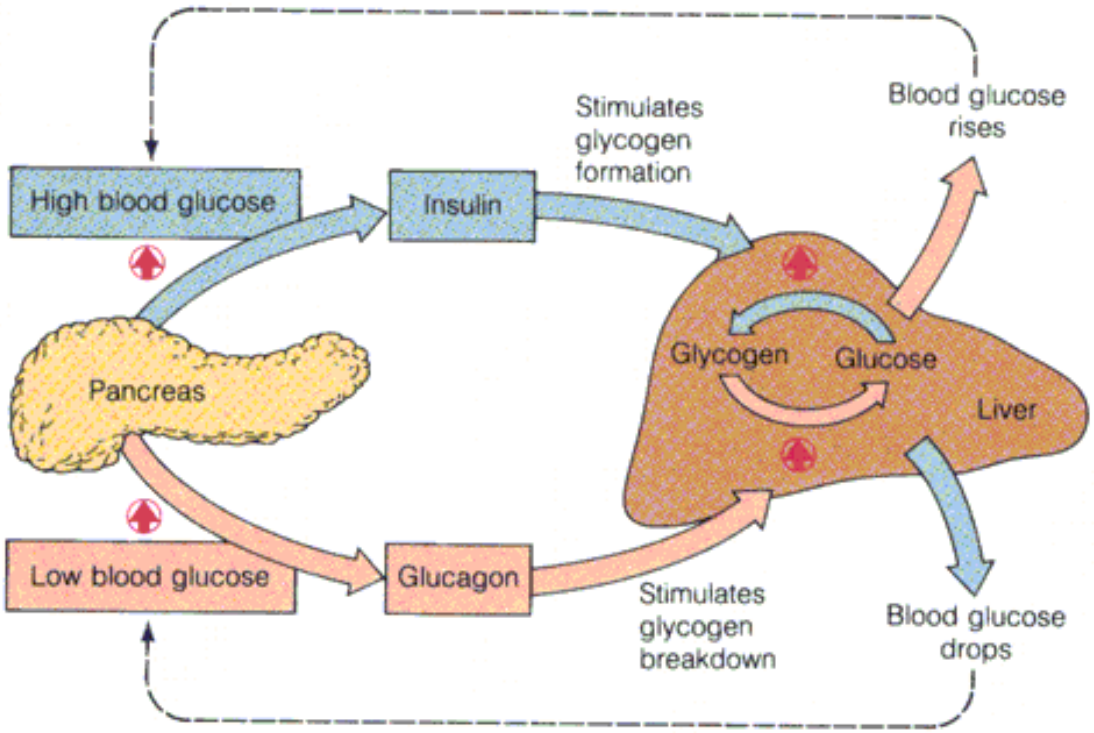
8. REGULATION OF FUEL METABOLISM

(CHAPTER 15, 23 LEHNINGER)

HORMONAL REGULATION OF FUEL METABOLISM

- Animals must maintain blood glucose levels within rather narrow limits to ensure proper functioning of the nervous system.
- The liver plays a major role in this process.
- The amounts of glucose available to the blood vary with the nutritional status. In response to dietary glucose, homeostatic mechanisms come into play to promote uptake of glucose into cells and its use by tissues, thereby lowering glucose in the blood. When glucose levels fall, several hours after a meal, other mechanisms promote both glucose release, from intracellular glycogen stores, and gluconeogenesis, so that the normal level is maintained. Some of the homeostatic mechanisms are regulated hormonally.
- The most important hormone promoting glucose uptake and use is insulin, whereas both glucagon and epinephrine act conversely, to increase blood glucose levels.



HORMONAL REGULATION OF FUEL METABOLISM

What Hormones Regulate Metabolism?

- Insulin
- Glucagon
- Epinephrine (adrenaline)
- Thyroid hormone
- Cortisol

Most regulation occurs in order to maintain stable blood glucose concentrations for supplying fuel to the brain!

INSULIN PRODUCTION AND RELEASE

1. Glucose is transported In the pancreas cells through GLUT2 transporter
2. It is converted into glucose 6-phosphate by hexokinase IV and catabolised through glycolisis
3. The increase in glucose catabolism leads to an increase in ATP concentration that close the K+ channels => membrane depolarization that causes the opening of Ca^{2+} channels
4. Intracellular Ca^{2+} concentration increases and
5. Induces the release of insulin through exocytosis

A feedback inhibition mechanism (decrease in hexokinase activity) stops insulin release

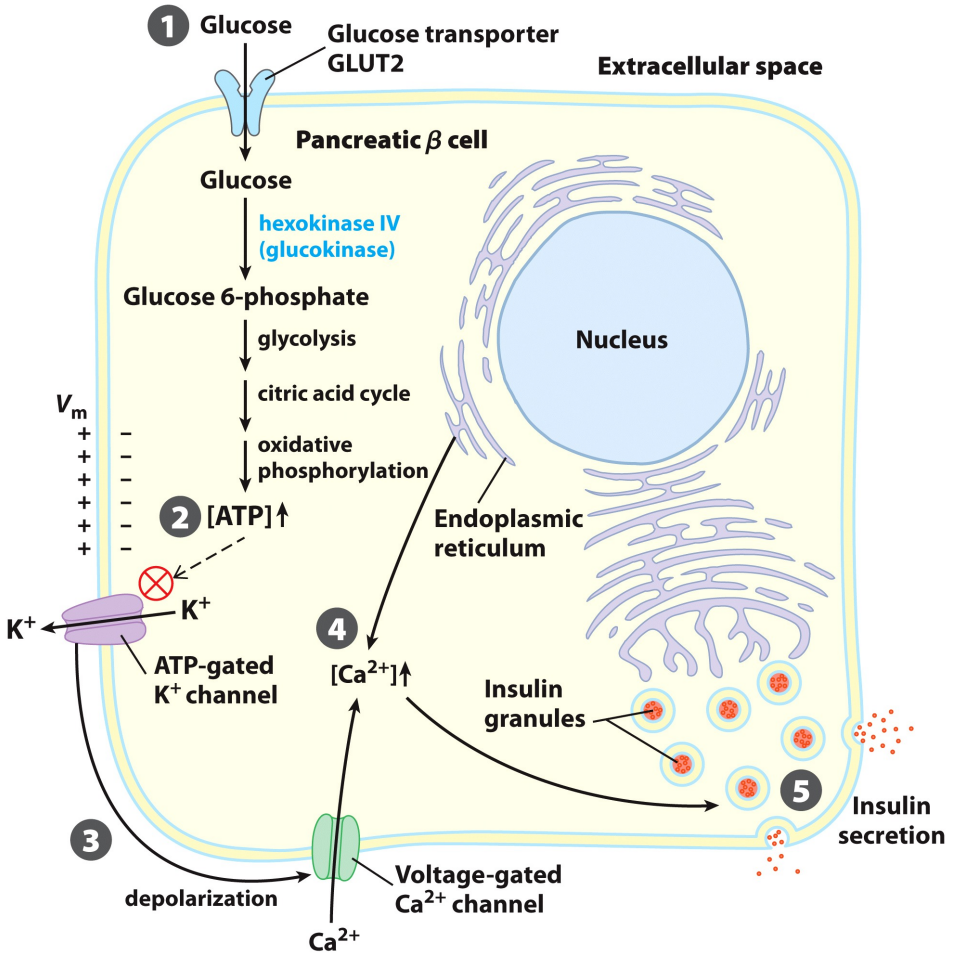


Figure 23-27
Lehninger Principles of Biochemistry, Sixth Edition

HIGH LEVELES OF GLUCOSE

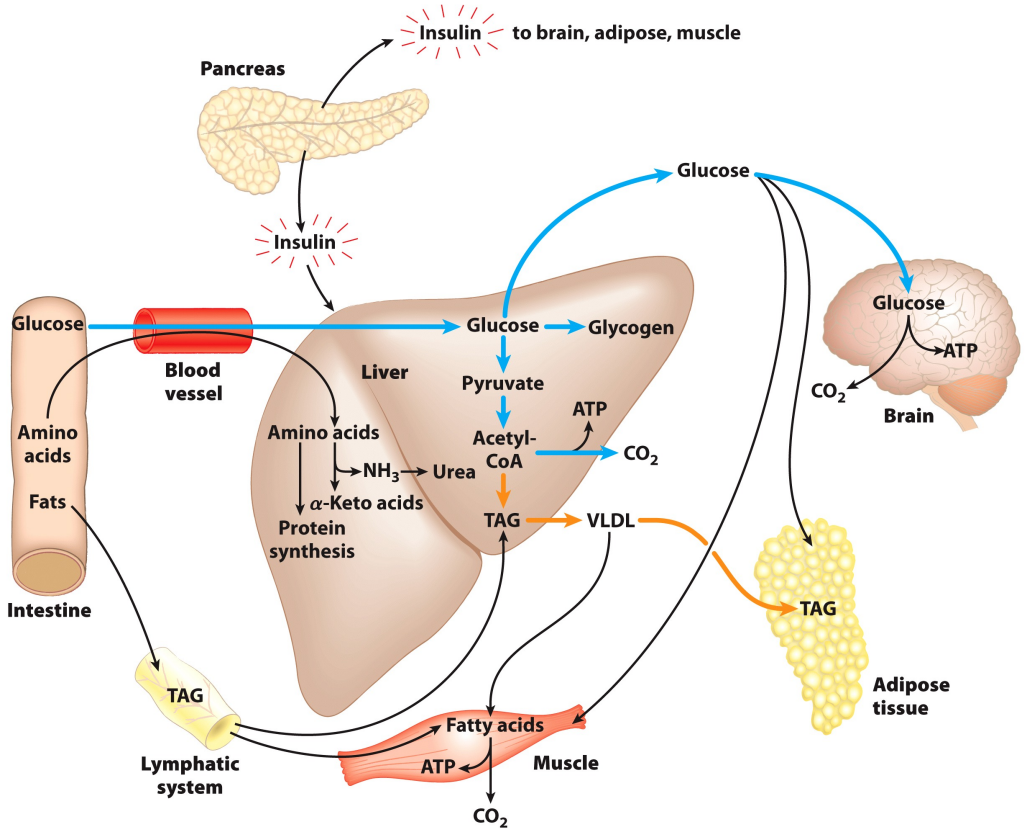


Figure 23-25
Lehninger Principles of Biochemistry, Sixth Edition

Insulin is released and:

1. Stimulates glucose uptake into tissues;
2. Part of glucose is used by brain;
3. In the liver part of glucose is stored as glycogen, part is converted in acetyl-CoA, used for fatty acids synthesis;
4. Fatty acids are transported to muscle and adipose tissue;
5. NADPH necessary for lipid biosynthesis is provided by glucose oxidation through pentose phosphate pathway;
6. Excess of amino acids are converted into pyruvate and acetyl-Coa, used for lipid biosynthesis;
7. Fats are adsorbed and transported by chylomicrons to muscle and adipose tissue.

HIGH LEVELES OF GLUCOSE

Insulin is a 5.8-kilodalton protein hormone synthesized in the so-called β cells, which are endocrine cells in the pancreas.

Insulin promotes

1. Uptake of fuel substrates into some cells;

2. Storage of fuels (lipids and glycogen); and

3. Biosynthesis of macromolecules (nucleic acids and protein).

Because insulin promotes biosynthesis, insulin can be considered a **growth hormone**. Specific effects of insulin include the following:

1. Increased uptake of glucose in muscle and adipose tissue;

2. Activation of glycolysis in liver;

3. Increased synthesis of fatty acids and triacylglycerols in liver and adipose tissue;

4. Inhibition of gluconeogenesis in liver;

5. Increased glycogen synthesis in liver and muscle;

6. Increased uptake of amino acids into muscle with consequent activation of muscle protein synthesis; and

7. Inhibition of protein degradation.

Insulin stimulates glucose uptake into muscle and adipose cells, at least partly by **translocating the glucose transporter** (a membrane protein that carries out facilitated diffusion of glucose) from the cytosol (where it resides in the absence of insulin) to the cell surface, in response to insulin.

TABLE 23–3 **Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen**

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2) ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

Table 23-3
Lehninger Principles of Biochemistry, Sixth Edition

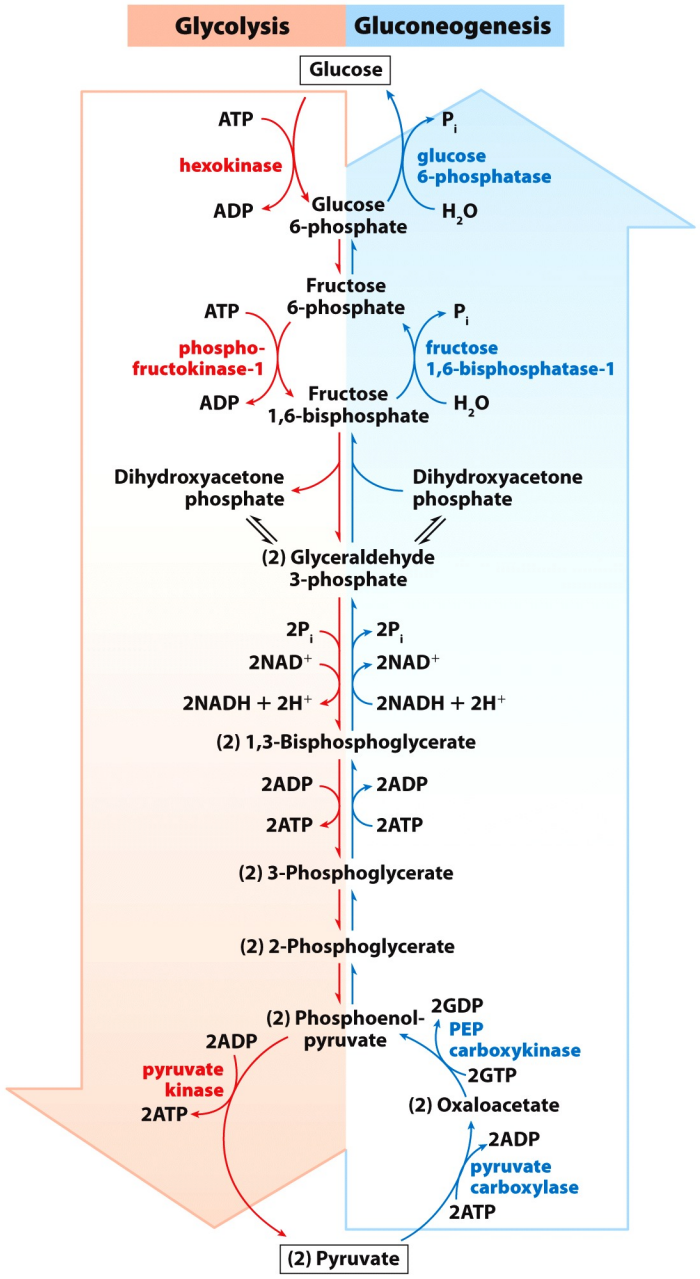


Figure 14-17
Lehninger Principles of Biochemistry, Sixth Edition

HIGH LEVELES OF GLUCOSE

1. Insulin inhibits transcription of the enzyme phosphoenolpyruvate carboxykinase (PEPCK). PEPCK is a key enzyme in gluconeogenesis and transcription is the primary means of regulating it. By inhibiting PEPCK transcription, insulin can depress glucose production tremendously. (Conversely, the hormone glucagon, which increases blood glucose levels, stimulates PEPCK transcription.)

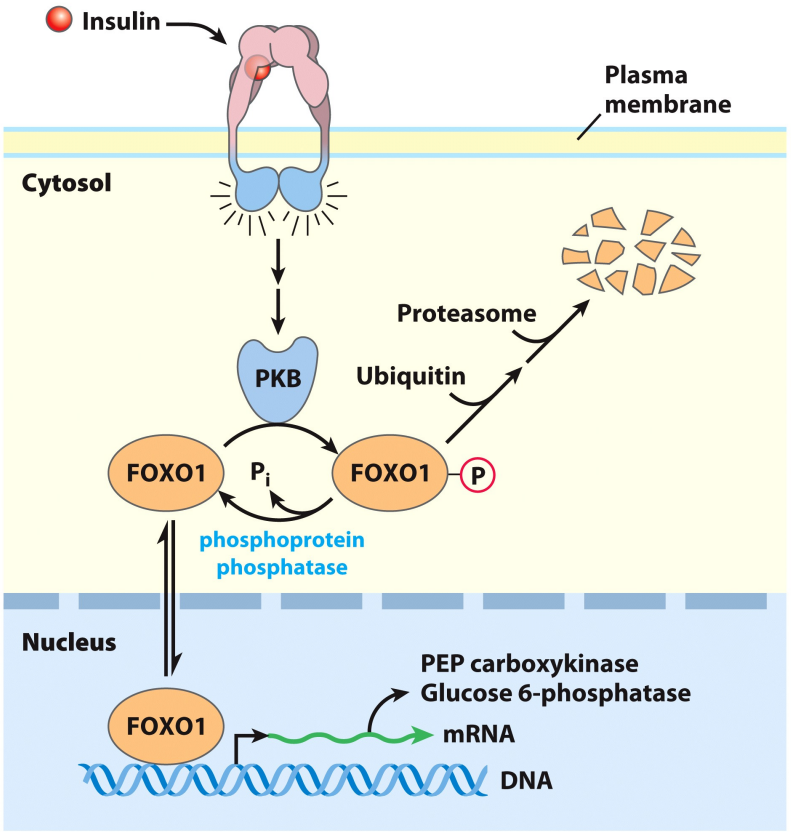


Figure 15-24
Lehninger Principles of Biochemistry, Sixth Edition

HIGH LEVELES OF GLUCOSE

2. Insulin stimulates translocation of the glucose transporter protein from cytosol to the cell surface. Glucose transport protein carries out the facilitated transport of glucose.

3. Insulin activates hexokinase

4. Insulin activates glycogen synthase

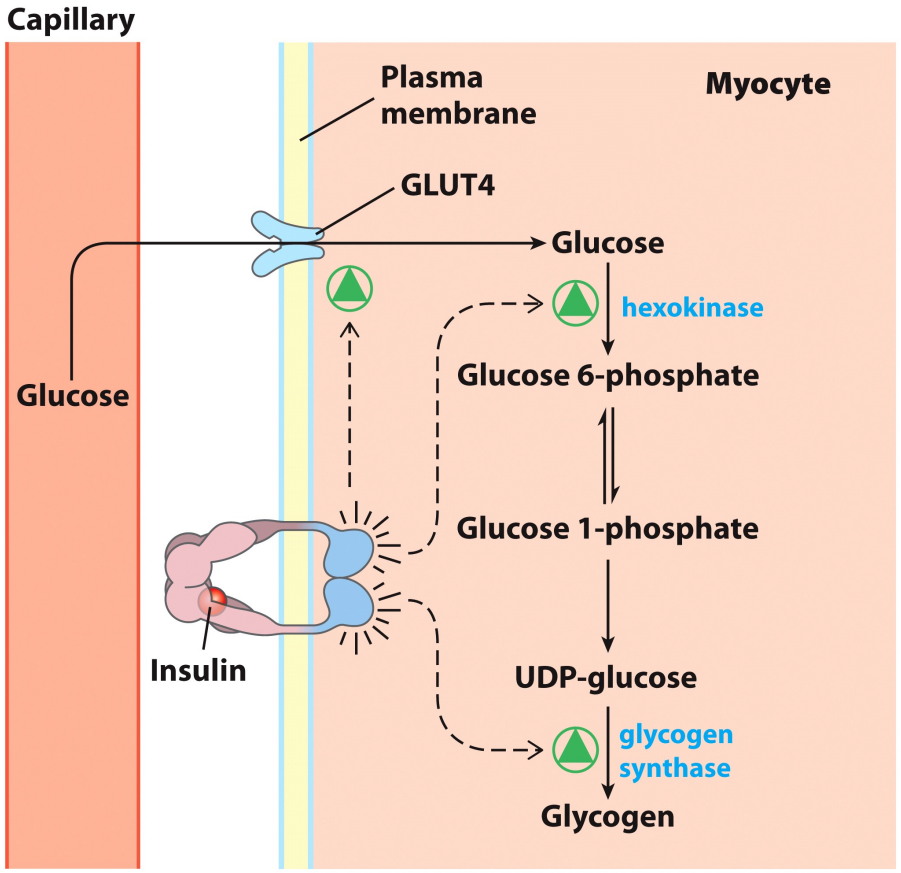


Figure 15-12
Lehninger Principles of Biochemistry, Sixth Edition

HIGH LEVELES OF GLUCOSE

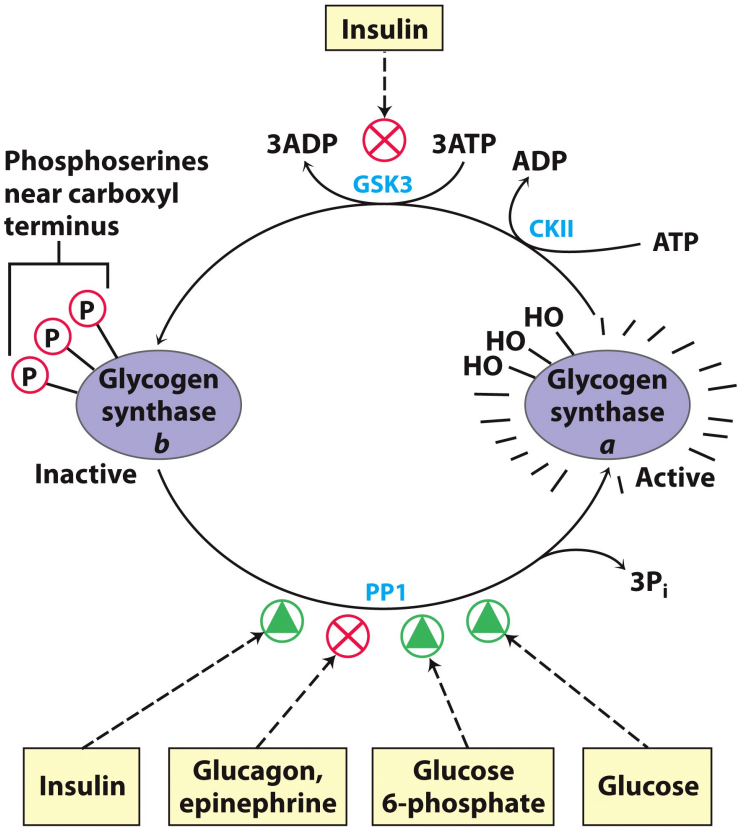


Figure 15-39
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

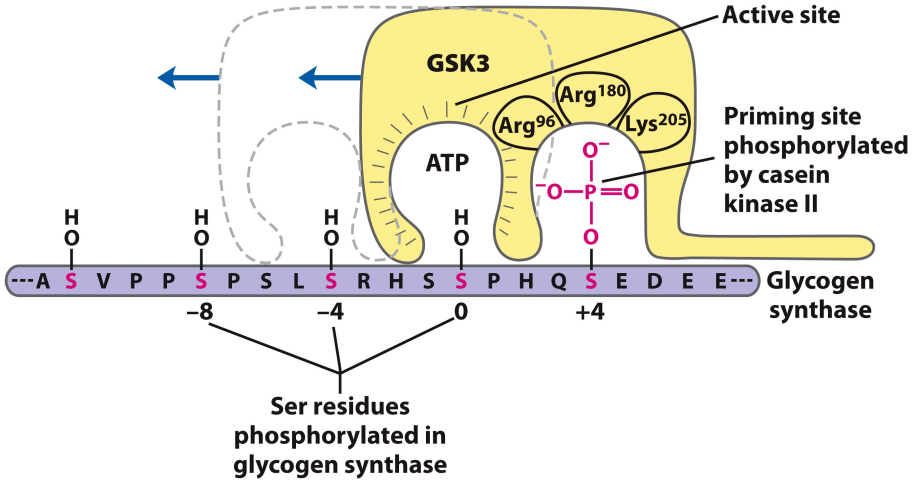


Figure 15-40a
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

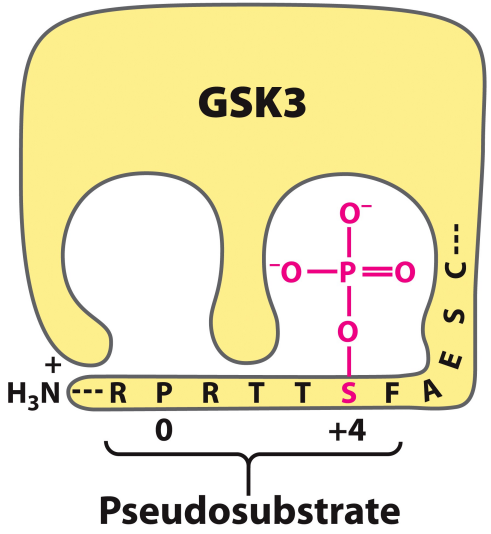


Figure 15-40b
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

- Glycogen synthase has 3 Ser residues at the C-term that can be phosphorylated by glycogen synthase kinase 3 (GSK3);
- Phosphorylation inactivates the enzyme;
- Insulin inhibits GSK3 and activates a phosphoprotein phosphatase (PP1 in muscle)

HIGH LEVELES OF GLUCOSE

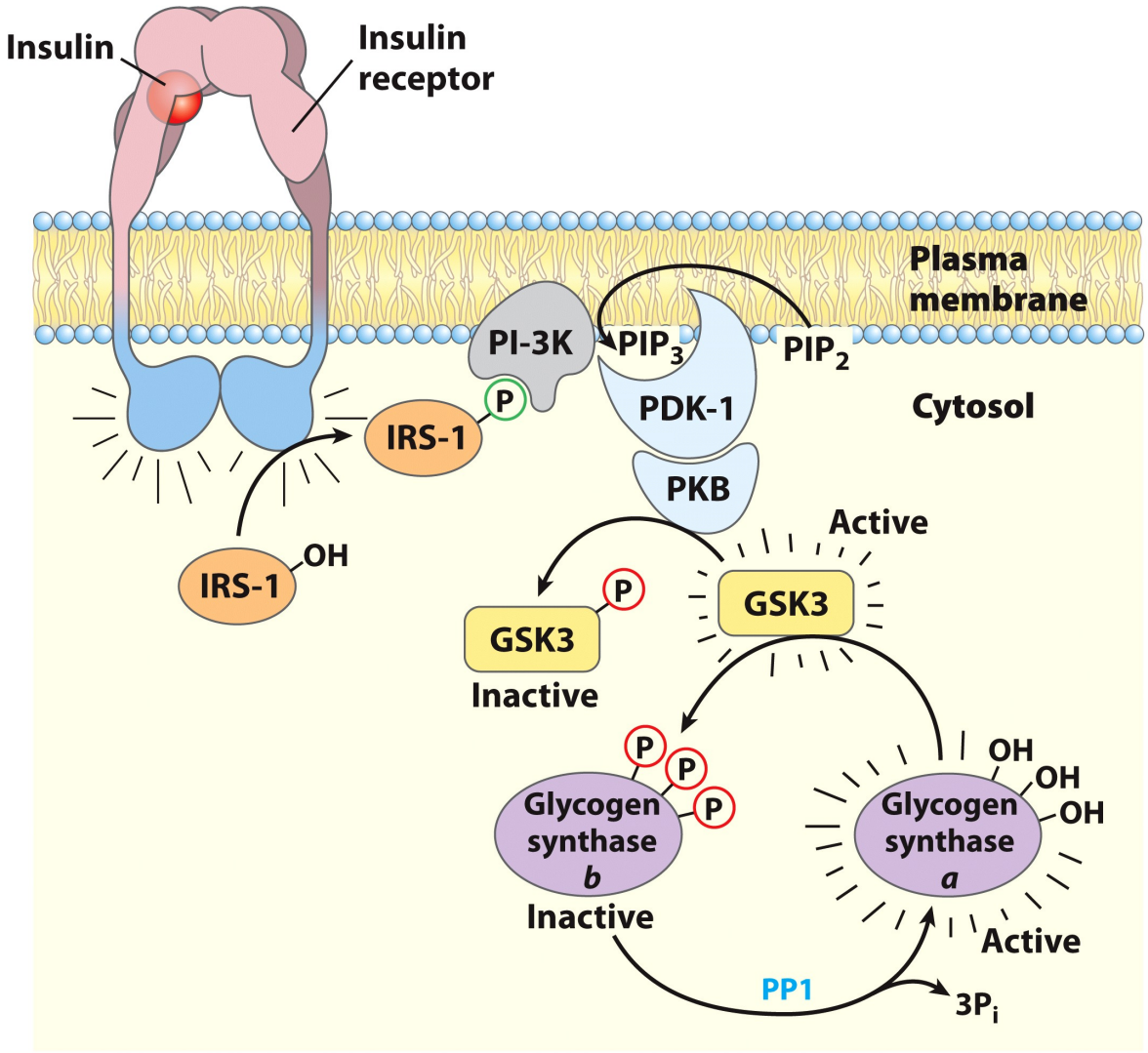


Figure 15-41
Lehninger Principles of Biochemistry, Sixth Edition

INSULIN RECEPTOR

- The insulin receptor is a glycoprotein with an $\alpha_2\beta_2$ tetrameric structure, stabilized by disulfide bonds.
- Both the α chain (735 residues) and the β chain (620 residues) are translated from a single mRNA, giving a polypeptide chain that then undergoes proteolytic processing.
- The α chain, which is thought not to span the membrane, is believed to bind insulin near its C-terminus. The β chain has a transmembrane domain, with its C-terminus in the cell interior.
- The C-terminal region of the β-chain is the site of a protein tyrosine kinase activity, which is stimulated by the binding of insulin to the extracellular part of the receptor.
- The kinase activity of insulin receptor is essential to its biological activity, because some cases of non-insulin-dependent diabetes are associated with receptor mutations that abolish the kinase activity.

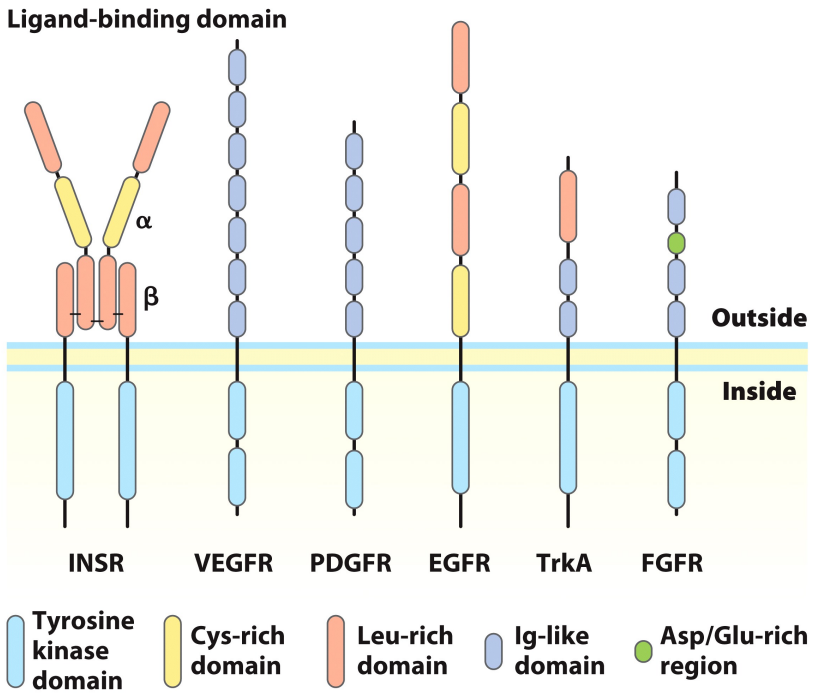


Figure 12-17
Lehninger Principles of Biochemistry, Sixth Edition

INSULIN RECEPTOR

- Insulin binds causing a conformational change transmitted via the transmembrane portion to the intracellular domains;
- The two tyrosine kinase domains are activated upon insulin binding to the receptor and phosphorylate each other on 3 tyrosine residues;
- In the inactive state (c), the loop containing the 3 tyr rsidues covers the site for other proteins to be phosphrylated;
- This conformation is stabilised by a hydrogen bond between a Tyr and a Asp residues;
- When phosphorylated, the loops moves 30 Å away from the site where other proteins can bind and get phosphorylated.

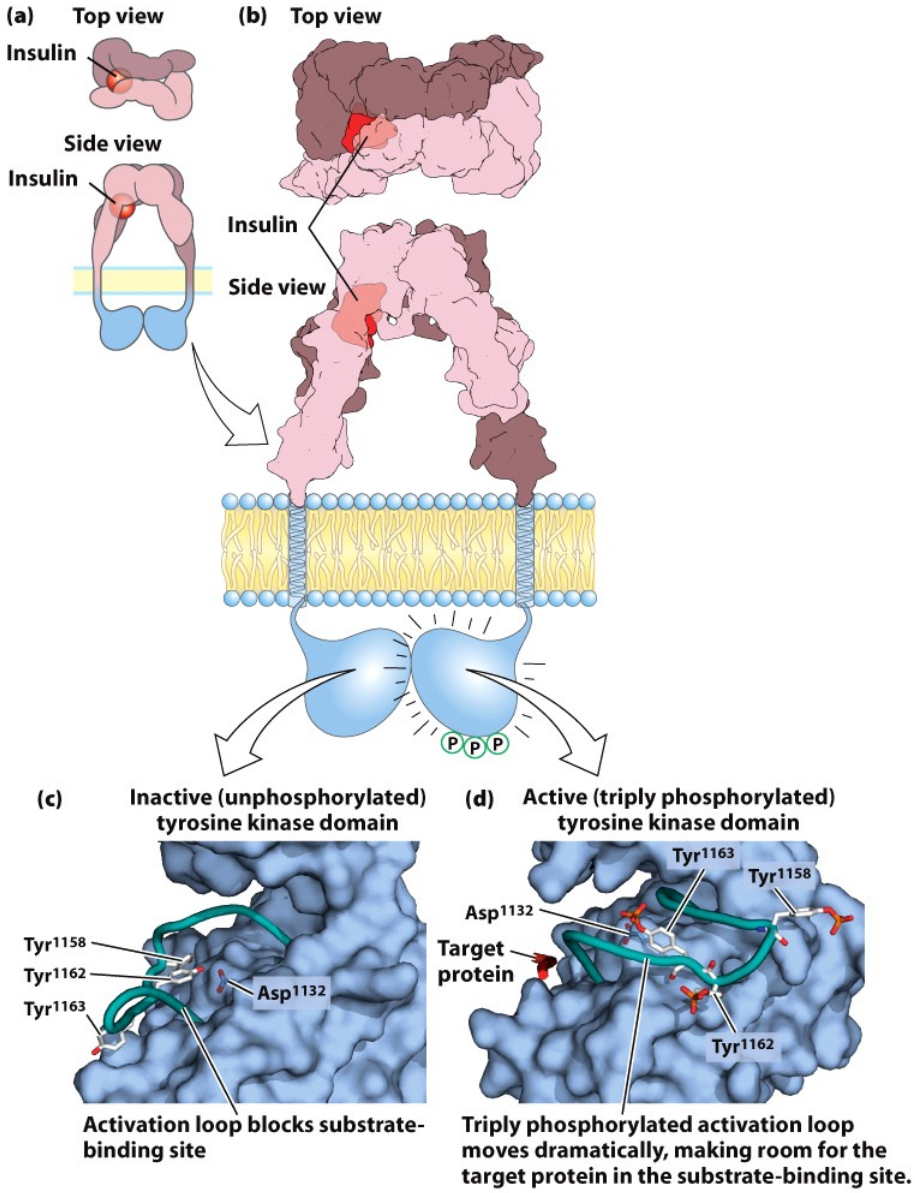


Figure 12-14
Lehninger Principles of Biochemistry, Sixth Edition

INSULIN AS A GROWTH FACTOR

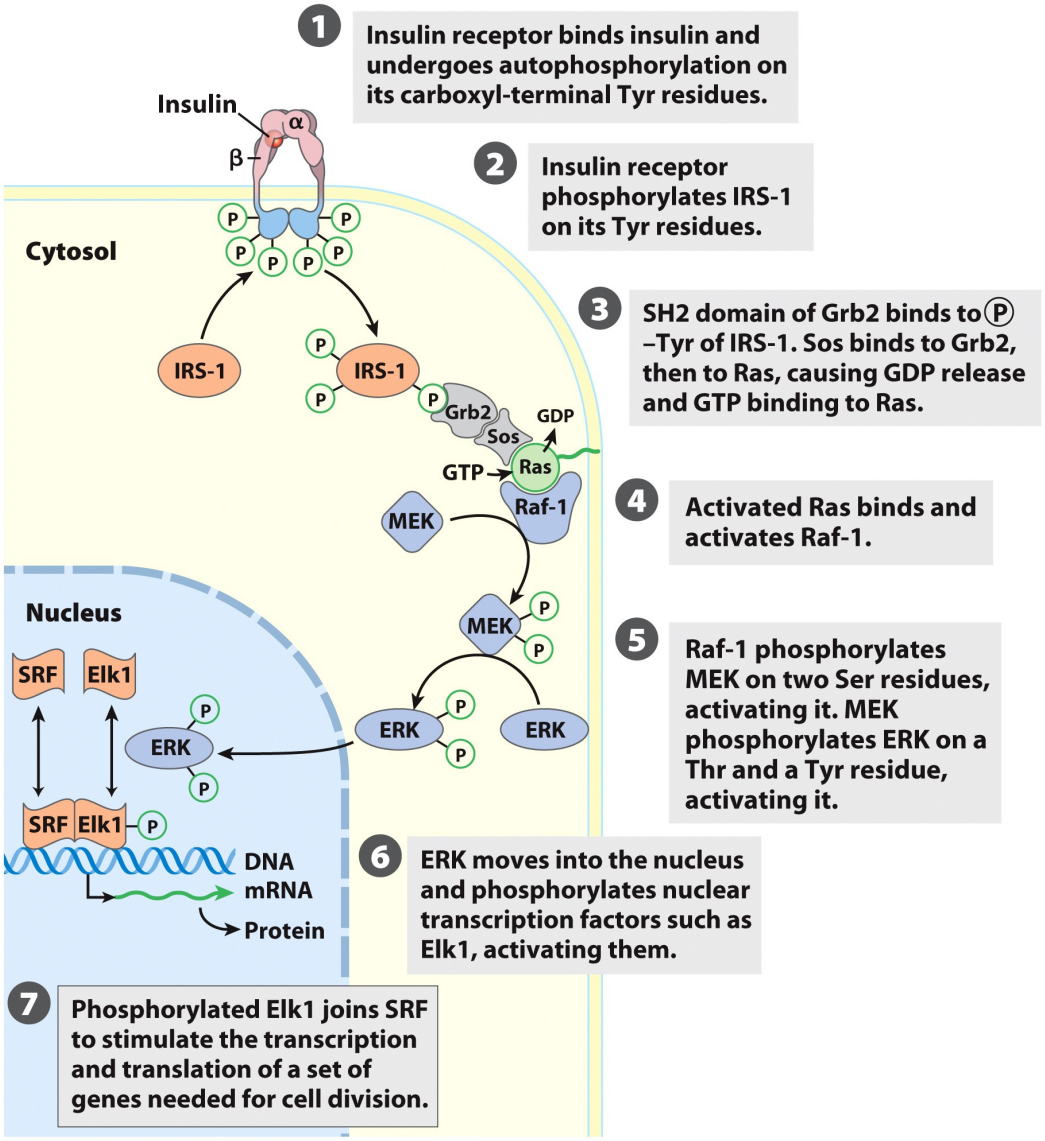
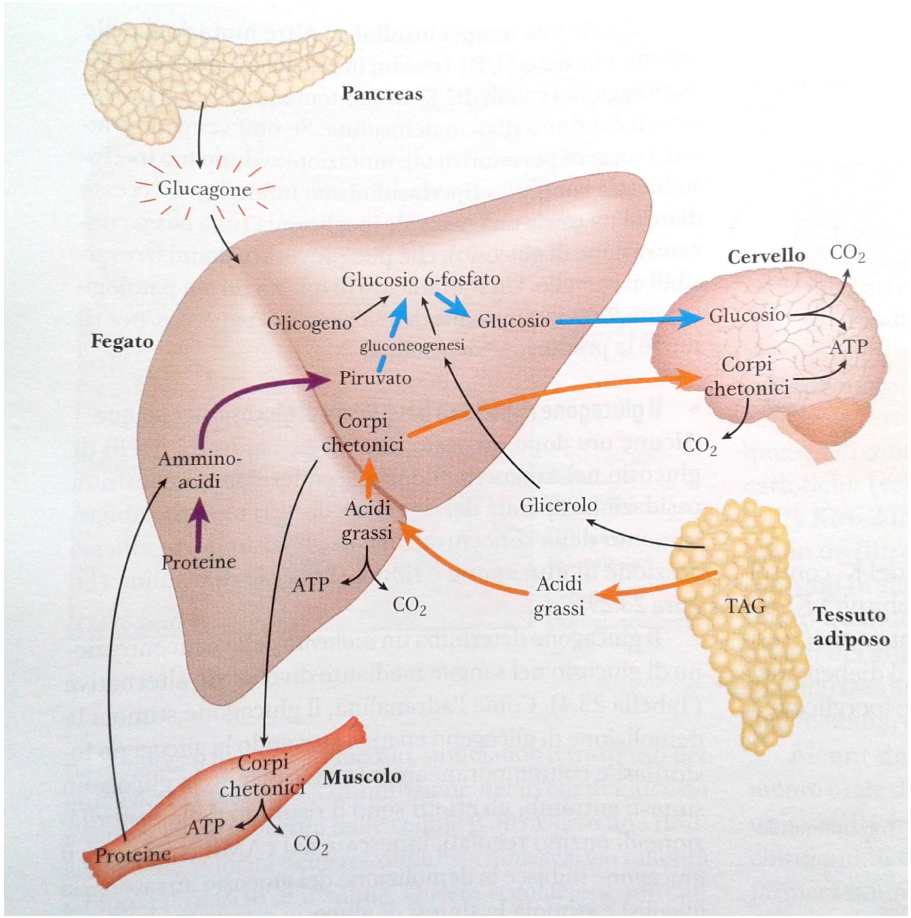


Figure 12-15
Lehninger Principles of Biochemistry, Sixth Edition

LOW LEVELS OF GLUCOSE



- After few hours after meal, liver provides glucose to brain
- Glycogen is degraded and G 1-P converted into G 6-P, dephosphorylated and sent to brain.
- Amino acids and glycerol from triacylglycerols are used for gluconeogenesis
- For liver, fatty acids are used as fuel and acetyl-CoA is partially converted to ketone bodies

LOW LEVELS OF GLUCOSE

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

TABLE 23–6 Physiological and Metabolic Effects of Epinephrine: Preparation for Action

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

Table 23-6
Lehninger Principles of Biochemistry, Sixth Edition

LOW LEVELS OF GLUCOSE

- Glycogen breakdown (and synthesis) is regulated by hormones.
- Epinephrine (also called adrenalin) and glucagon stimulate breakdown. Insulin stimulates synthesis.
- Breakdown occurs as a result of a kinase cascade that arises from binding of the appropriate hormone to the appropriate cell surface receptor. Recall that a regulatory cascade is a process in which the intensity of an initial regulatory signal is amplified many folds through a series of enzyme activations.
- The cascade depicted in the figure provides a way for cells to rapidly turn on glycogen breakdown and release of glucose. This is useful in emergency situations (e.g., the need to catch prey or the need to avoid being caught).

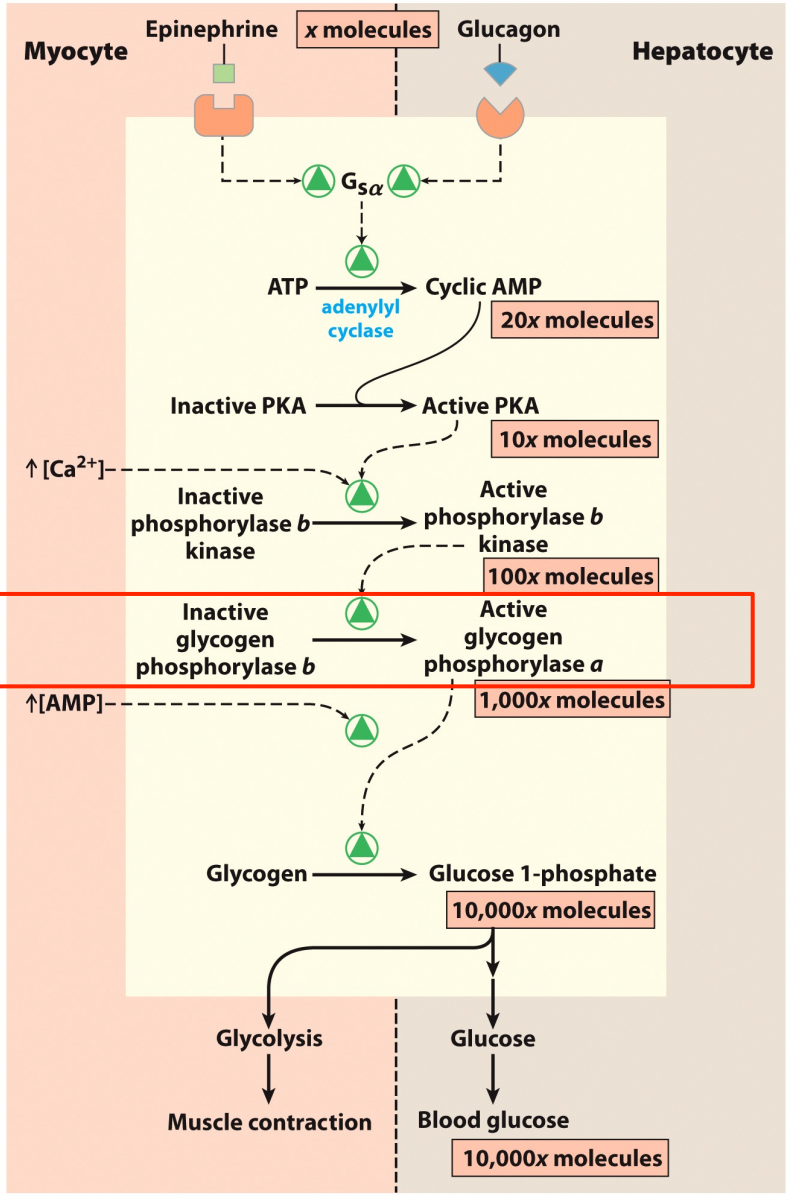


Figure 15-37
Lehninger Principles of Biochemistry, Sixth Edition

GLYCOGEN PHOSPHORYLASE

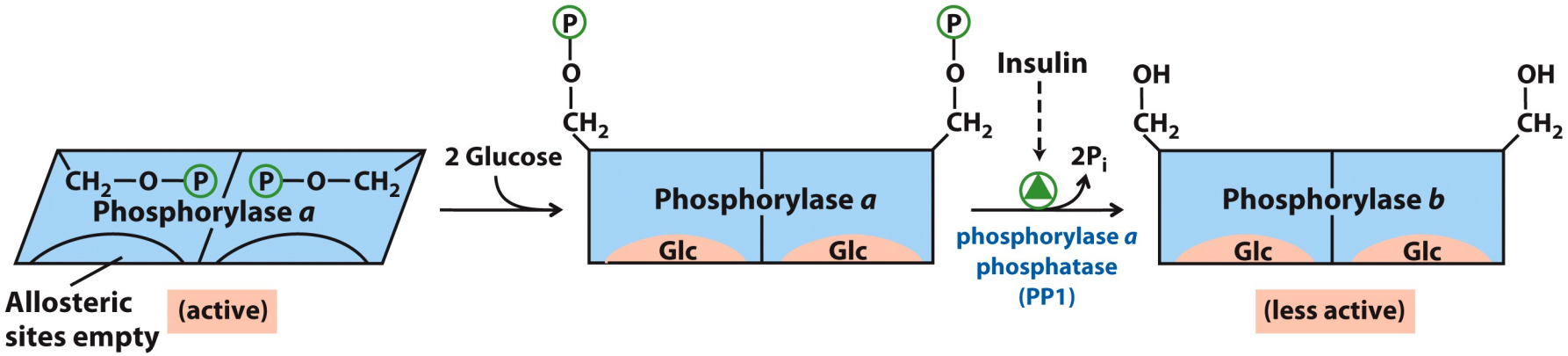


Figure 15-38
Lehninger Principles of Biochemistry, Sixth Edition

- Glucose is an allosteric regulator of phosphorylase in the liver
- Glucose binding induces a conformational change so that the protein exposes the phosphoserine residues to the action of PP1
- Dephosphprylation decreases the activity of the enzyme so that glycogen degradation is inhibited as a consequence of a high glucose concentration.
- Insulin acts also by stimulating PP1

STARVATION

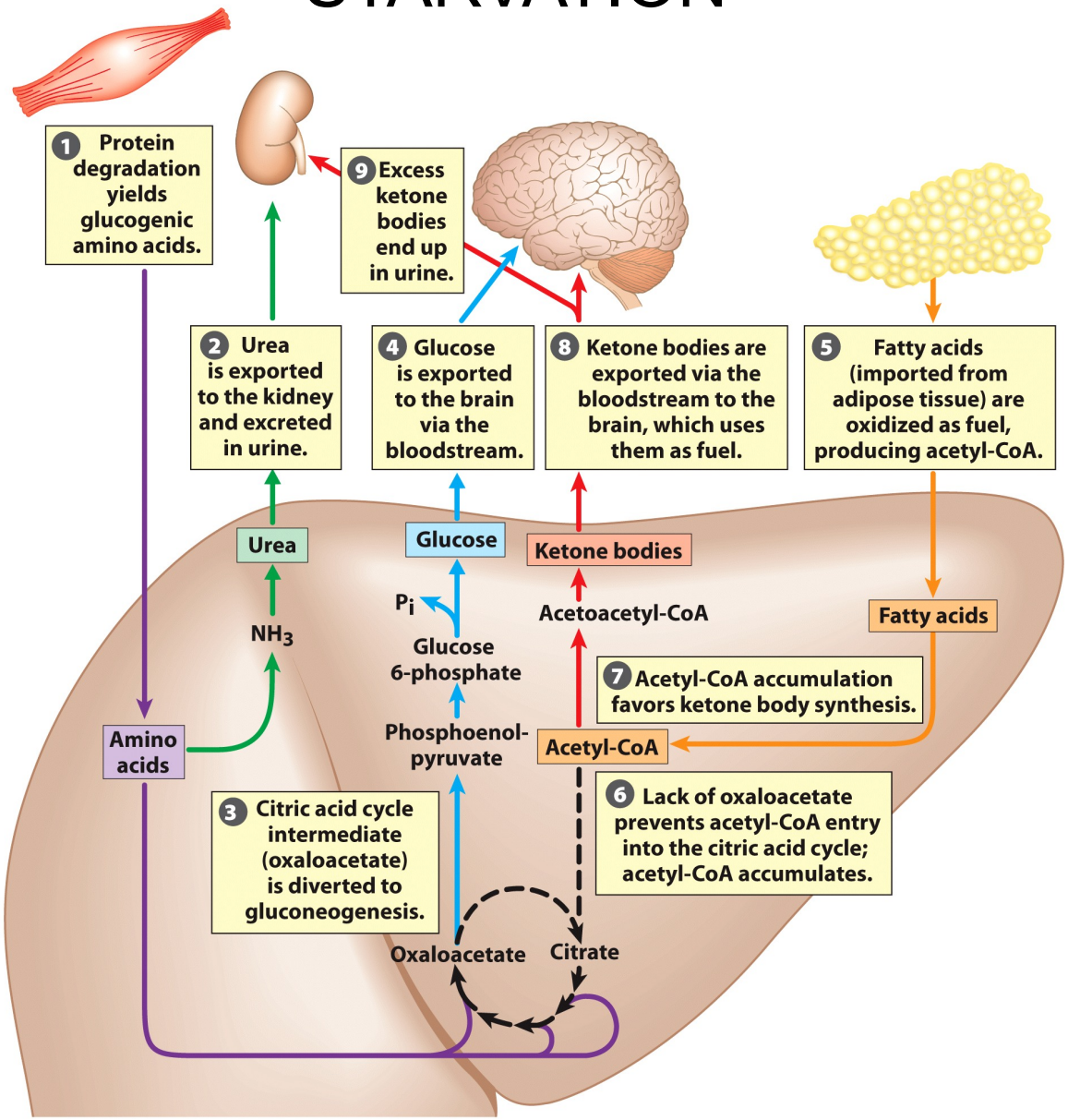


Figure 23-30
Lehninger Principles of Biochemistry, Sixth Edition

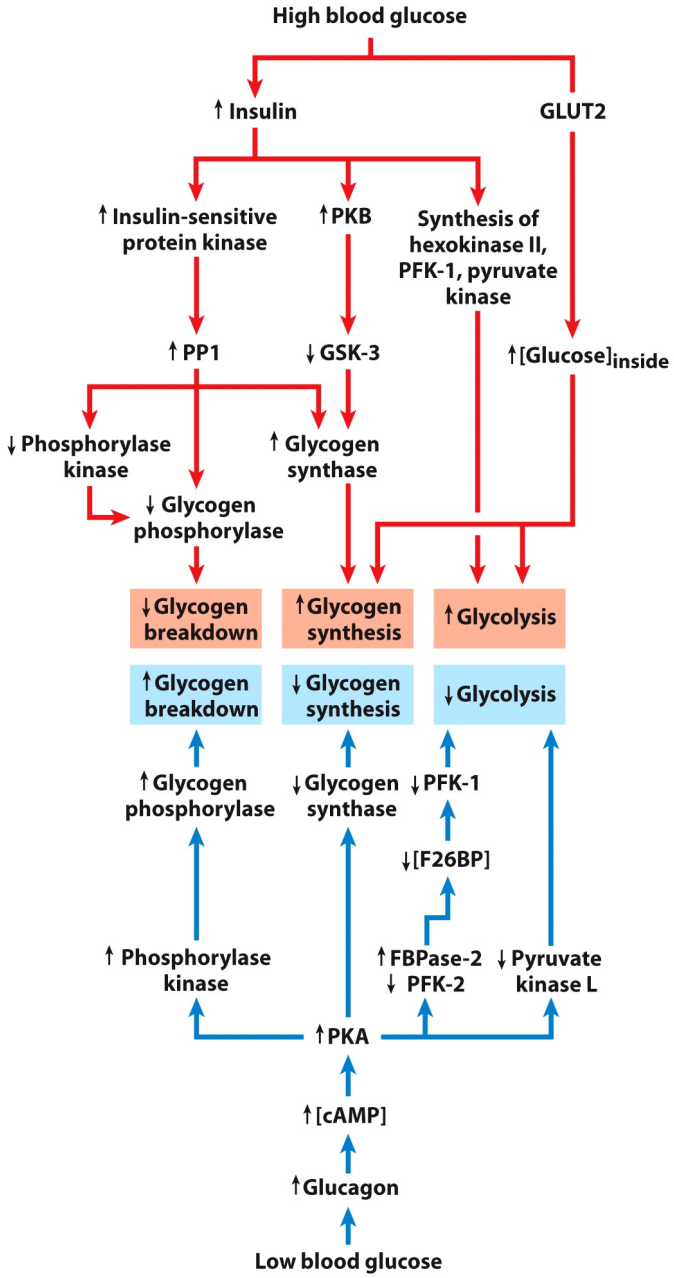


Figure 15-43
Lehninger Principles of Biochemistry, Sixth Edition

SUMMARY

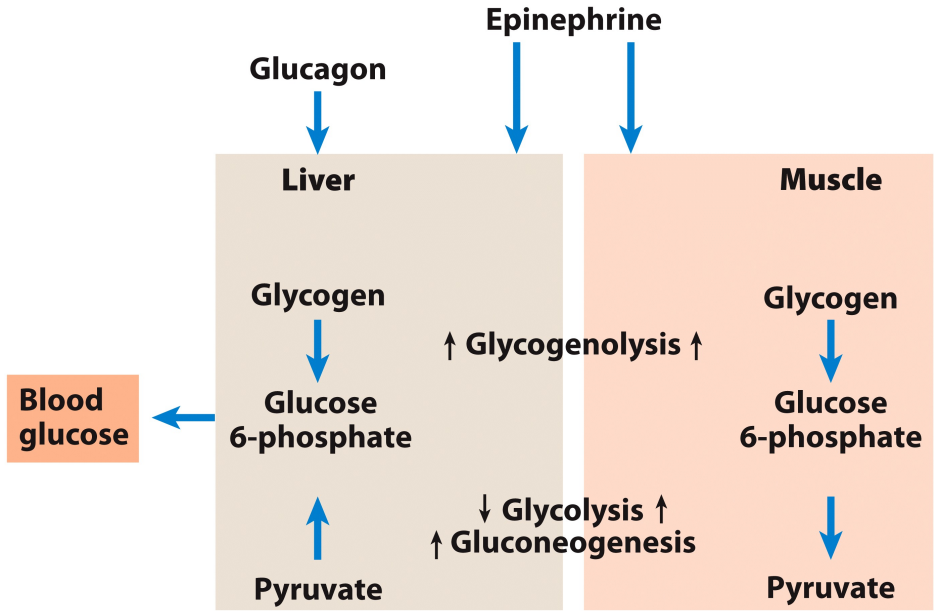
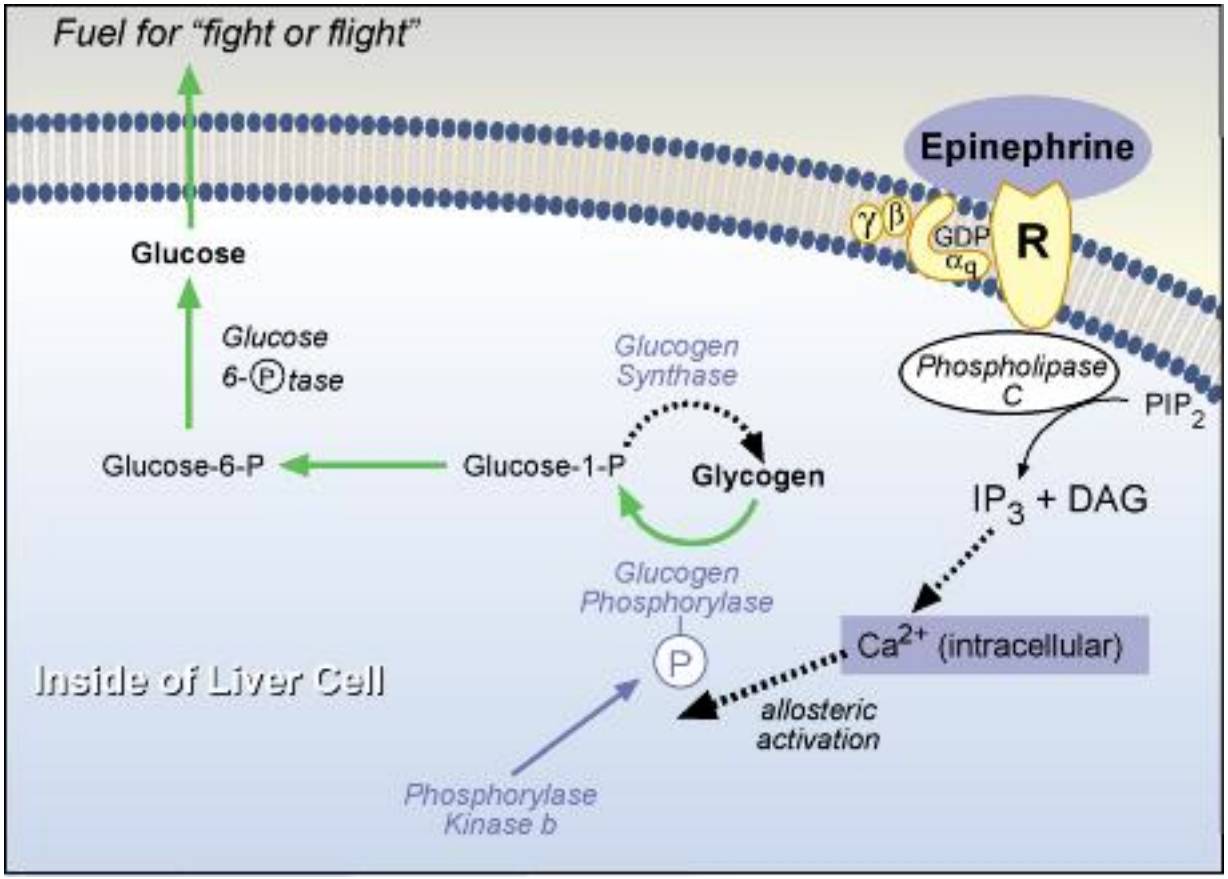


Figure 15-44
Lehninger Principles of Biochemistry, Sixth Edition

- Glucagon and adrenaline have the same effect in liver.
- Adrenaline has a different effect in muscle where it increases glycolisis to produce ATP for muscle contraction

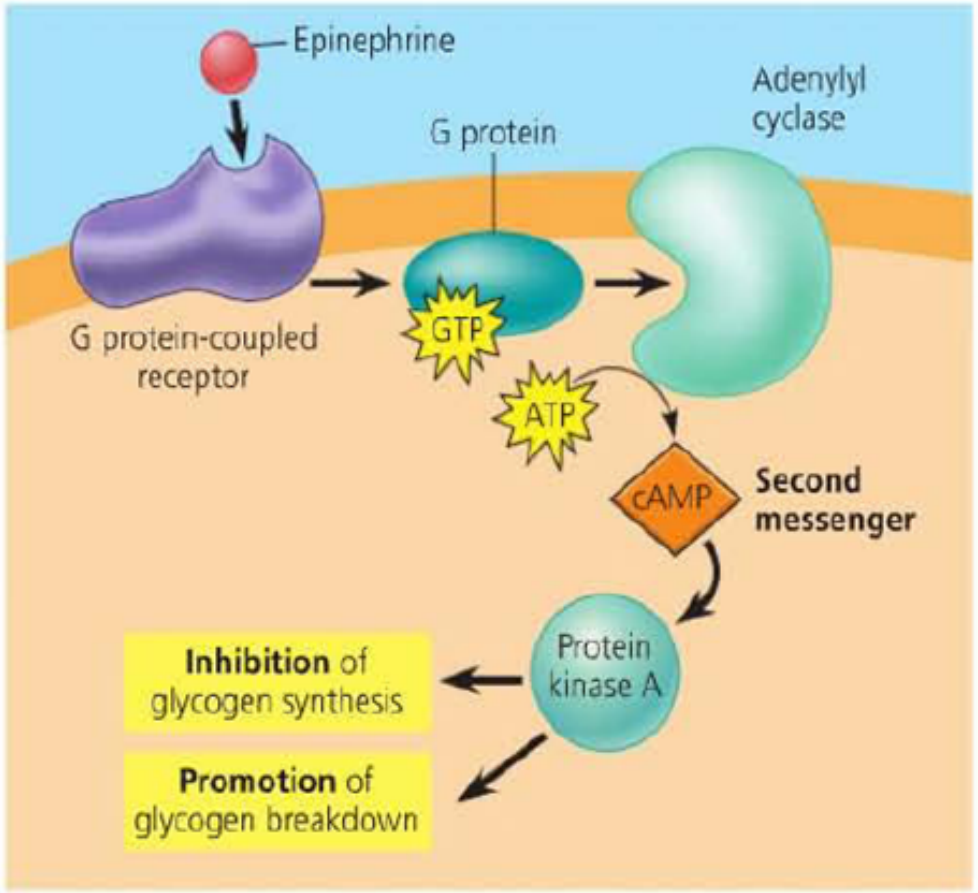
EPINEPHRINE

- Epinephrine works on cells via Ca^{2+} as a second messenger
- Increases glycogenolysis and gluconeogenesis
- Increases release of glucagon and cortisol



EPINEPHRINE

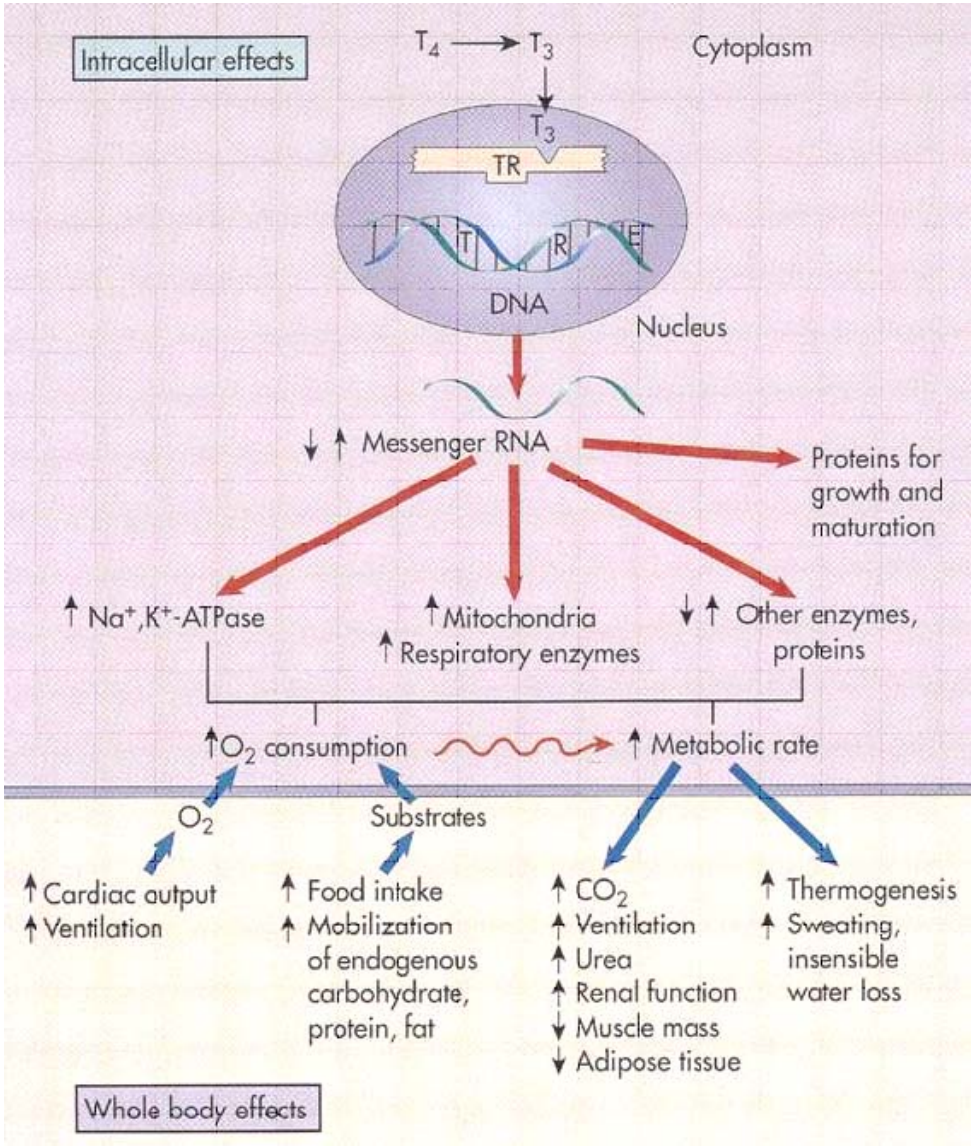
- Epinephrine works on cells via Ca^{2+} as a second messenger
- Increases glycogenolysis and gluconeogenesis
- Increases release of glucagon and cortisol



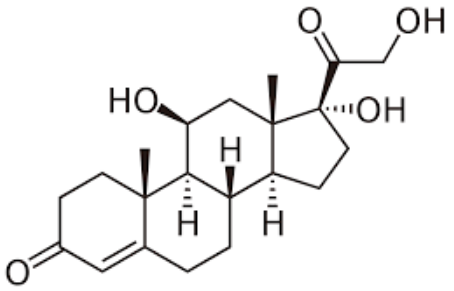
▲ **Figure 45.6 Cell-surface hormone receptors trigger signal transduction.**

THYROID HORMONES

- Thyroid hormones triiodothyronine (T3) and thyroxine (T4) stimulates energy producing metabolsim in liver and muscle
- They act through nuclear receptors activating genes coding for catabolic key enzymes



CORTISOL



- It is an hormone released upon stress and low glucose levels
- Its action is relatively slow
- It acts mainly at genic levels in the transcription of enzymes
- It stimulates fatty acids release from adipose tissue that are used as fuel in other tissues
- Glycerol is used by liver for gluconeogenesis
- It stimulates muscle proteins degradation and amino acids are used by liver for gluconeogenesis
- It activates PEPCK
- It balance insulin effects