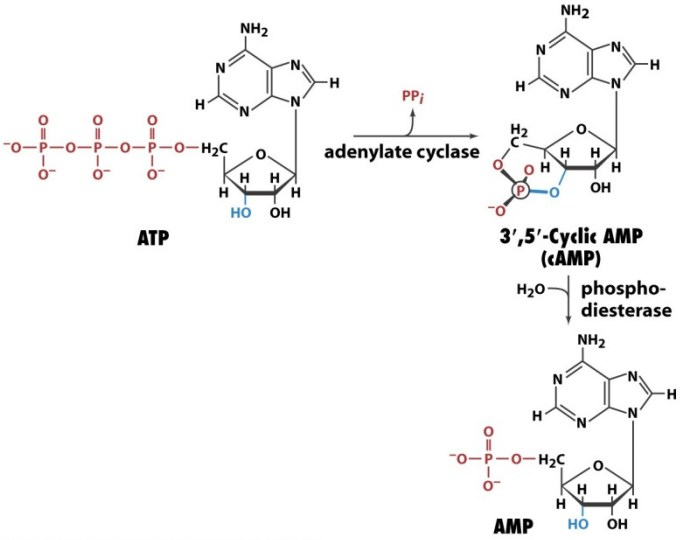
Figure 15-12 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

PKA (protein kinase A)

cAMP-dependent protein kinase (cAPK)

Ser/Thr of numerous cellular proteins

R2C2 (inactive) + 4 cAMP ↔ 2 C + R2 (cAMP)4



Unnumbered figure pg 490 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

Autoinhibitor segment

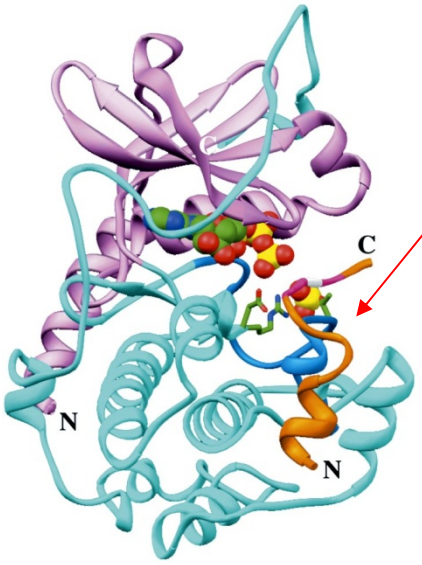


Figure 15-14 Fundamentals of Biochemistry, 2/e

C subunit

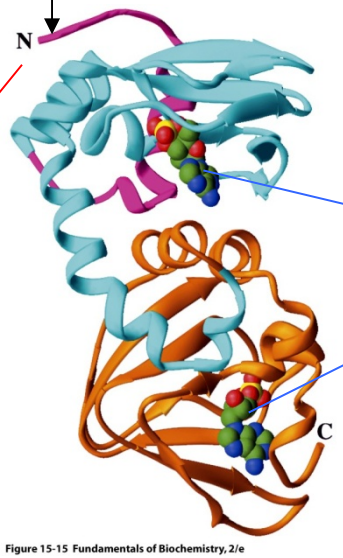


Figure 15-15 Fundamentals of Biochemistry, 2/e

R subunit

cAMP

Phosphorylase kinase

4 subunits: αβγδ (γ, catalytic subunit; αβδ, regulatory subunits)

Catalytic subunit structure is similar to the C subunit of PKA (autoinhibition)

Activation of the catalytic subunit

- Phosphorylation of αβ
- Ca^{++} binding to δ (calmodulin)

Phosphorylase kinase

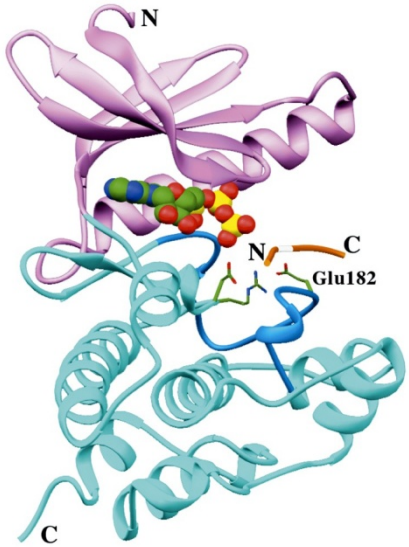


Figure 15-16 Fundamentals of Biochemistry, 2/e

PKA

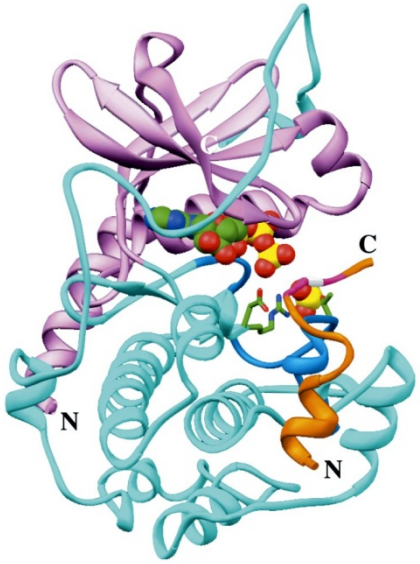


Figure 15-14 Fundamentals of Biochemistry, 2/e

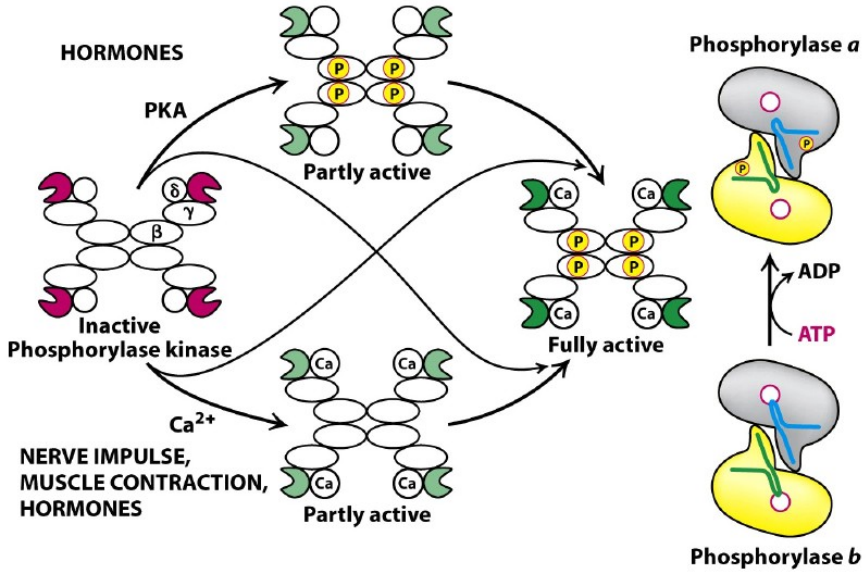


Figure 21-13
Biochemistry, Sixth Edition

Calmodulin (CaM)

Ca^{2+}-binding protein

Highly conserved in eukaryotes

Helix-loop-helix motif: EF hand

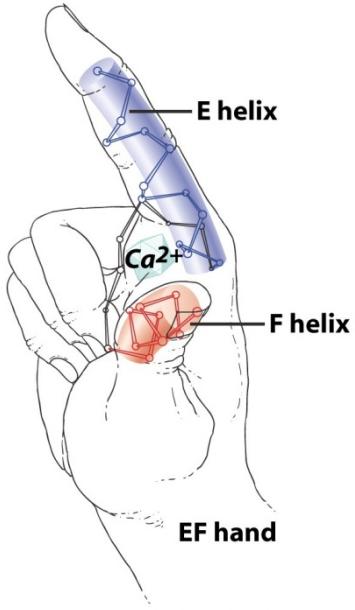


Figure 15-18 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

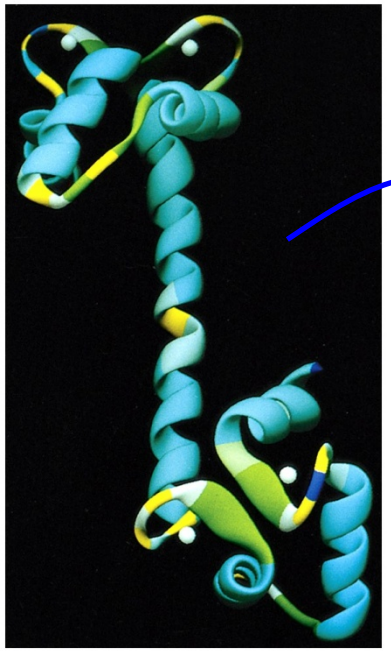
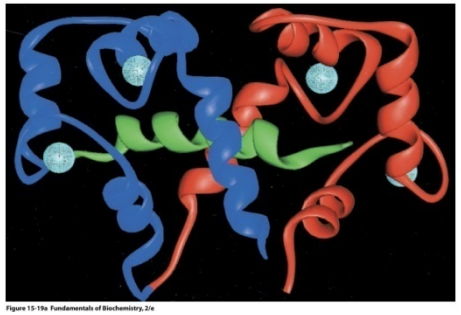
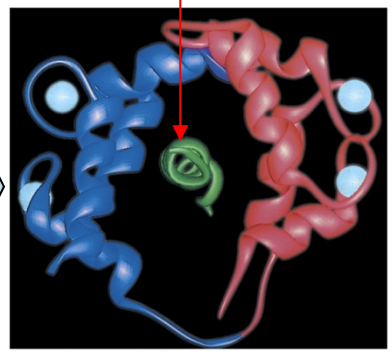


Figure 15-17 Fundamentals of Biochemistry, 2/e

Conformational change
by calcium binding





Target polypeptide

Phosphoprotein phosphatase-1

Control in muscle

Catalytic subunit (PP1c) + glycogen binding subunit (G_M subunit)

Active only when bound to glycogen: regulated by the phosphorylation of G_M subunit

Further regulation by phosphoprotein phosphatase inhibitor 1 (inhibitor-1)

Dual effect of cAMP

PKA: activate phosphorylase & inhibitor-1

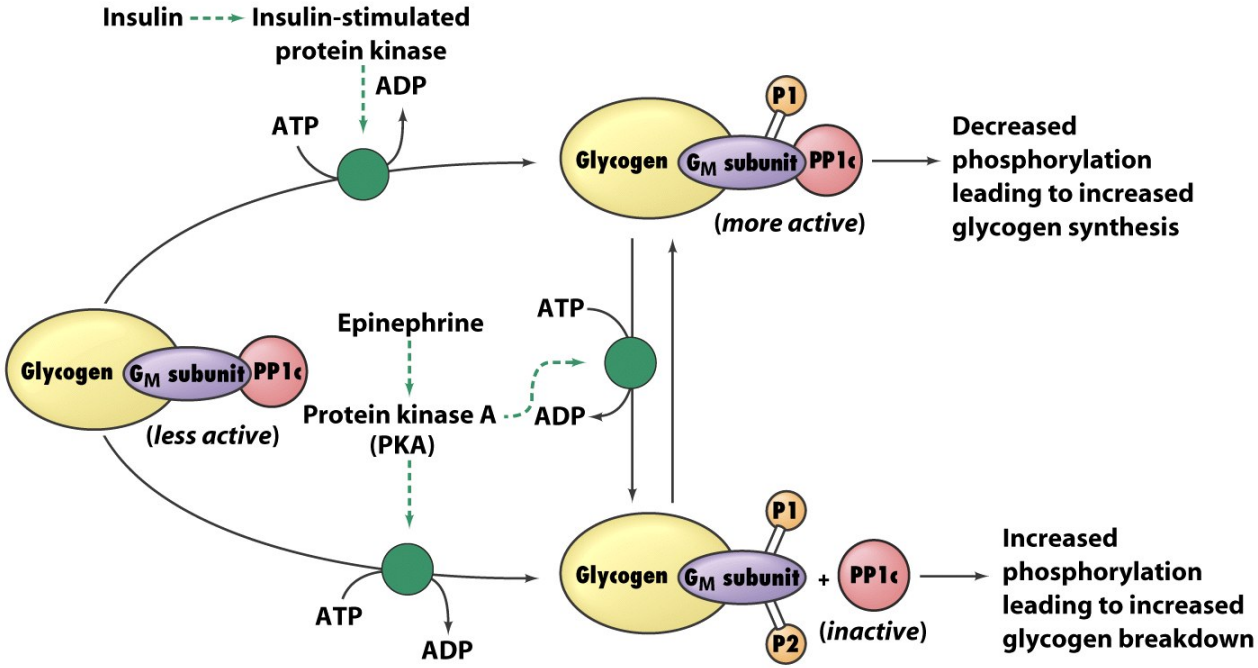
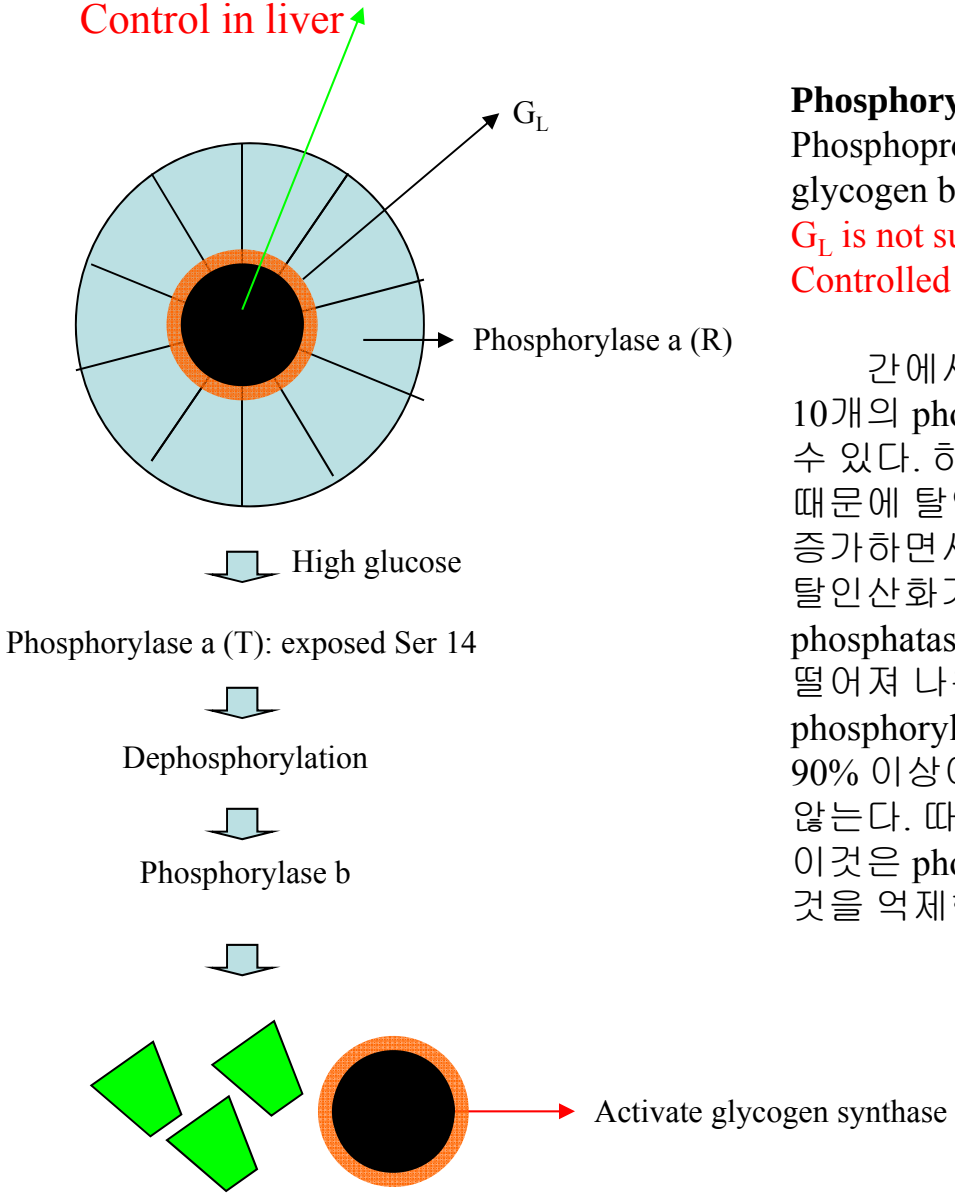


Figure 15-20 Fundamentals of Biochemistry, 2/e

Phosphoprotein phosphatase-1

Control in liver



Phosphorylase a is a glucose sensor in liver

Phosphoprotein phosphatase-1 is bound to glycogen through glycogen binding subunit (G_L)

G_L is not subject to control via phosphorylation

Controlled by binding to phosphorylase a

간에서는 phosphorylase a에 결합된 상태로 조절된다 (보통 10개의 phosphorylase a에 1개꼴로 존재). T와 R 모두에 결합할 수 있다. 하지만 R form의 경우는 Ser14 잔기가 감추어져 있기 때문에 탈인산화가 일어나지 않는다. glucose의 농도가 증가하면서 T form으로 전환되면 Ser14가 노출되면서 탈인산화가 일어나 phosphorylase b로 전환된다. 이것은 phosphatase-1와의 친화력이 떨어지기 때문에 phosphatase-1은 떨어져 나온다. 그렇지만 phosphatase-1은 보통 10개의 phosphorylase a에 1개꼴로 존재하기 때문에 phosphorylase의 90% 이상이 phosphorylase b로 바뀌기 전에는 완전히 떨어지지 않는다. 따라서 glycogen synthase를 활성화시키지 못한다. 이것은 phosphorylase와 glycogen synthase가 동시에 활성화되는 것을 억제한다.

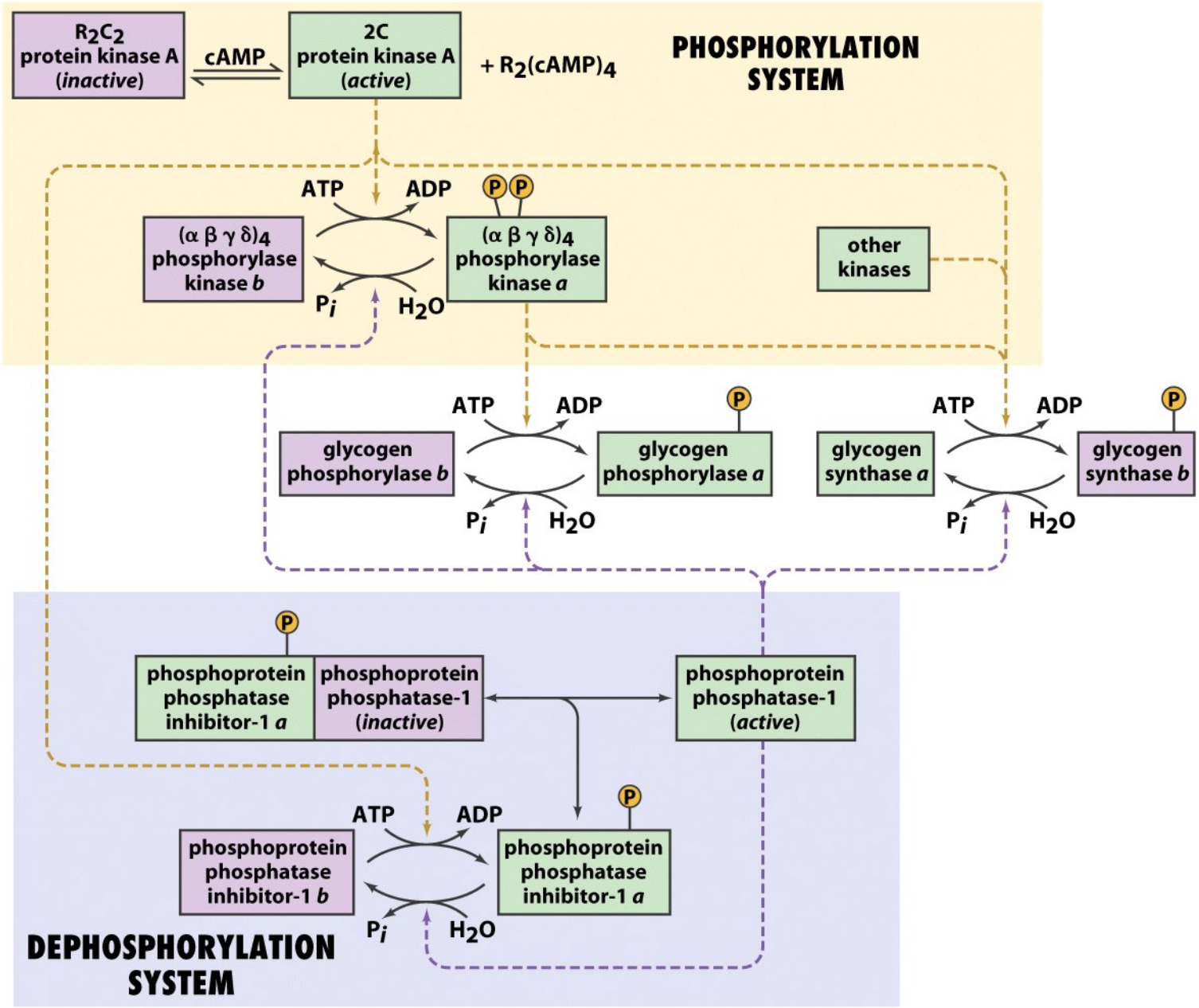
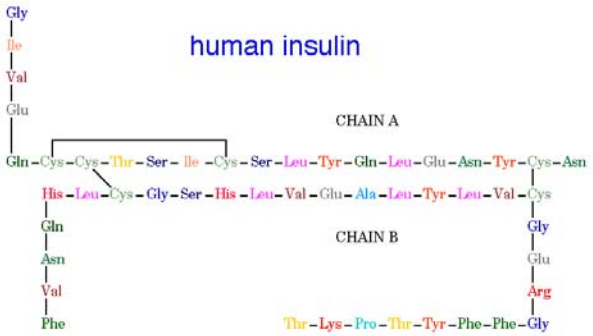


Figure 15-21 Fundamentals of Biochemistry, 2/e

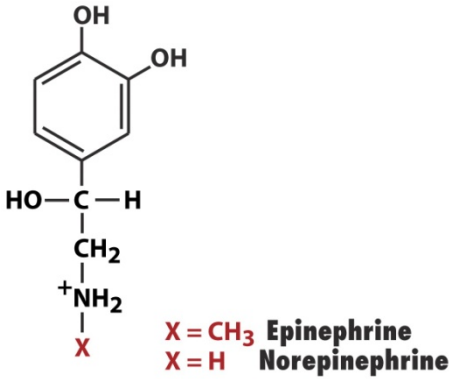
Hormonal effects on glycogen metabolism

Insulin & glucagon: control blood glucose

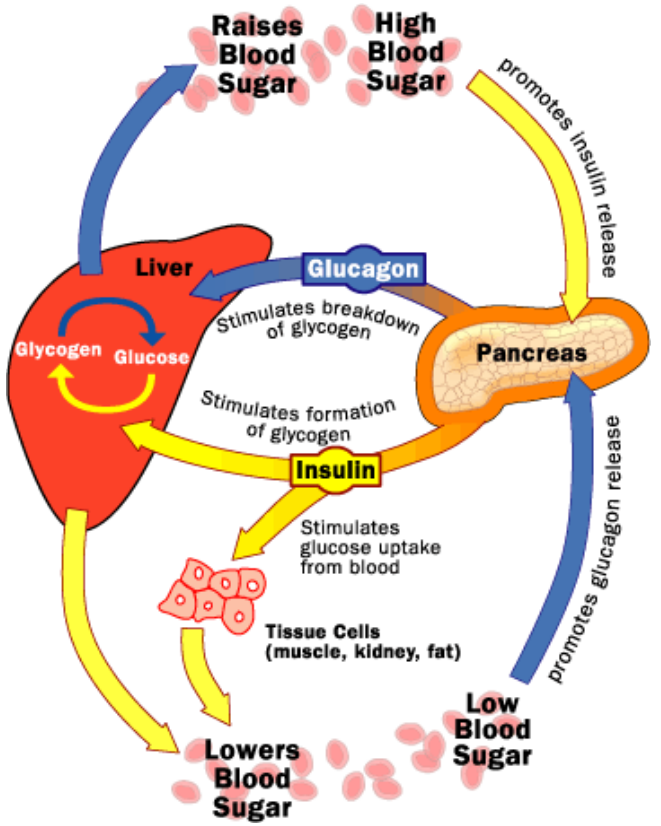
Epinephrine & norepinephrine (in response to stress) from adrenal gland

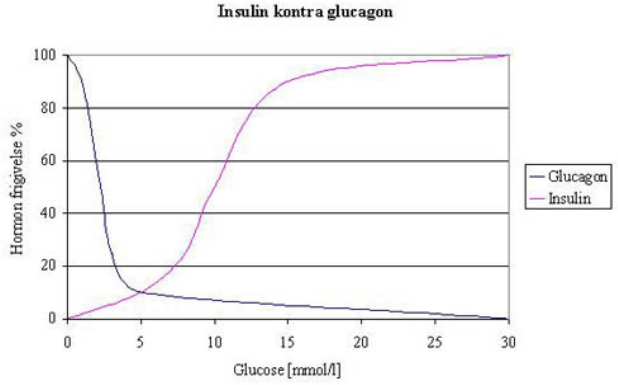


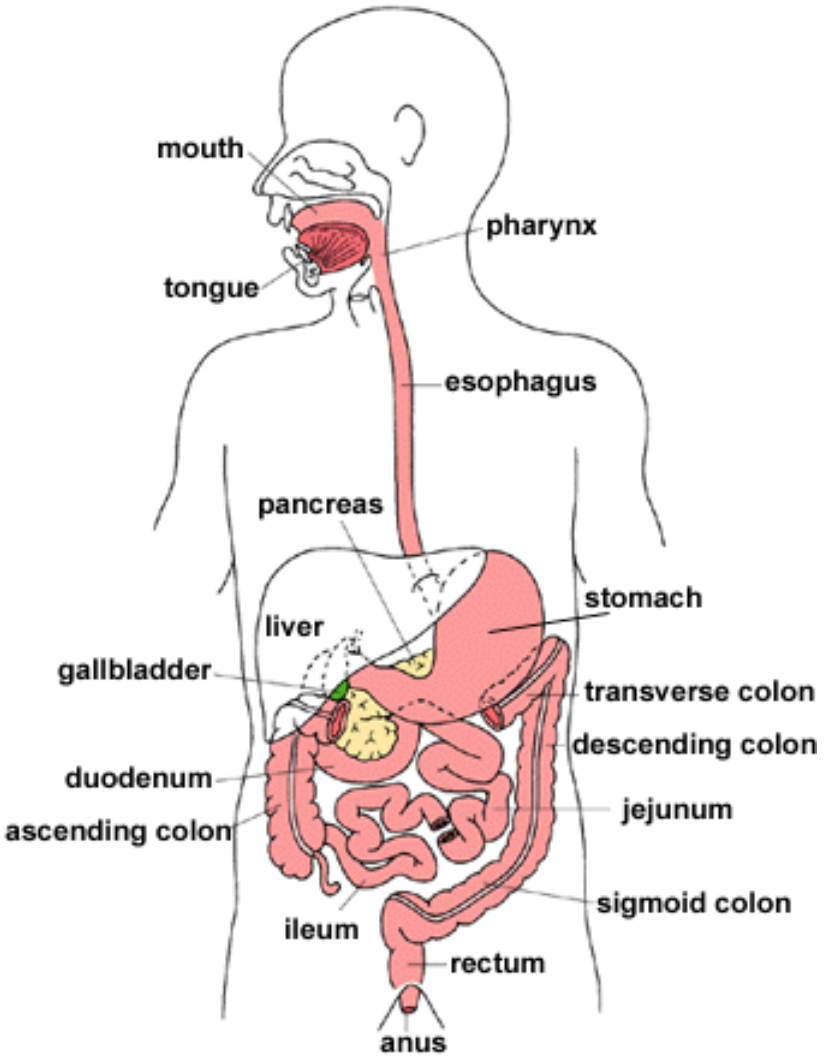
Unnumbered figure pg 497 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

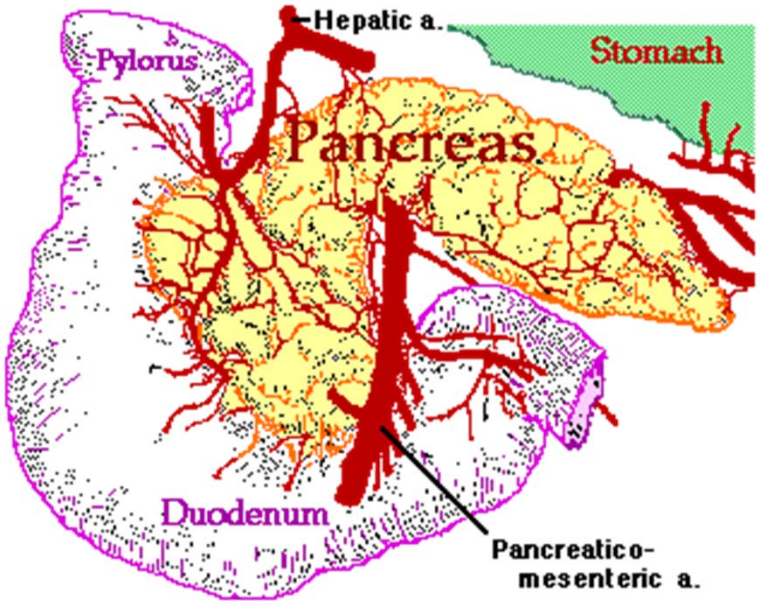


Unnumbered figure pg 498 Fundamentals of Biochemistry, 2/e
© 2006 John Wiley & Sons

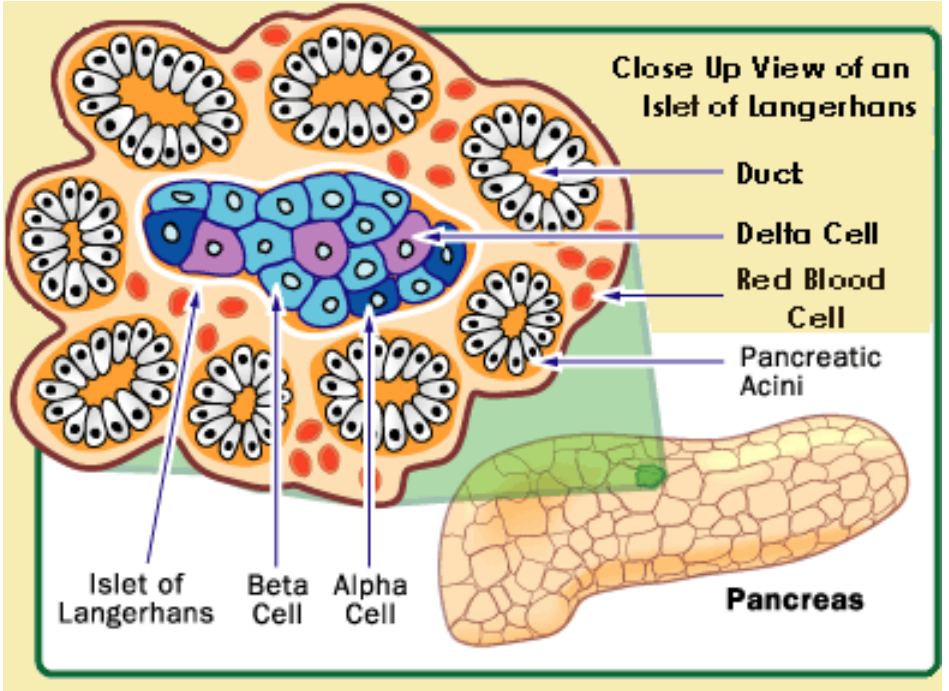








α-cells: glucagon
β-cells: insulin



Stimulate pancreas to secrete glucagon

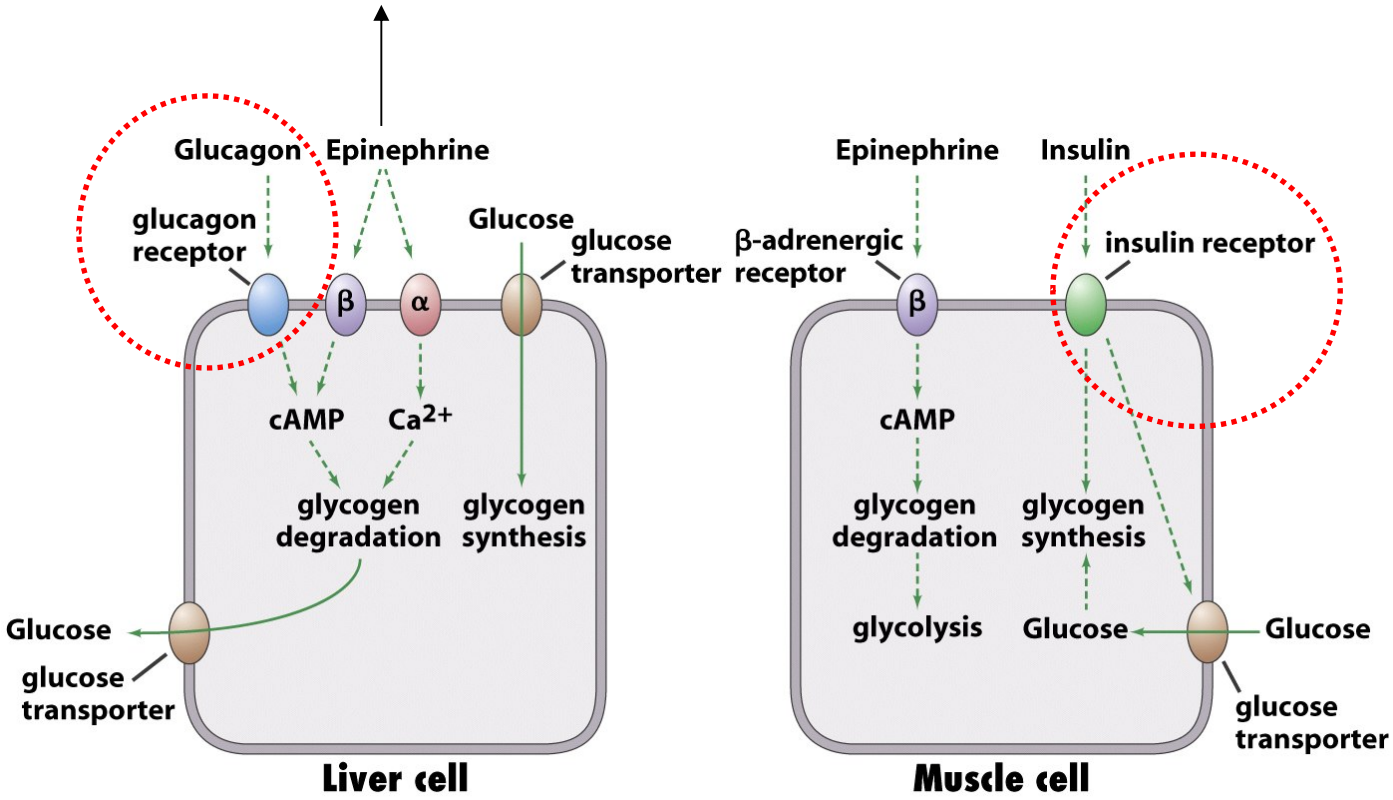
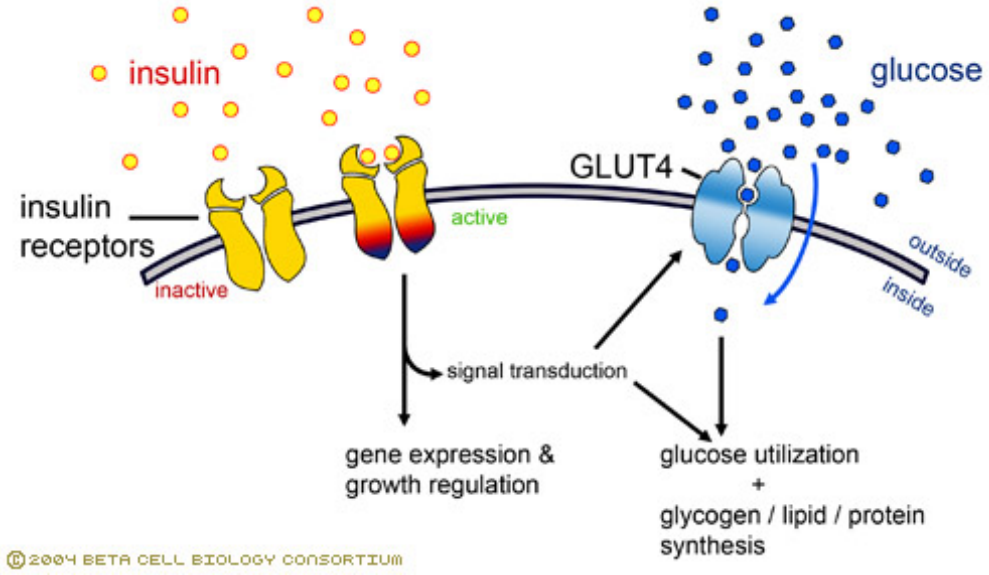


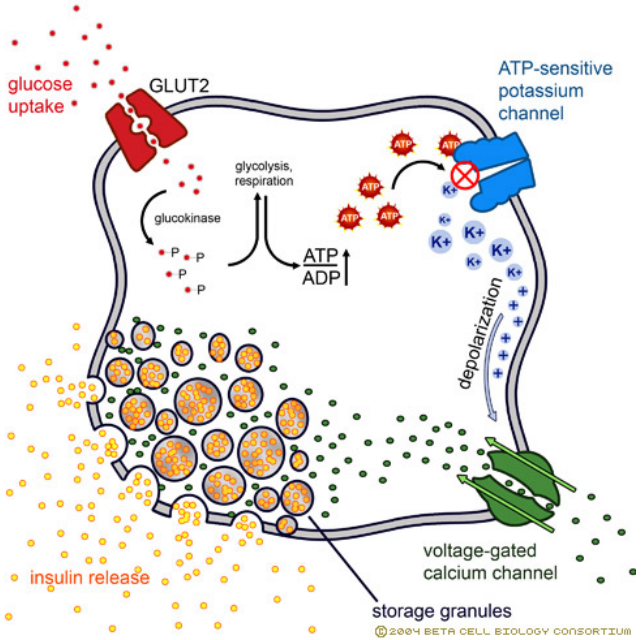
Figure 15-22 Fundamentals of Biochemistry, 2/e

Adrenergic receptors: β-adrenergic (cAMP, Gs coupled), α-adrenergic (calcium ion, Gi coupled) GPCRs

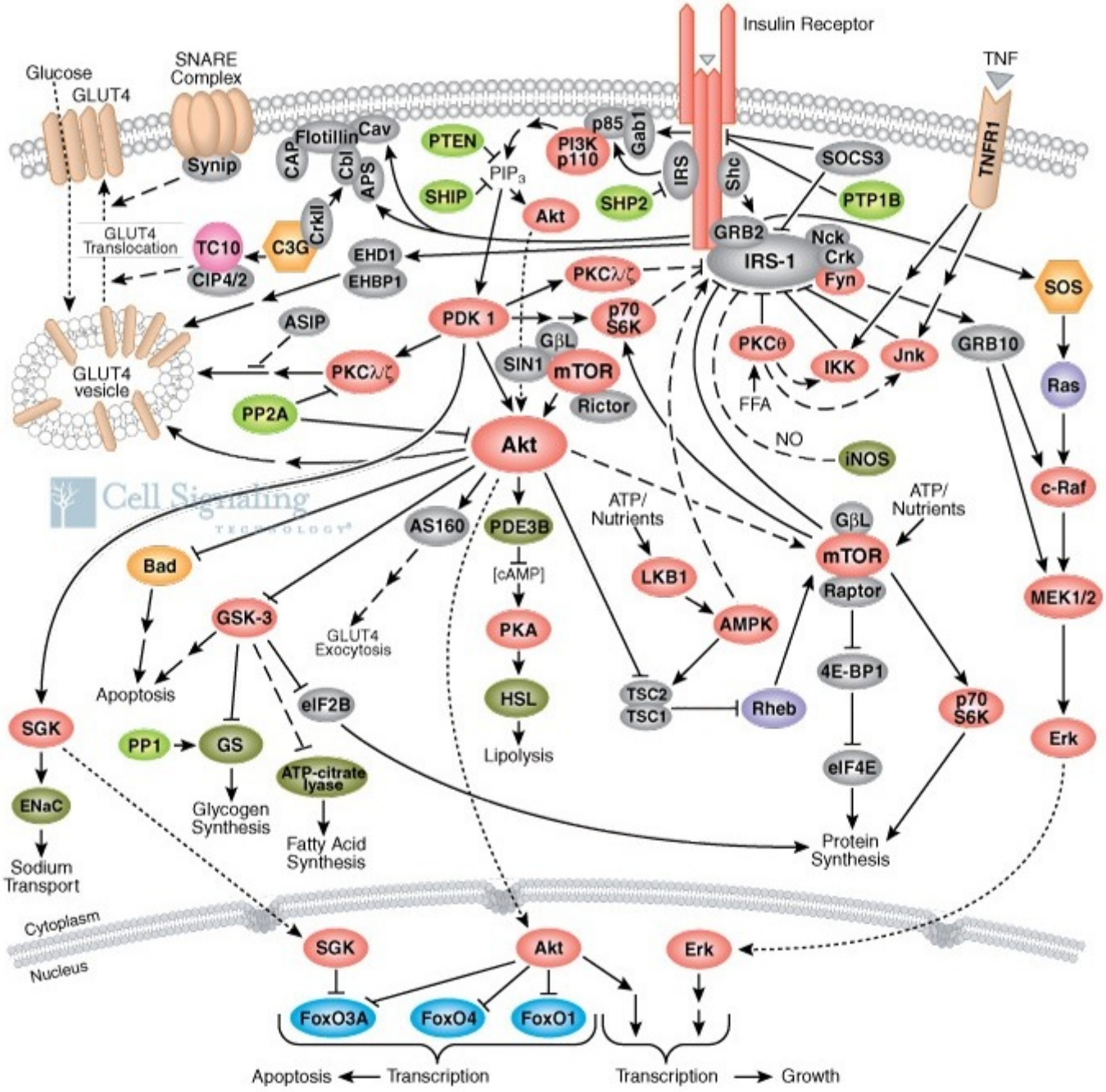
Insulin receptors:

- The receptors for insulin are found on most mammalian cells – action of insulin is mediated through these receptors.
- Impaired action of insulin can result from defects in the receptors or defects in post-receptor events.

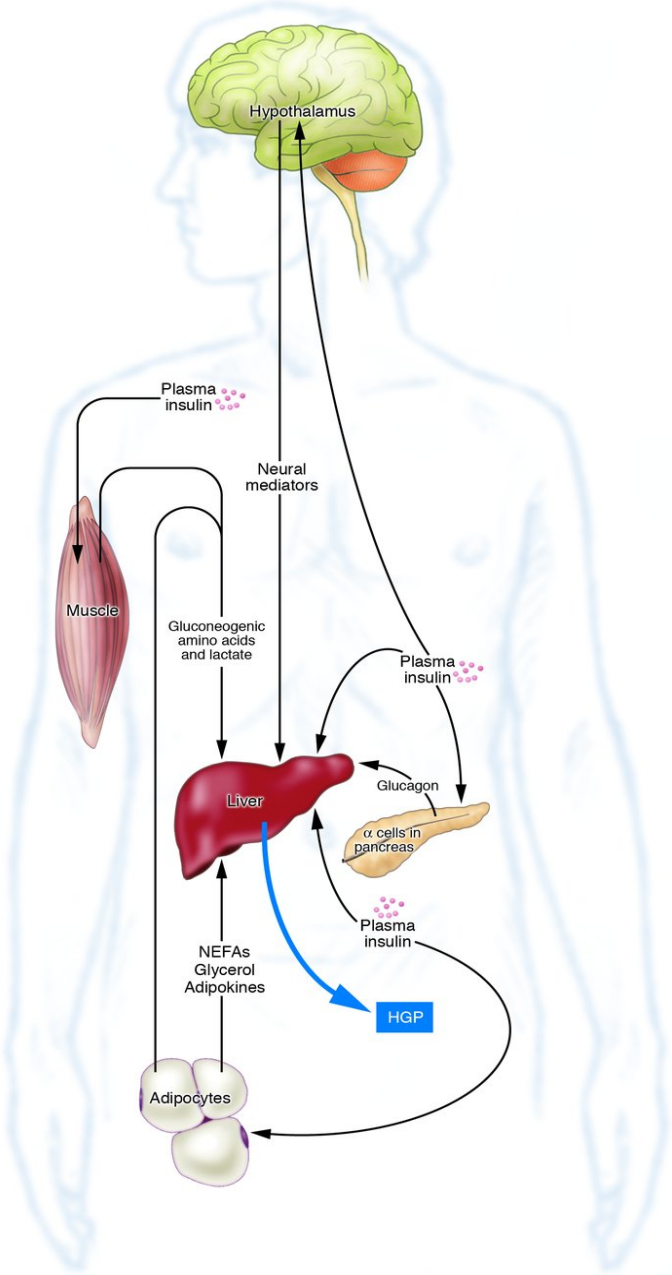




Signal transduction: insulin receptor pathway



Mechanisms by which insulin can inhibit hepatic glucose production in vivo.



The inability of insulin to suppress hepatic glucose production (HGP) is a key defect found in type 2 diabetes. Insulin inhibits HGP through both direct and indirect means, the latter of which include inhibition of glucagon secretion, reduction in plasma nonesterified fatty acid level, decrease in the load of gluconeogenic substrates reaching the liver, and change in neural signaling to the liver. Two studies in this issue of the *JCI* demonstrate that selective changes in the expression of insulin receptors in mouse liver do not have a detectable effect on the ability of insulin to inhibit HGP (see the related articles beginning on pages 1306 and 1314). These provocative data suggest that the indirect effects of insulin on the liver are the primary determinant of HGP in mice.
J Clin Invest. 2005;115(5):1136–1139