Integration of Metabolism

References

Harvey, RA and Ferrier, DR. Biochemistry 5th ed

Lippincott's Illustrated Reviews (2011)

Unit V Chapters 23, 24, 25 pp 307-356

Objectives

1. **Recognize that Integration is controlled mainly via hormonal action:**
    - **A. Insulin**
        - **i. Structure**
        - **ii. Synthesis**
        - **iii. Regulation of secretion**
            - **a. Stimulants**
            - **b. Inhibitors**
        - **iv. Metabolic effects**
        - **v. Mechanism of action**
    - **B. Glucagon**
        - **i. Regulations of secretions**
            - **a. Stimulants**
            - **b. Inhibitors**
        - **ii. Metabolic effects**
        - **iii. Mechanism of action**

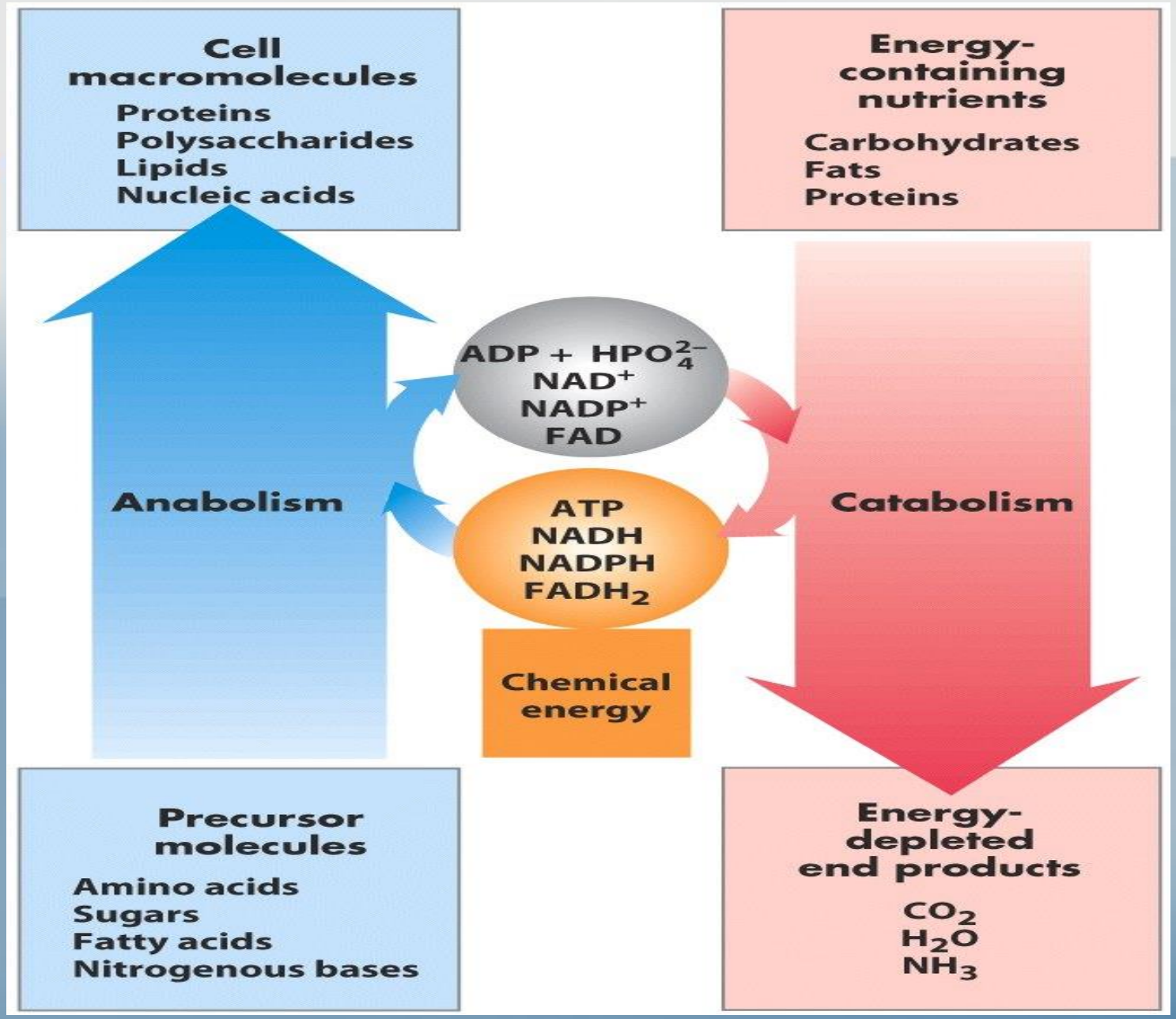
2. Recognize symptoms and types of Hypoglycemia
    A. Relate to ethanol consumption
3. Recognize that 4 major organs function in Metabolism
    A. Liver
        i. CHO Metabolism
        ii. Fat Metabolism
        iii. Amino Acid Metabolism
    B. Adipose Tissue
        i. CHO Metabolism
        ii. Fat Metabolism
    C. Muscle
        i. CHO Metabolism
        ii. Fat Metabolism
        iii. Amino Acid Metabolism
    D. Brain
        i. CHO Metabolism
        ii. Fat Metabolism

4. Interpret and Predict changes occurring in these 4 organs in the Fasted State

5. Define and Recognize types of Diabetes:
    a. Type I
        i. Diagnosis
        ii. Metabolic changes
        iii. Treatment
    b. Type II
        i. Insulin resistance
        ii. Metabolic changes
        iii. Treatment

Metabolic Processes

- Glycogenolysis
- Gluconeogenesis
- Fatty Acid Synthesis
- Lipogenesis
- TCA Cycle Activity
- Amino Acid Oxidation
- Proteolysis
- Glycogenesis
- Glycolysis
- Lipolysis
- Glutaminolysis
- Ketogenesis
- Protein Synthesis
- Urea Synthesis


Cell macromolecules
Proteins
Polysaccharides
Lipids
Nucleic acids
Energy-containing nutrients
Carbohydrates
Fats
Proteins
Anabolism
ADP + HPO_4^{2-}
NAD^+
$NADP^+$
FAD
ATP
NADH
NADPH
$FADH_2$
Chemical energy
Catabolism
Precursor molecules
Amino acids
Sugars
Fatty acids
Nitrogenous bases
Energy-depleted end products
CO_2
H_2O
NH_3

ANAPLEROTIC REACTIONS

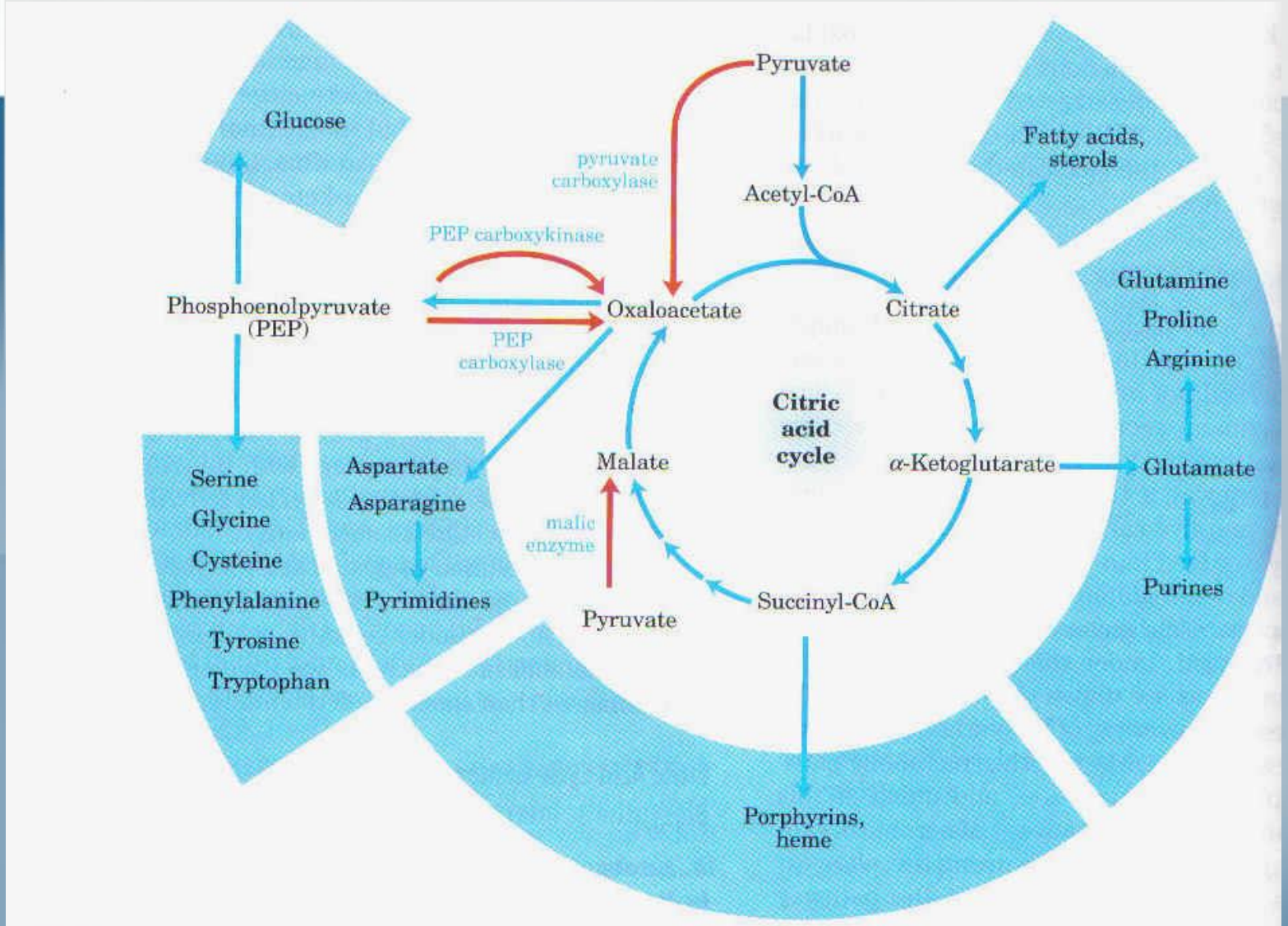


FIGURE 16–15 Role of the citric acid cycle in anabolism. Intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways. Shown in red are four anaplerotic plenish depleted cycle intermediates (see Table 16–2)

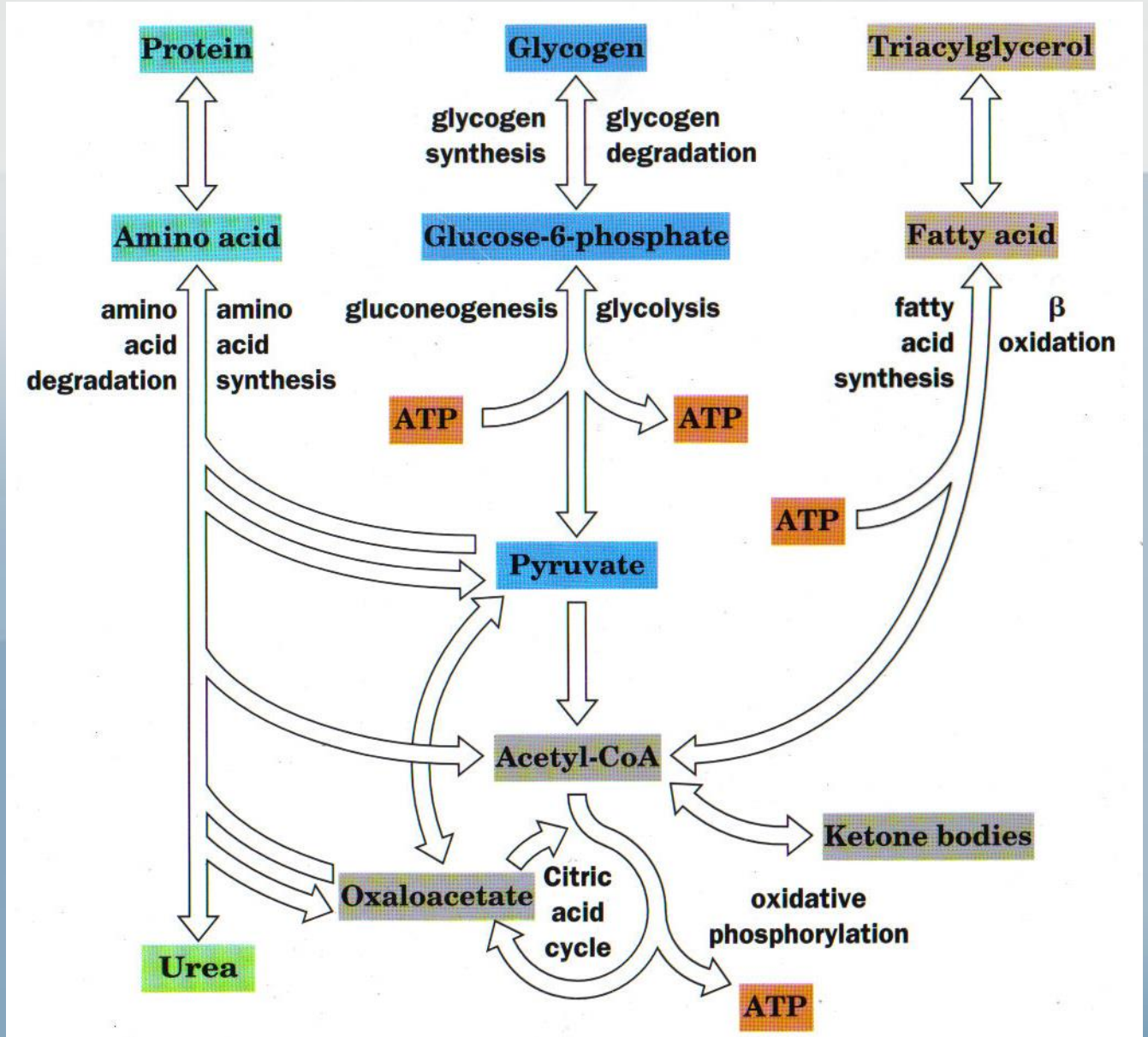


Figure 21-1. The major pathways of fuel metabolism in mammals.

Metabolism
The “Big” Picture

- Total available genes are the same for each cell but only a fraction of them are expressed (effective “genome” of that cell type).
- Of these expressed genes, some are used throughout the life of the cell but others (ie control of cell timing) are present only transiently. The set of proteins recovered at any moment in the life of a cell is called the “proteome.”
- The complex set of small molecules in a cell represents its “metabolome.” The metabolome is constantly changing. Maintaining the elements of the metabolome within certain ranges is called “homeostasis.”

Maintenance of Homeostasis

- In humans about 4,000 genes (12% of total) encode regulatory proteins including a variety of receptors, regulators of gene expression, and more than 500 different protein kinases.
- In many cases, the regulatory mechanisms overlap, one enzyme is subject to regulation by several different mechanisms.
- Homeostasis in living organisms occurs far from equilibrium which is a condition referred to as “steady state.” This requires expenditure of energy which is ATP.

Importance of ATP as Energy Source

- In a typical cell, ATP is consumed within l minute of its formation
- Although total ATP in the body is only about 100g, the TURNOVER is very high
- For example a resting human consumes about 40 Kg of ATP in 24 hrs
- During strenuous exercise the rate of utilization of ATP may be as high as 0.5 Kg/min and for a 2 hr run, 60 Kg (132#) are utilized
- Motion, active transport, biosynthesis, etc require ATP as well. On the average an individual turns over his body weight in ATP every day.
- Clearly mechanisms for regenerating ATP are vital

- Ranges can be broad such as glucose (to be discussed later) or narrow such as intracellular ATP concentration.
- Example of ATP control is the “Energy Charge Value”

$$\text{Energy charge} = \tfrac{1}{2}\left(\frac{2\,[\text{ATP}] + [\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}\right)$$

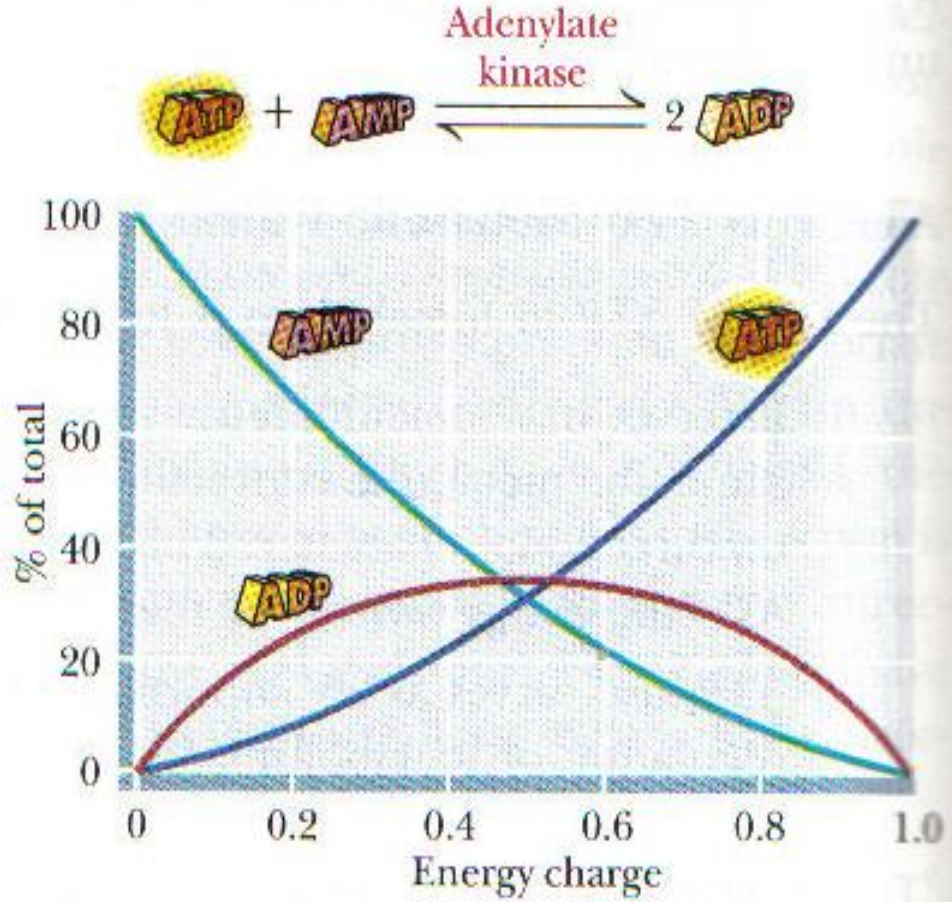


***Figure* 25.5** Relative concentrations of AMP, ADP, and ATP as a function of energy charge. (This graph was constructed assuming that the adenylate kinase reaction is at equilibrium and that $\Delta G^{\circ\prime}$ for the reaction is -473 J/mol; $K_{eq} = 1.2$.)

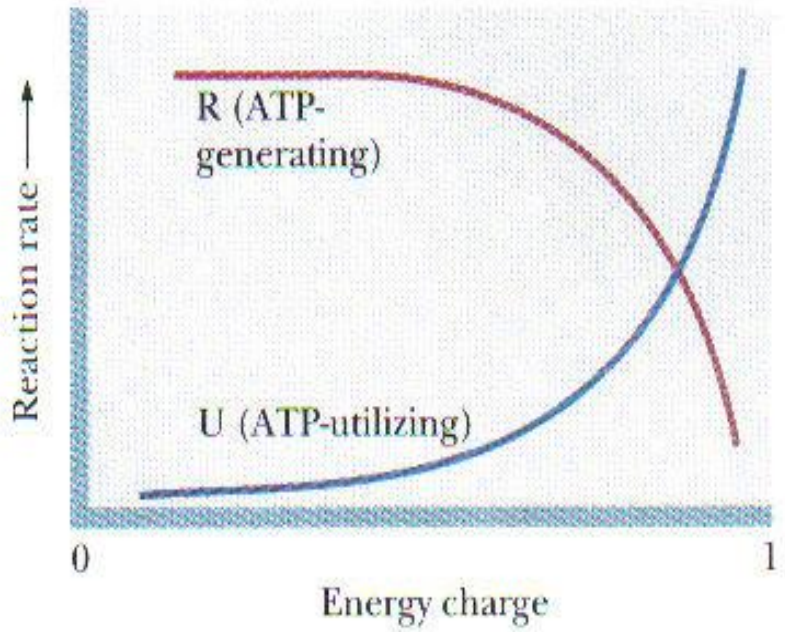


***Figure* 25.6** Responses of regulatory enzymes to variation in energy charge. Enzymes in catabolic pathways have as their ultimate metabolic purpose the regeneration of ATP from ADP. Such enzymes show an **R** pattern of response to energy charge. Enzymes in biosynthetic pathways utilize ATP to drive anabolic reactions; these enzymes follow the **U** curve in response to energy charge.

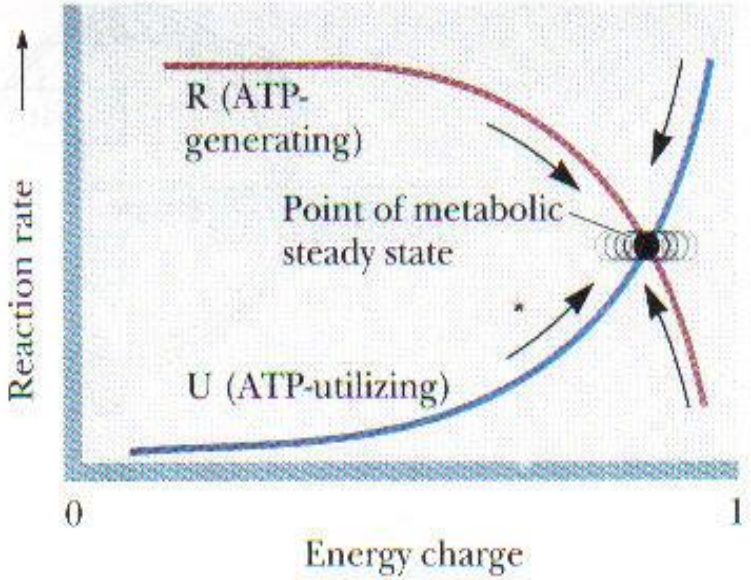


***Figure* 25.7** The oscillation of energy charge (E.C.) about a steady-state value as a consequence of the offsetting influences of **R** and **U** processes on the production and consumption of ATP. As E.C. increases, the rates of **R** reactions decline, but **U** reactions go faster. ATP is consumed, and E.C. drops. Below the point of intersection, **R** processes are more active and **U** processes are slower, so E.C. recovers. Energy charge oscillates about a steady-state value determined by the intersection point of the **R** and **U** curves.

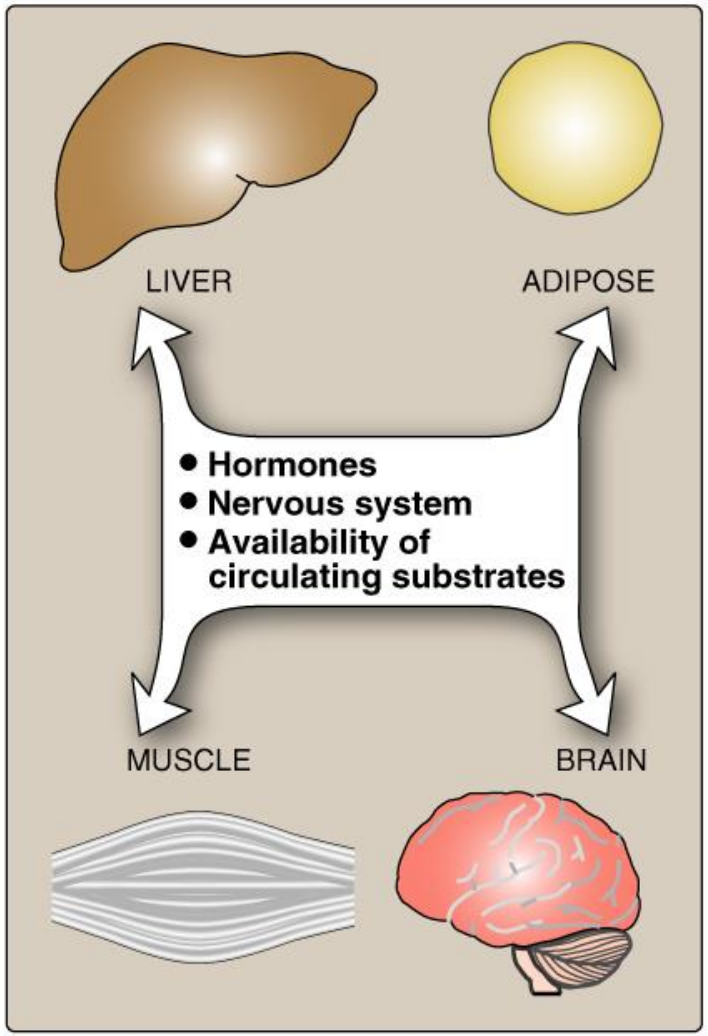


Figure 23.1
Mechanisms of communication between four major tissues.

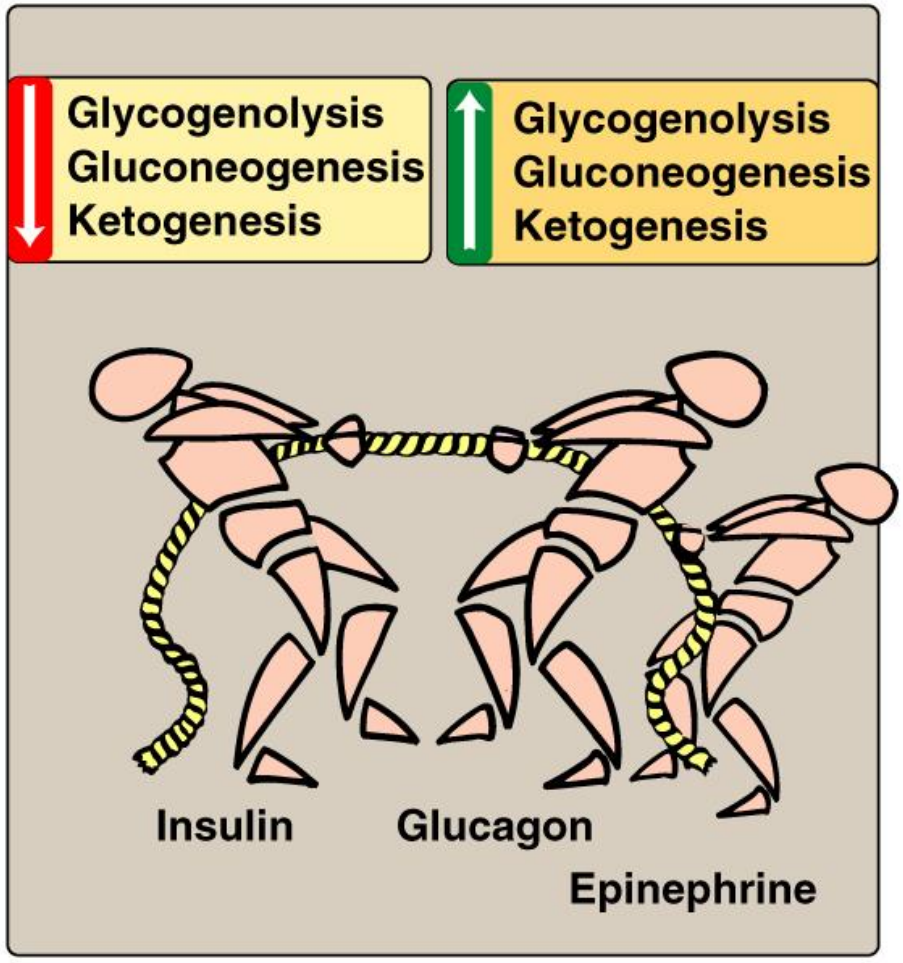


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

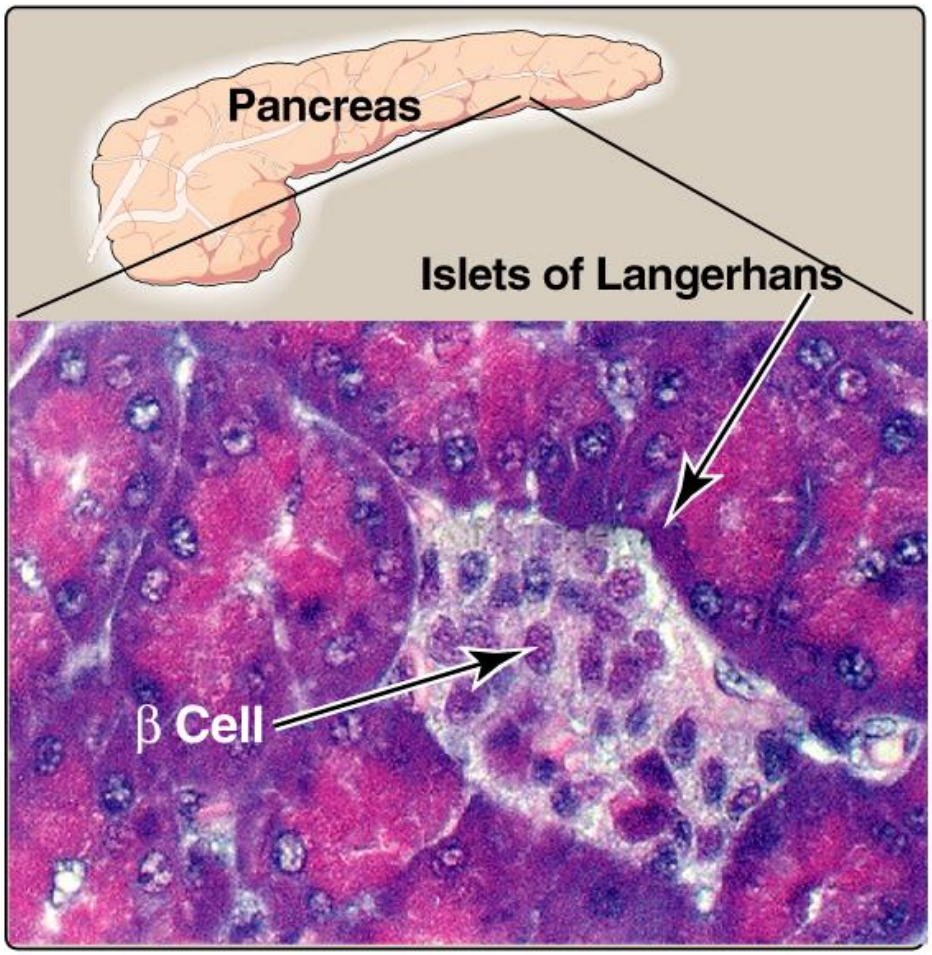


Figure 23.2
Islets of Langerhans.

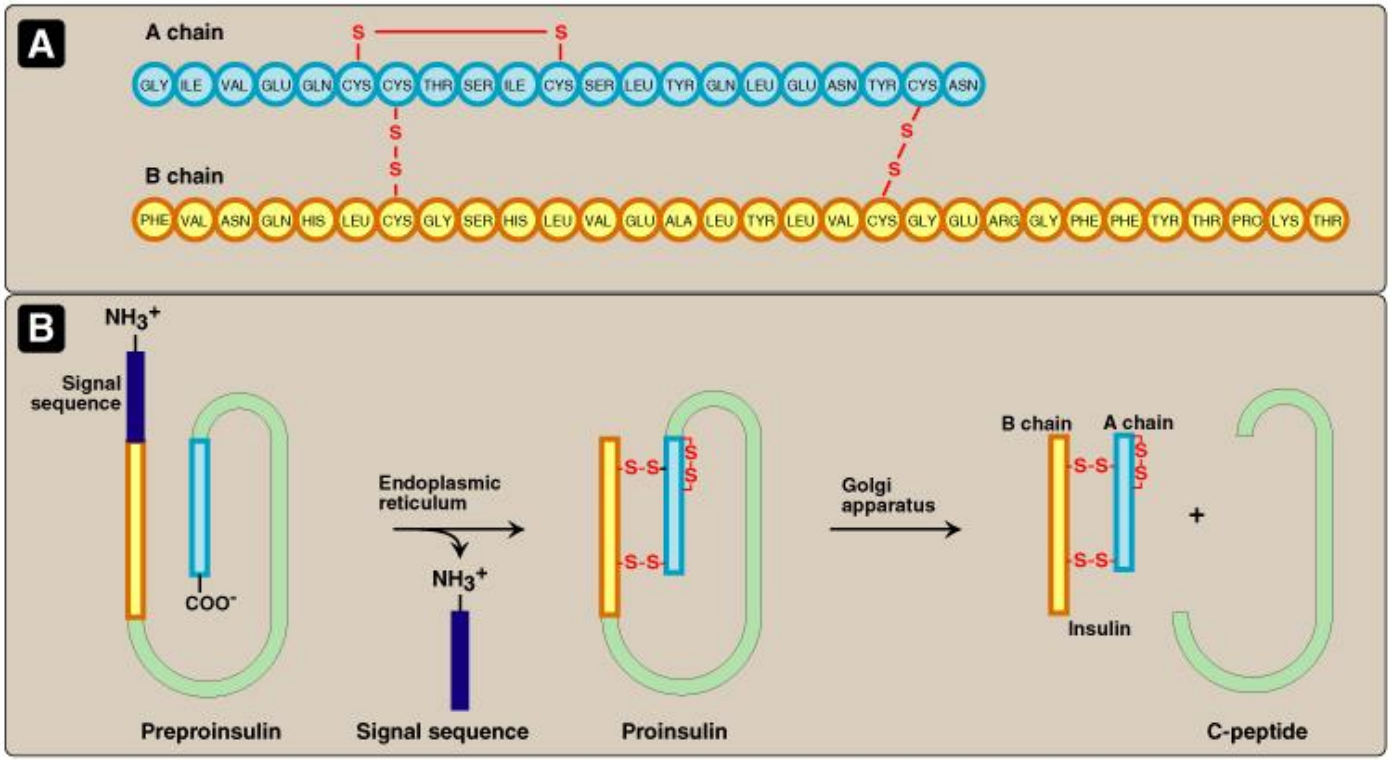


Figure 23.3

A. Structure of insulin. B. Formation of human insulin from preproinsulin.

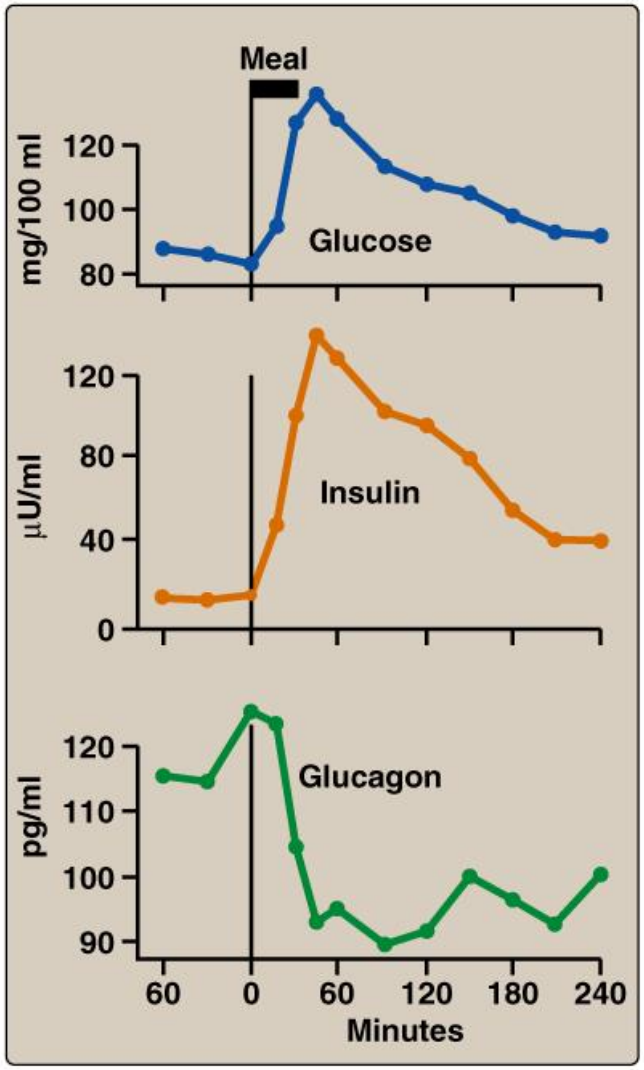


Figure 23.5
Changes in blood levels of glucose, insulin, and glucagon after ingestion of a carbohydrate-rich meal.

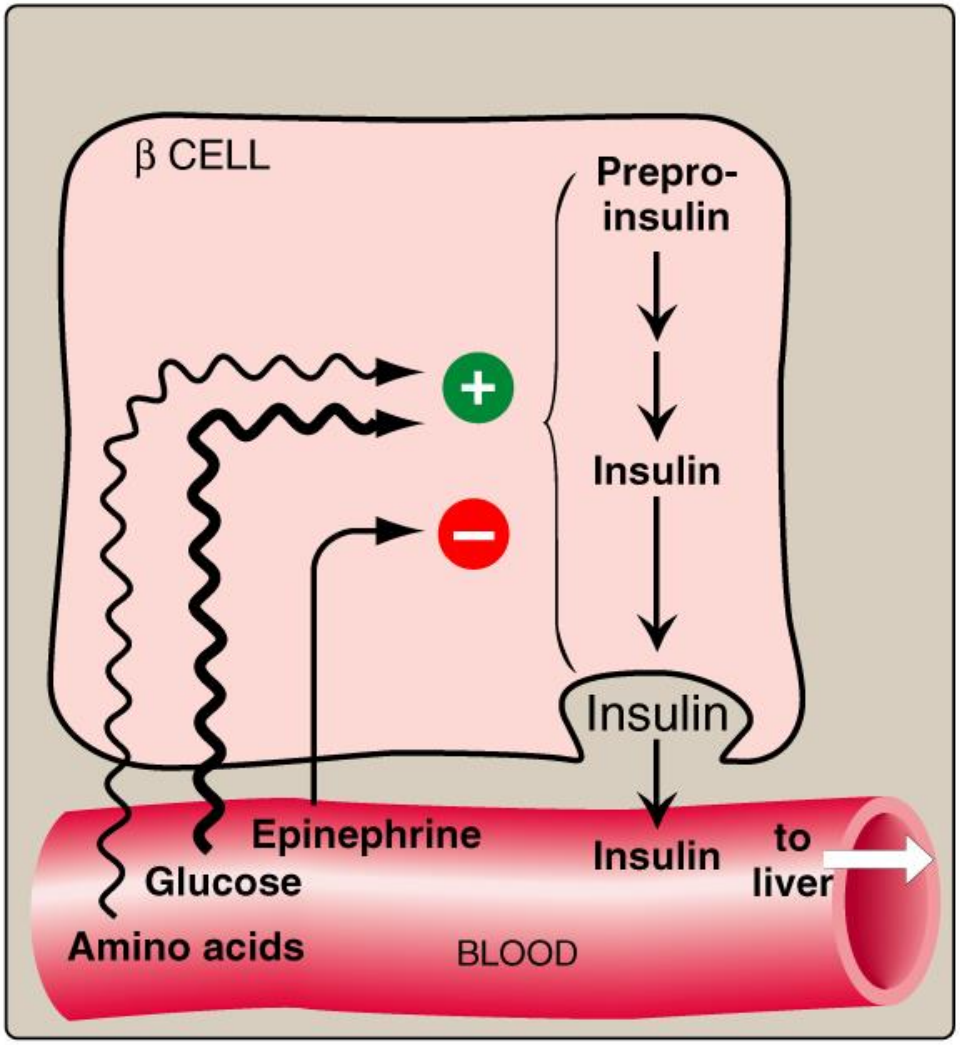


Figure 23.6
Regulation of insulin release from pancreatic β cells.

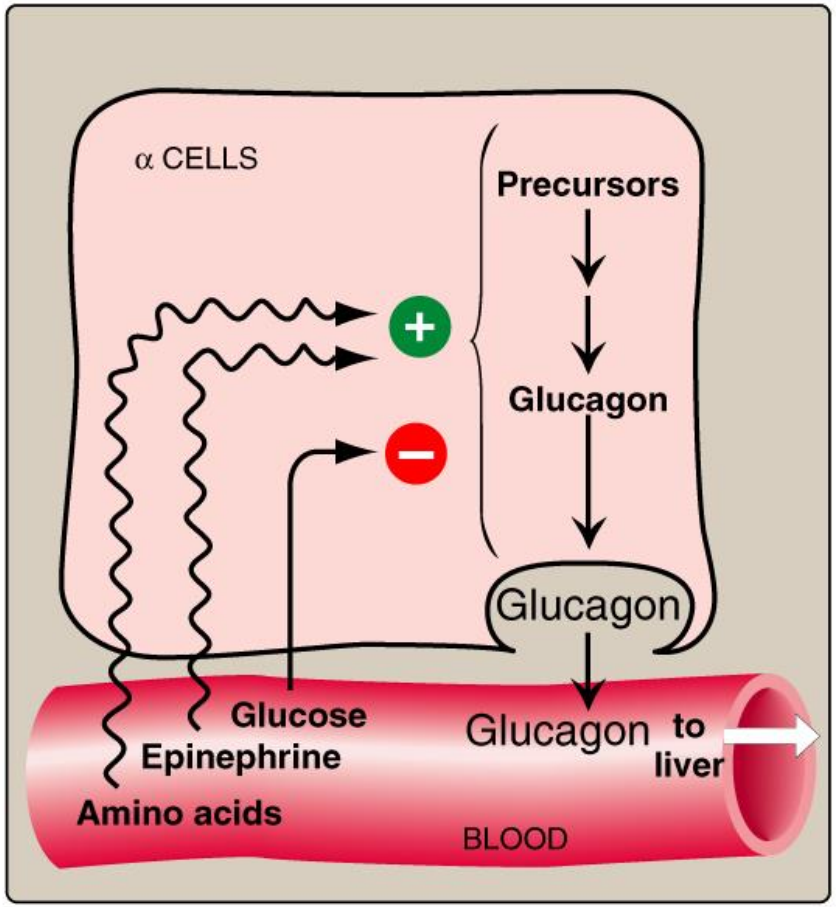


Figure 23.11
Regulation of glucagon release from pancreatic α cells.

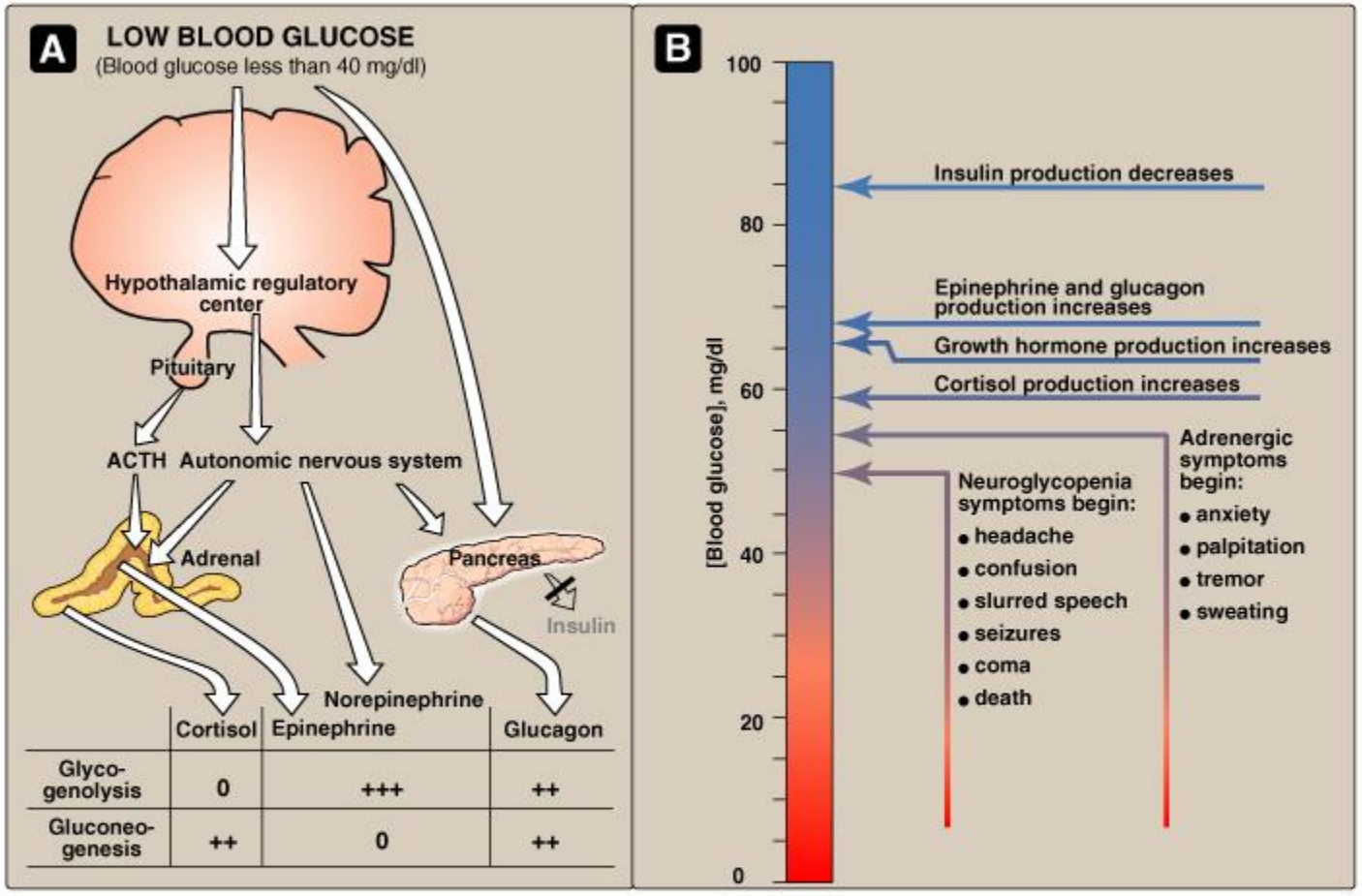


Figure 23.13

A. Actions of some of the glucoregulatory hormones in response to low blood glucose. B. Glycemic thresholds for the various resposes to hypoglycemia. + = Weak stimulation; ++ = moderate stimulation; +++ = strong stimulation; 0 = no effect.

HYPOGLYCEMIA

- 1. Insulin Induced
- 2. Postprandial
- 3. Fasting
- 4. Alcohol Intoxication

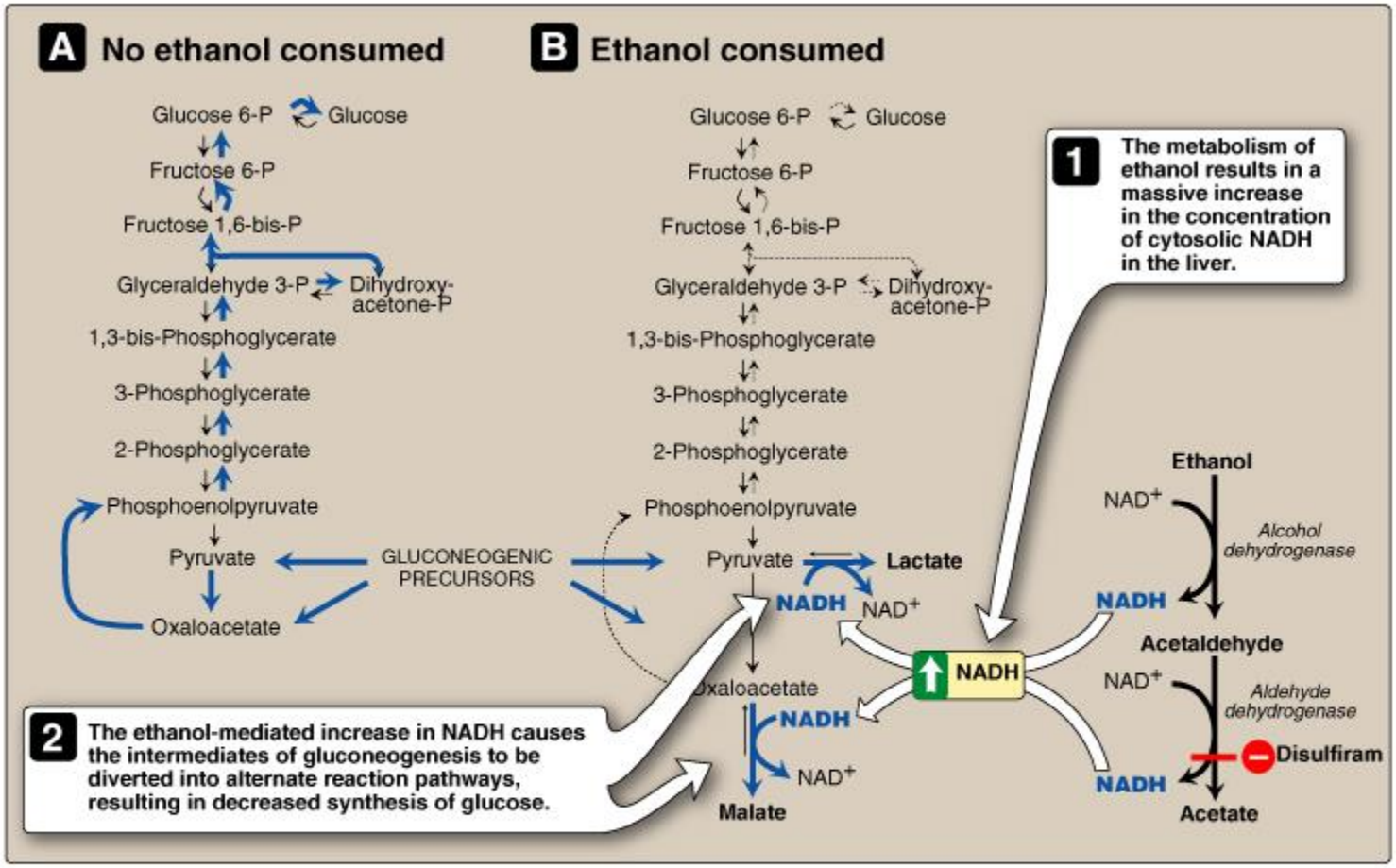


Figure 23.15

A. Normal gluconeogenesis in the absence of ethanol consumption. B. Inhibition of gluconeogenesis resulting from hepatic metabolism of ethanol.

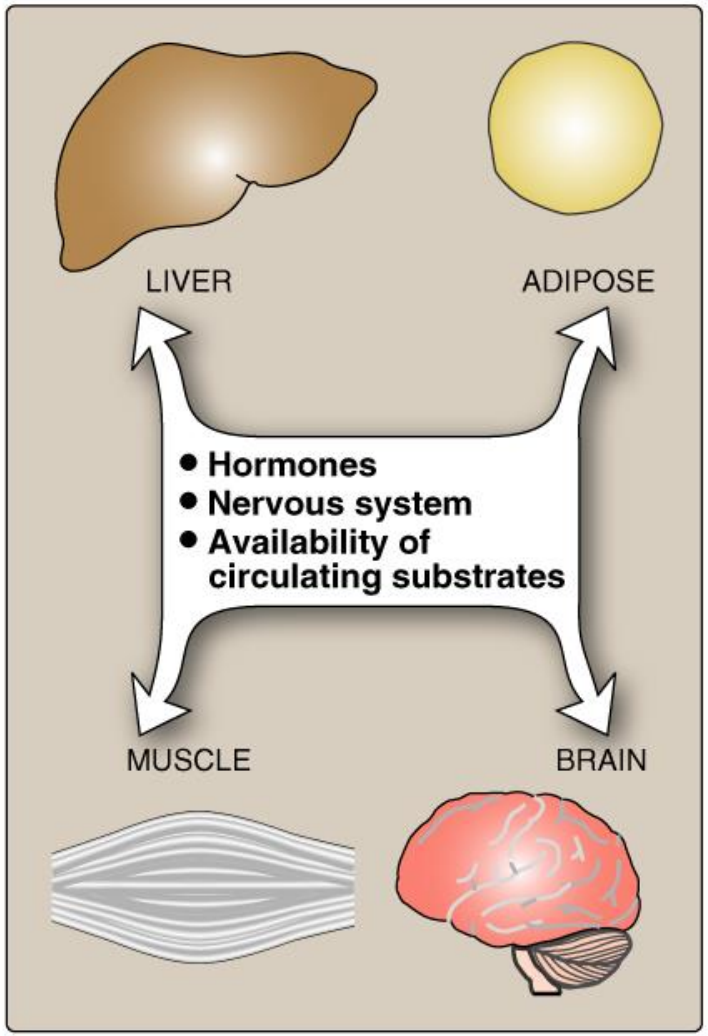


Figure 23.1
Mechanisms of communication between four major tissues.

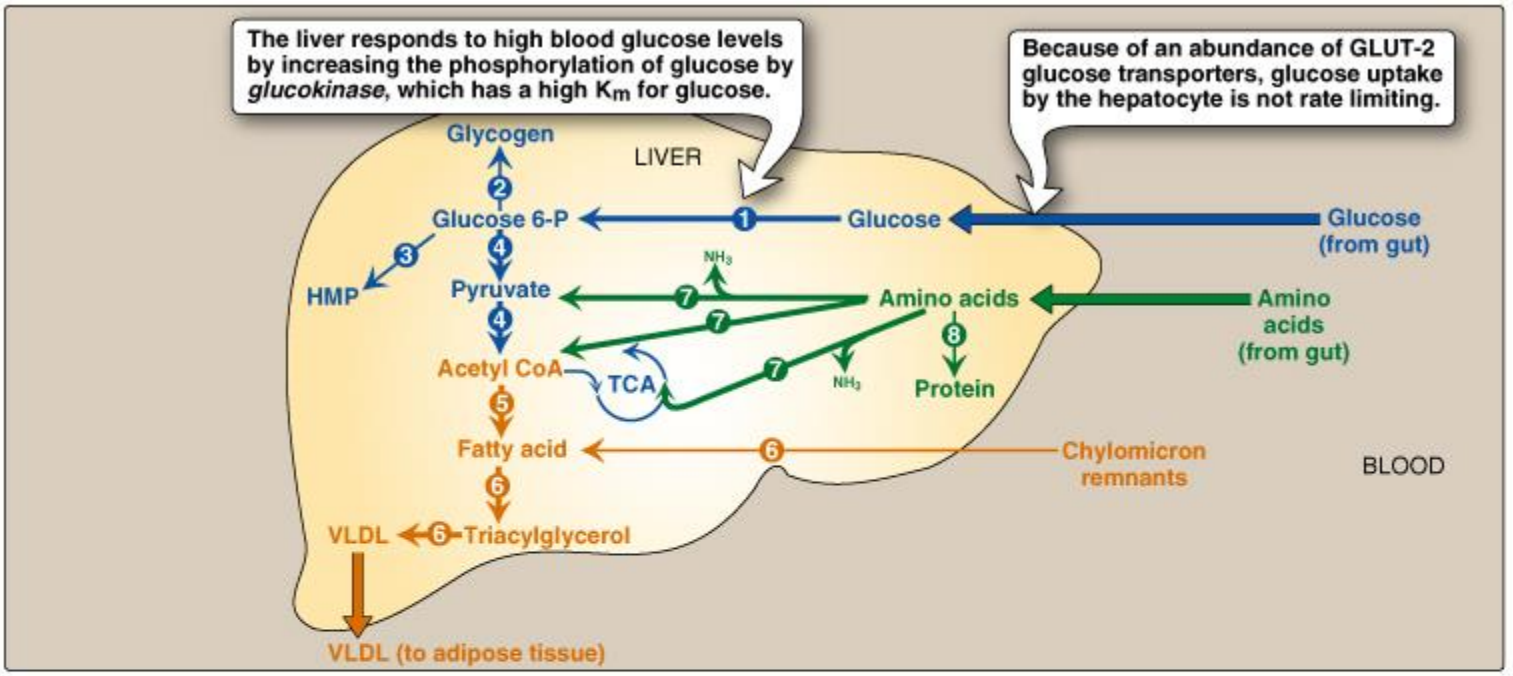


Figure 24.3

Major metabolic pathways in liver in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate, fat, or protein metabolism.] Key: **Blue text** = intermediates of carbohydrate metabolism; **Brown text** = intermediates of lipid metabolism; **Green text** = intermediates of protein metabolism.

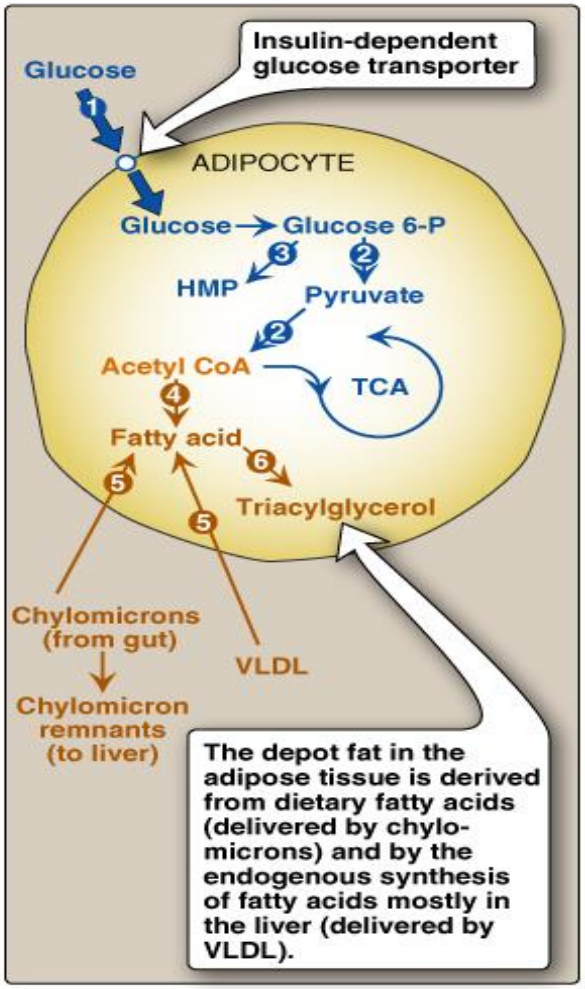


Figure 24.5
Major metabolic pathways in adipose tissue in the absorptive state. [Note: The numbers in the circles, which appear both on the figure and in the corresponding text, indicate important pathways for adipose tissue metabolism.]

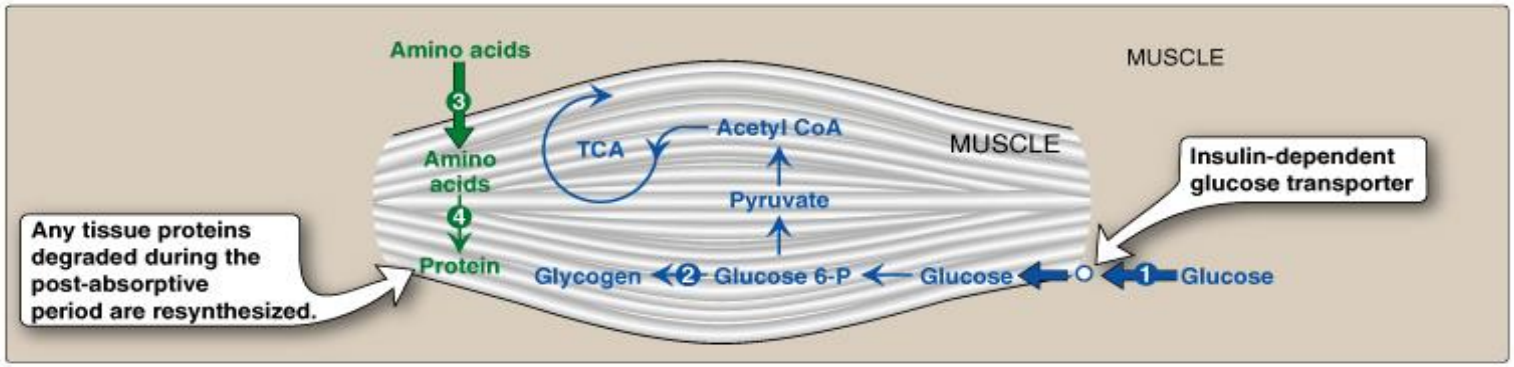


Figure 24.6

Major metabolic pathways in skeletal muscle in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate or protein metabolism.]

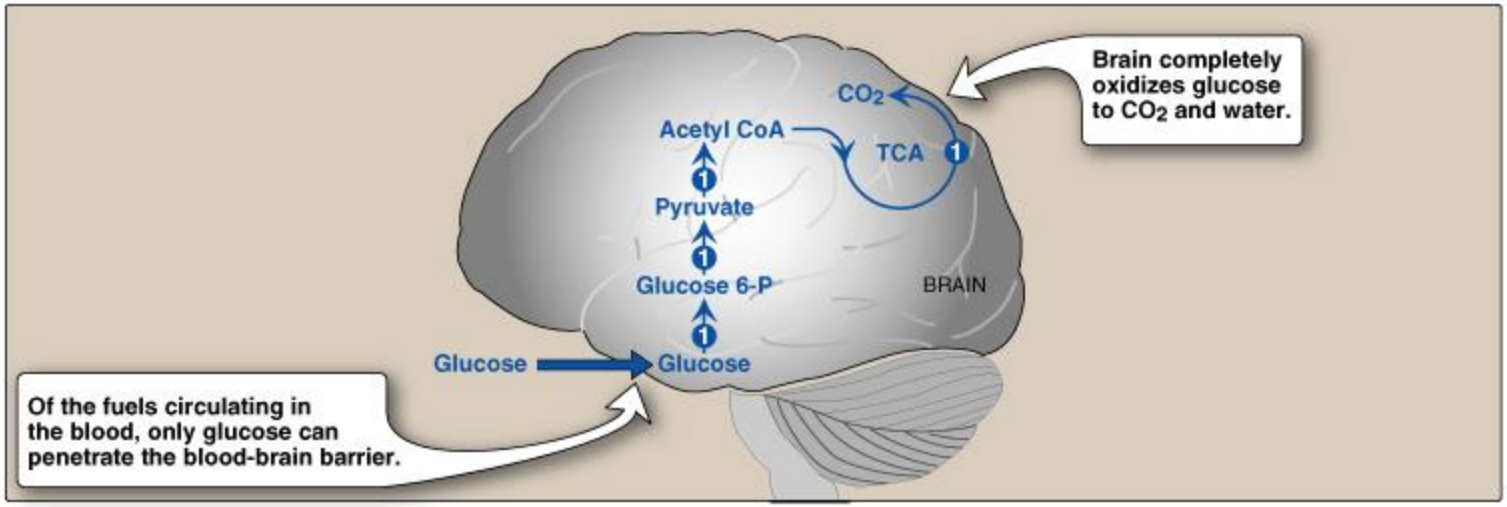


Figure 24 .7

Major metabolic pathways in brain in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate metabolism.]

Table 22–5 Available metabolic fuels in a normal 70 kg man and in an obese man at the beginning of a fast

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival time (months)*
Normal 70 kg man:			
Triacylglycerols (adipose tissue)	15	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese man:			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

* Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.

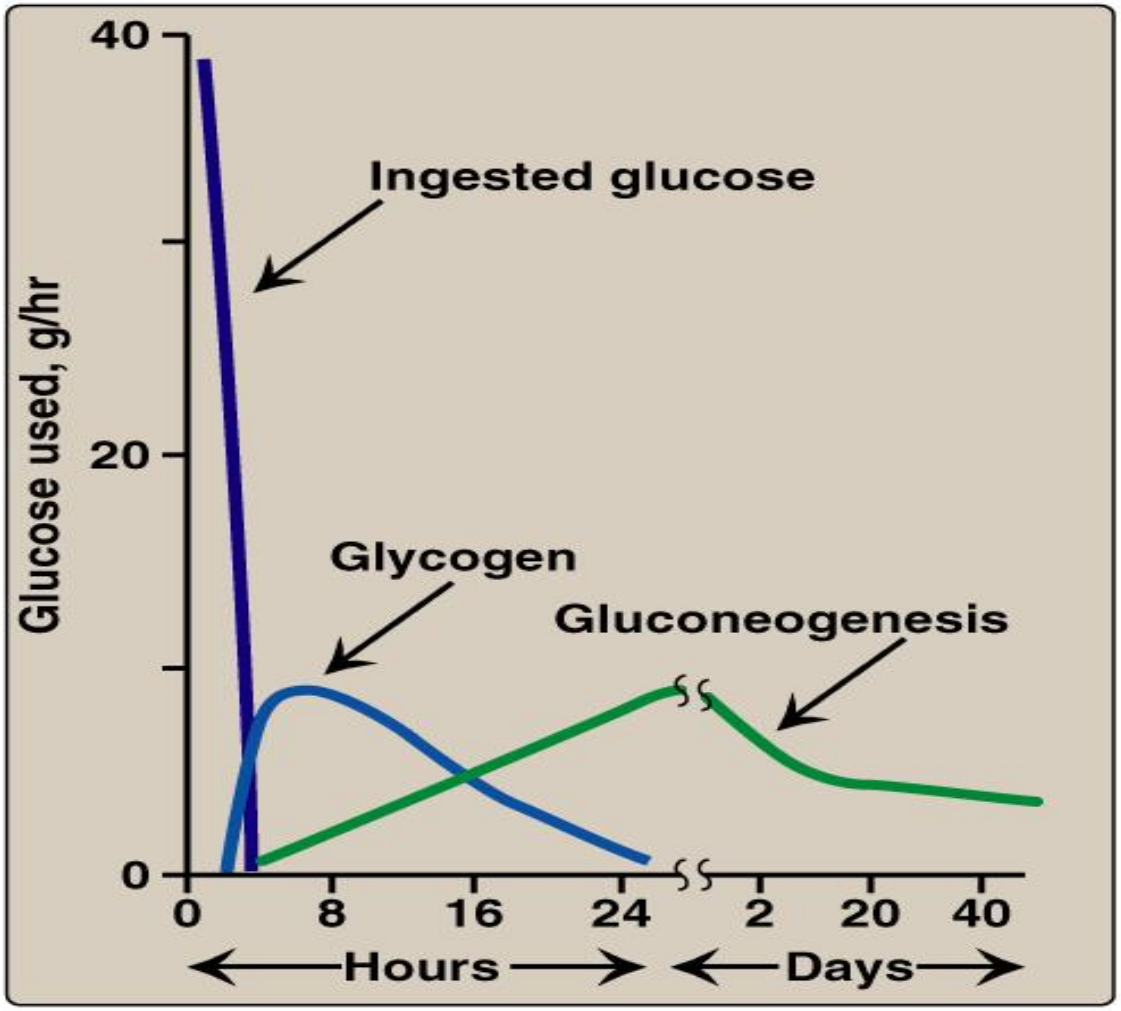


Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

TABLE 20.2 Substrate and Hormone Levels in Blood of Well-Fed, Fasting, and Starving Humans[a]

Hormone or Substrate (units)	*Very Well Fed*	*Postabsorptive 12 h*	*Fasted 3 days*	*Starved 5 weeks*
Insulin (μU mL^{-1})	40	15	8	6
Glucagon (pg mL^{-1})	80	100	150	120
Insulin/glucagon ratio (μU pg^{-1})	0.50	0.15	0.05	0.05
Glucose (mM)	6.1	4.8	3.8	3.6
Fatty acids (mM)	0.14	0.6	1.2	1.4
Acetoacetate (mM)	0.04	0.05	0.4	1.3
β-Hydroxybutyrate (mM)	0.03	0.10	1.4	6.0
Lactate (mM)	2.5	0.7	0.7	0.6
Pyruvate (mM)	0.25	0.06	0.04	0.03
Alanine (mM)	0.8	0.3	0.3	0.1
ATP equivalents (mM)	313	290	380	537

Source: From Ruderman, N. B., Aoki, T. T., and Cahill, G. F. Jr. Gluconeogenesis and its disorders in man. In: R. W. Hanson and M. A. Mehlman (Eds.), *Gluconeogenesis, Its Regulation in Mammalian Species*. New York: Wiley, 1976, p. 515.

[a]Data are for normal-weight subjects except for the 5-week starvation values, which are from obese subjects undergoing therapeutic starvation. ATP equivalents were calculated on the basis of the ATP yield expected on complete oxidation of each substrate to CO_2 and H_2O: 38 molecules of ATP for each molecule of glucose; 144 for the average fatty acid (oleate); 23 for acetoacetate; 26 for β-hydroxybutyrate; 18 for lactate; 15 for pyruvate; and 13 (corrected for urea formation) for alanine.

RESPIRATION QUOTIENT (RQ)

def: Vol of CO_2 produced divided by the volume of O_2 consumed for Carbohydrate (i.e. glucose)

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + E$$

$$RQ = \frac{6\ CO_2}{6\ O_2} = 1$$

For lipid (i.e. 2 molecules stearic acid + 1 molecule palmitic acid)

$$2\ (C_{55}\ H_{106}\ O_6) + 157\ O_2 \rightarrow 110\ CO_2 + 106\ H_2O + E$$

$$RQ = \frac{110\ CO_2}{157\ O_2} = 0.70$$

For protein RQ = 0.80

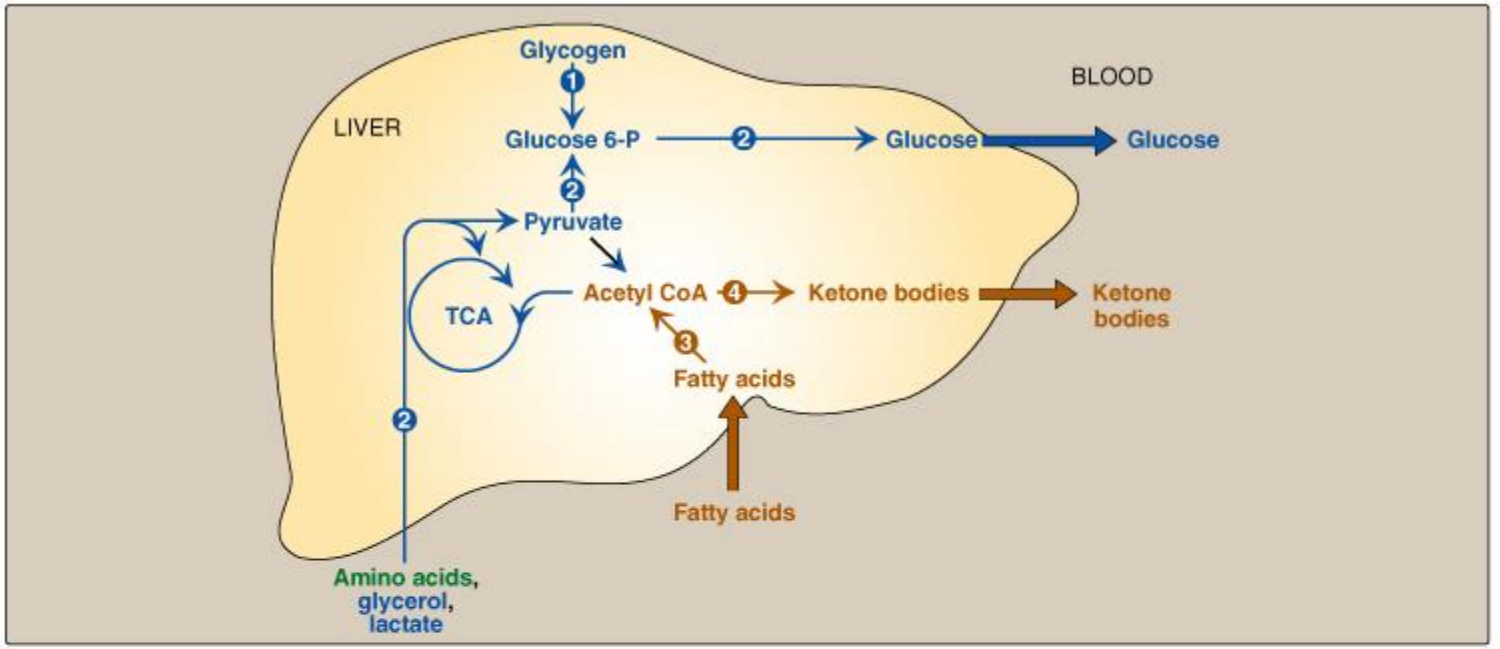


Figure 24.11

Major metabolic pathways in liver during starvation. The numbers in circles, which appear both on the figure and in the corresponding citation in the text, indicate important metabolic pathways for carbohydrate or fat.

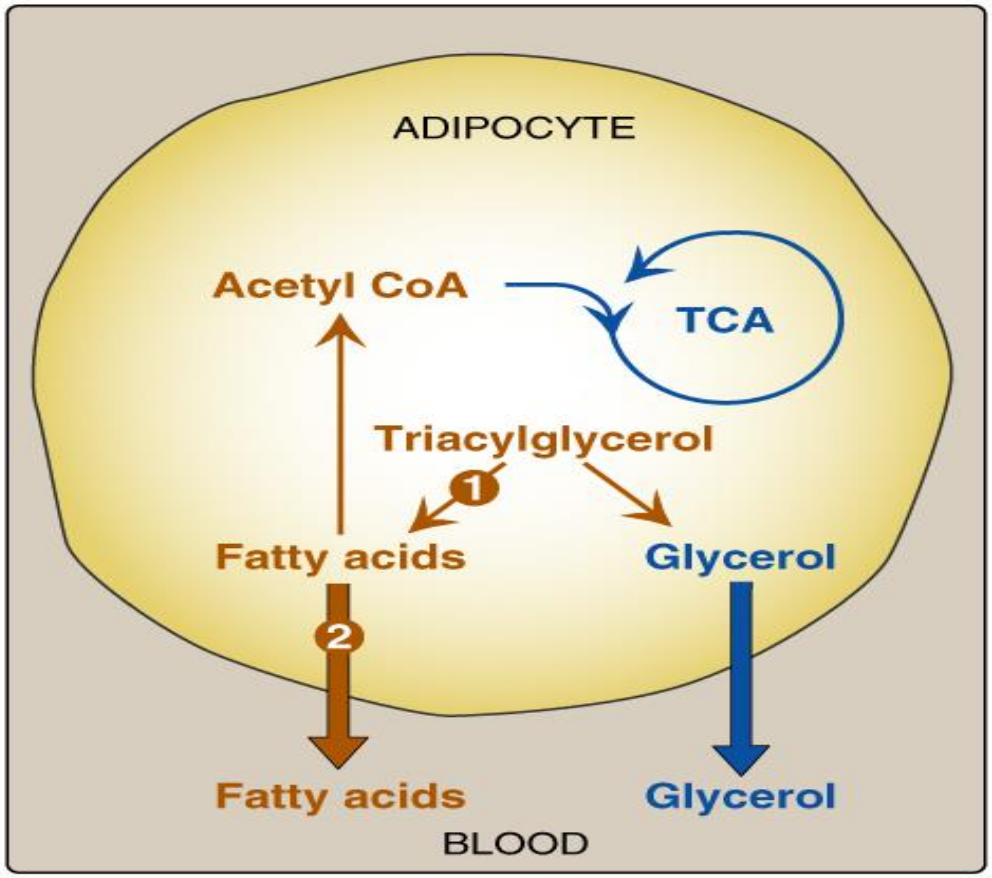


Figure 24.13
Major metabolic pathways in adipose tissue during starvation. The numbers in the circles, which appear both on the figure and in the corresponding citation in the text, indicate important pathways for fat metabolism.

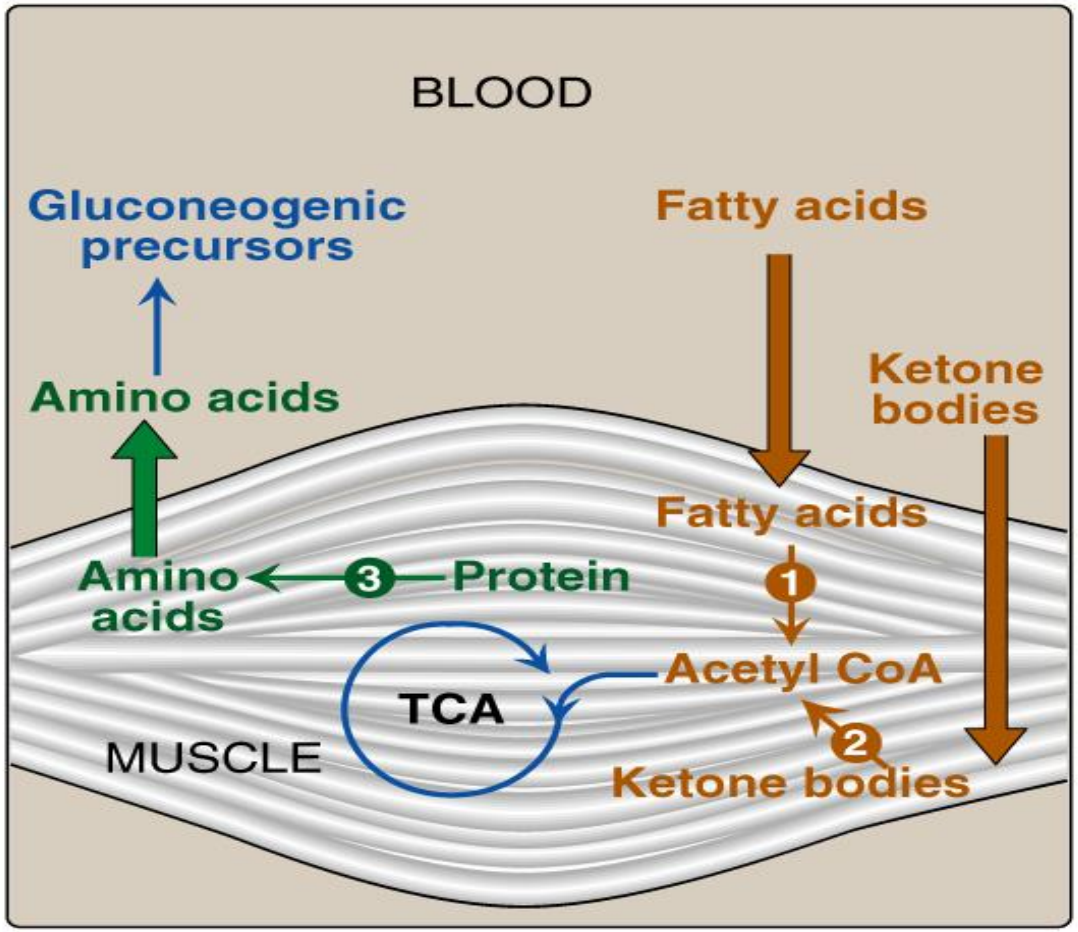


Figure 24.14
Major metabolic pathways in skeletal muscle during starvation. The numbers in the circles, which appear both on the figure and in the corresponding citation in the text, indicate important pathways for fat or protein metabolism.

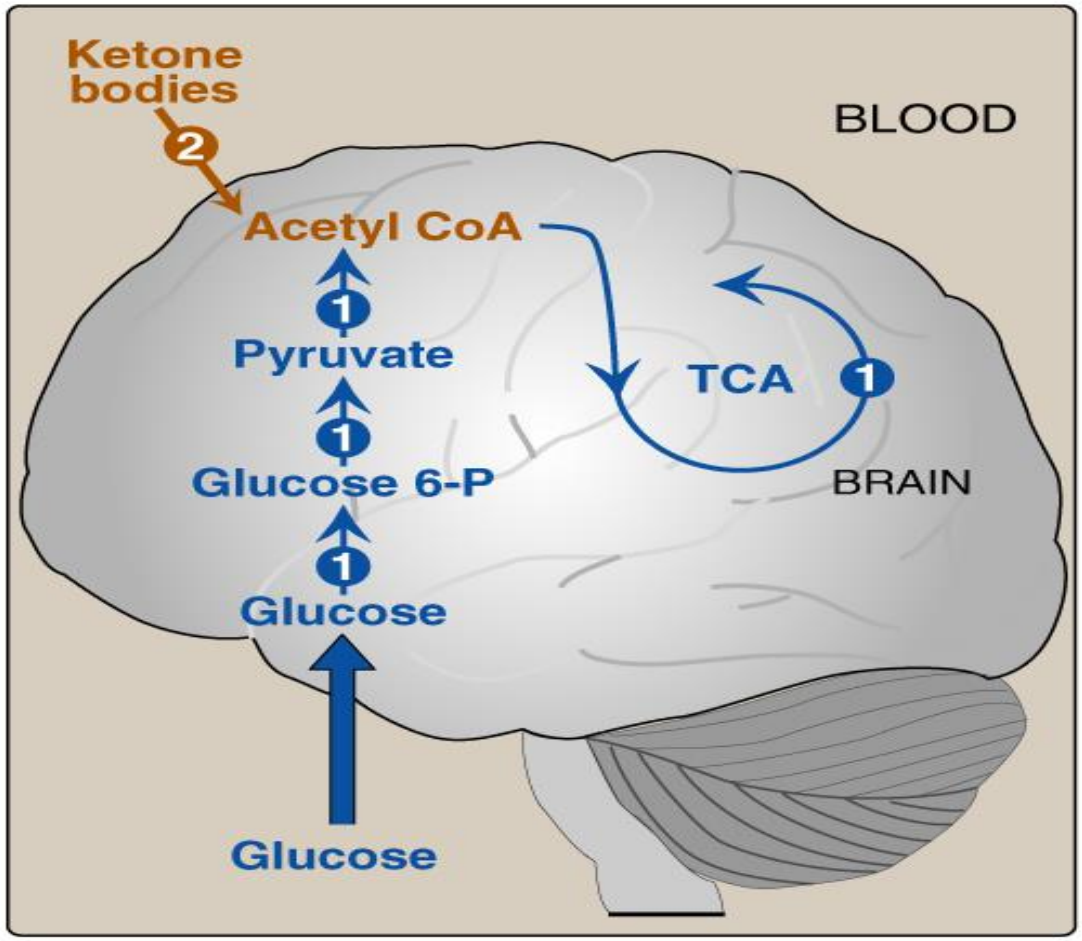


Figure 24.15

Major metabolic pathways in the brain during starvation. The numbers in the circles, which appear both on the figure and in the corresponding citation in the text, indicate important pathways for metabolism of fat or carbohydrates.

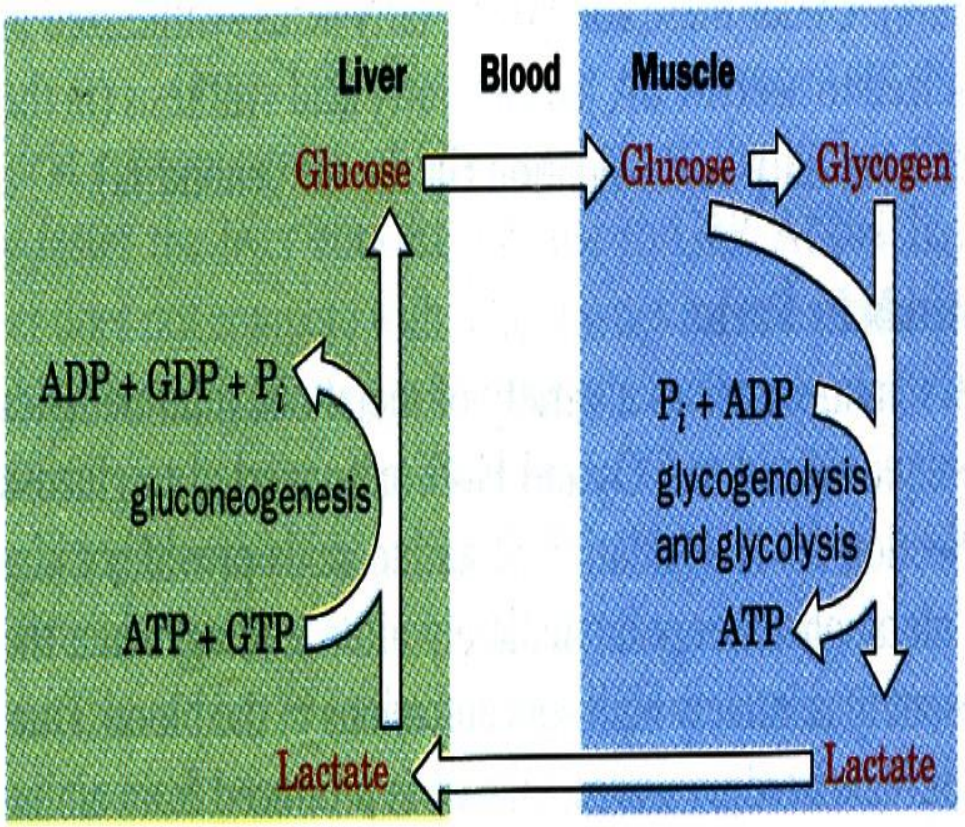


Figure 21-5. **The Cori cycle.** Lactate produced by muscle glycolysis is transported by the bloodstream to the liver, where it is converted to glucose by gluconeogenesis. The bloodstream carries the glucose back to the muscle, where it may be stored as glycogen. ✺ **See the Animated Figures.**

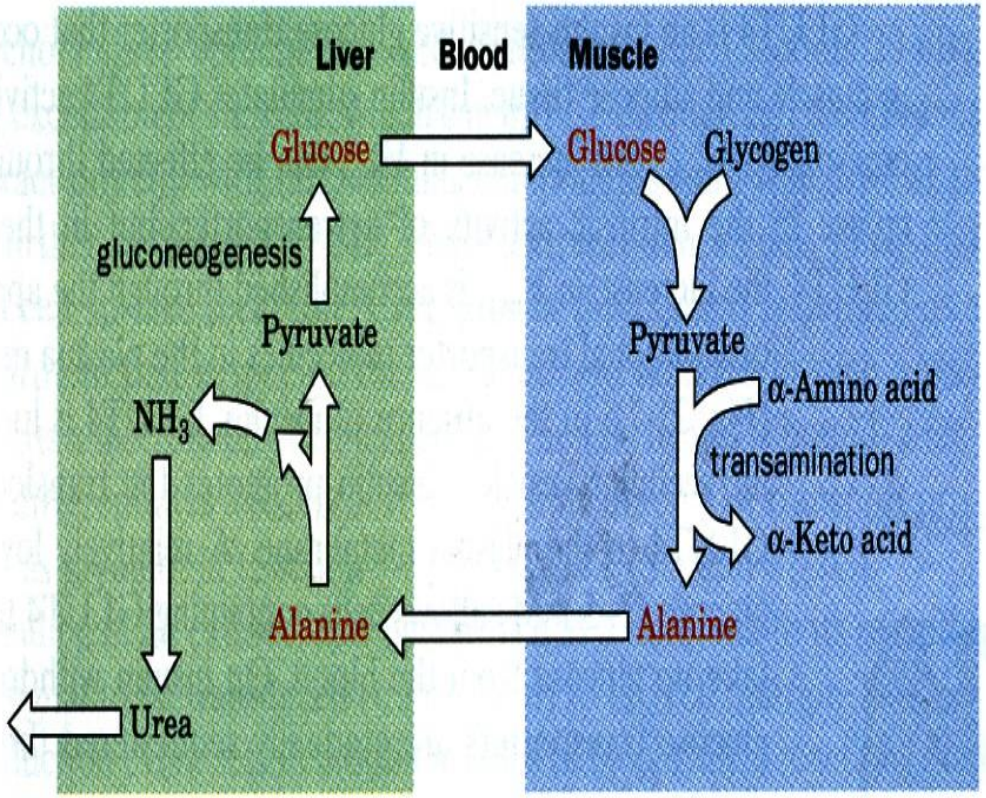


Figure 21-6. **The glucose–alanine cycle.** Pyruvate produced by muscle glycolysis is the amino-group acceptor for muscle aminotransferases. The resulting alanine is transported by the bloodstream to the liver, where it is converted back to pyruvate (its amino group is disposed of via urea synthesis). The pyruvate is a substrate for gluconeogenesis, and the bloodstream carries the resulting glucose back to the muscles.

✺ **See the Animated Figures.**

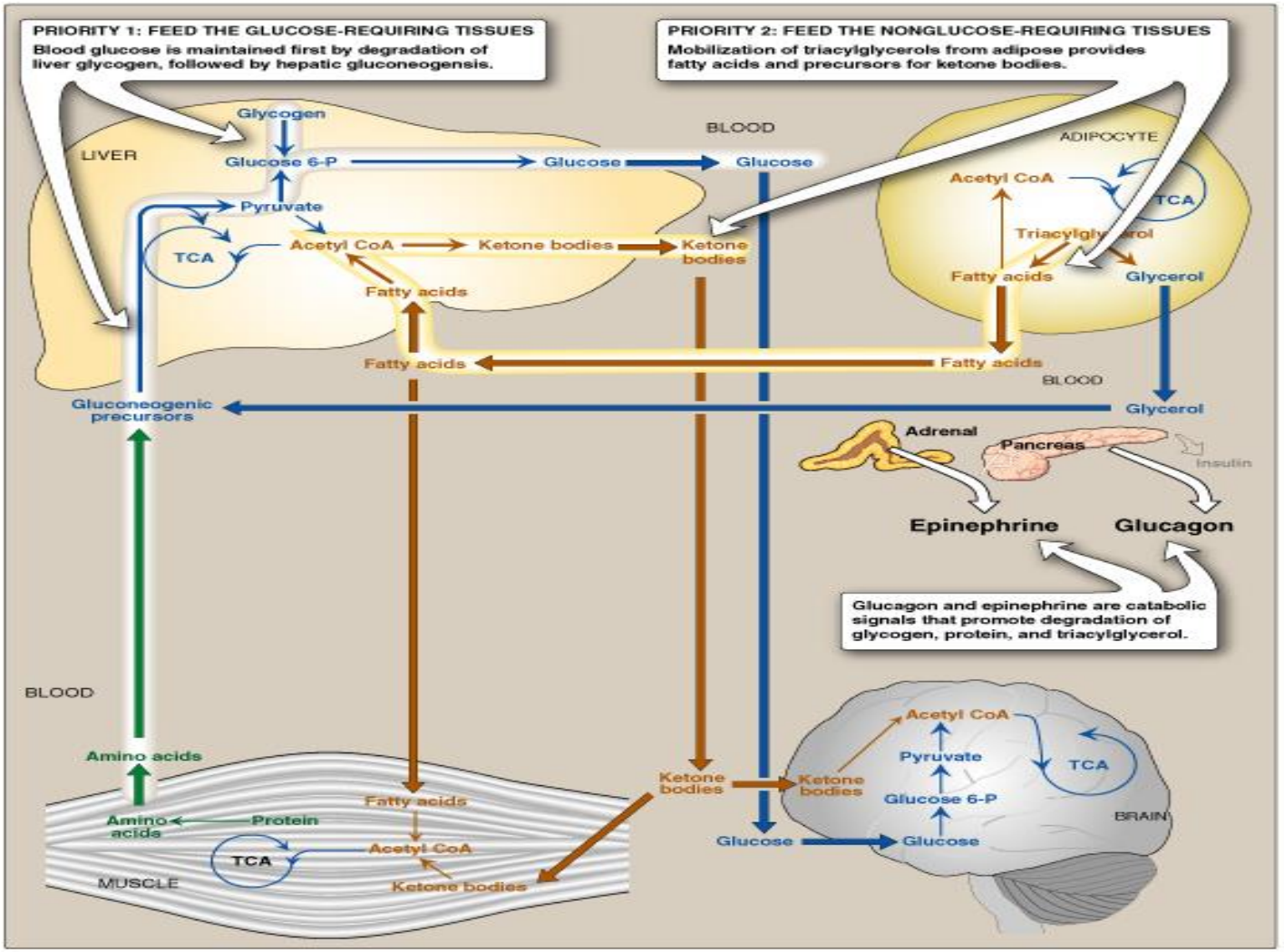


Figure 24.16
Intertissue relationships during starvation.

	Type 1 Diabetes	Type 2 Diabetes
AGE OF ONSET	Usually during childhood or puberty; symptoms develop rapidly	Frequently after age 35; symptoms develop gradually
NUTRITIONAL STATUS AT TIME OF DISEASE ONSET	Frequently undernourished	Obesity usually present
PREVALENCE	900,000 = 10% of diagnosed diabetics	10 Million = 90% of diagnosed diabetics
GENETIC PREDISPOSITION	Moderate	Very strong
DEFECT OR DEFICIENCY	β Cells are destroyed, eliminating production of insulin	Insulin resistance combined with inability of β cells to produce appropriate quantities of insulin
FREQUENCY OF KETOSIS	Common	Rare
PLASMA INSULIN	Low to absent	High early in disease; low in disease of long duration
ACUTE COMPLICATIONS	Ketoacidosis	Hyperosmolar coma
TREATMENT WITH ORAL HYPOGLYCEMIC DRUGS	Unresponsive	Responsive
TREATMENT	Insulin is always necessary	Diet, exercise, oral hypoglycemic drugs, +/– insulin

Figure 25.1
Comparison of type 1 and type 2 diabetes.

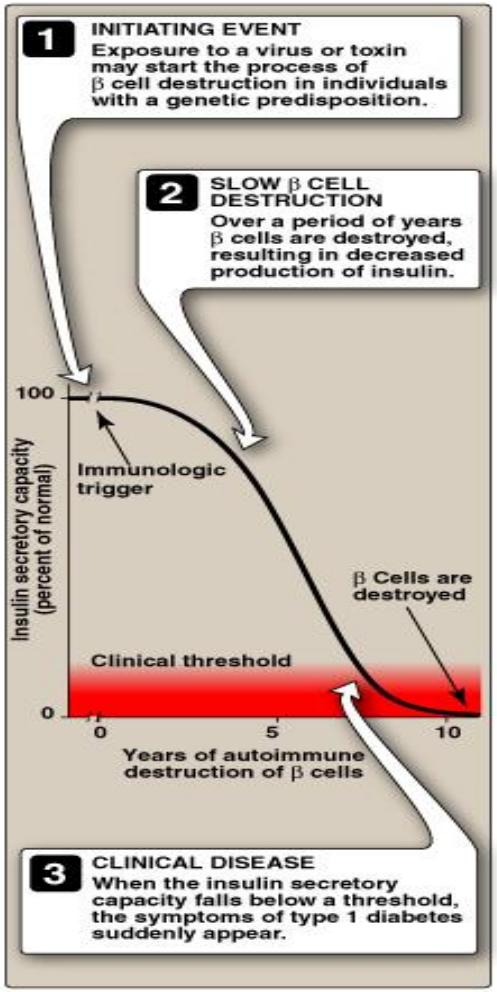


Figure 25.2
Insulin secretory capacity during onset of type 1 diabetes. [Note: Rate of autoimmune destruction of β cells may be faster or slower than shown.]

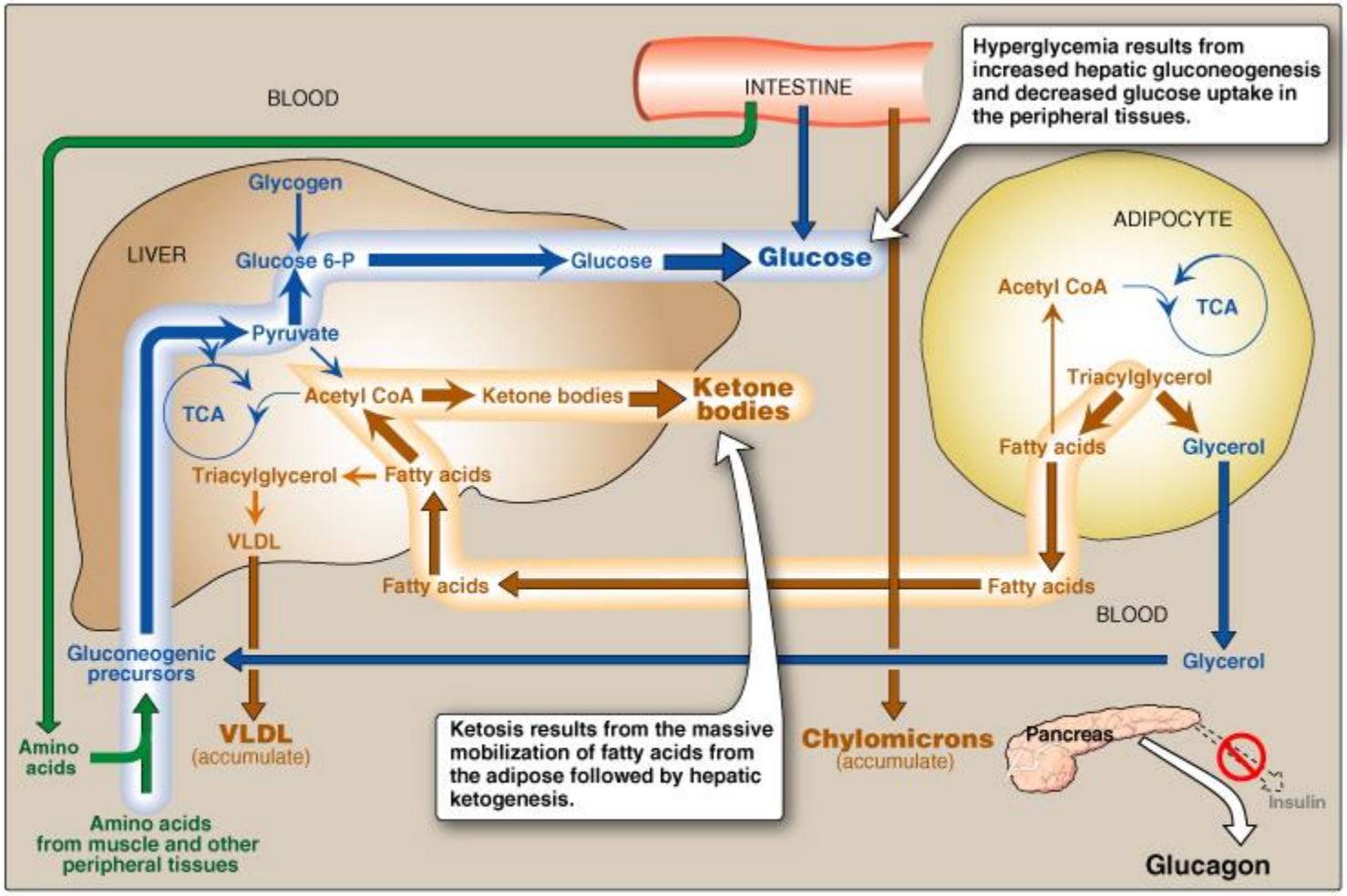


Figure 25.3
Intertissue relationships in type 1 diabetes.

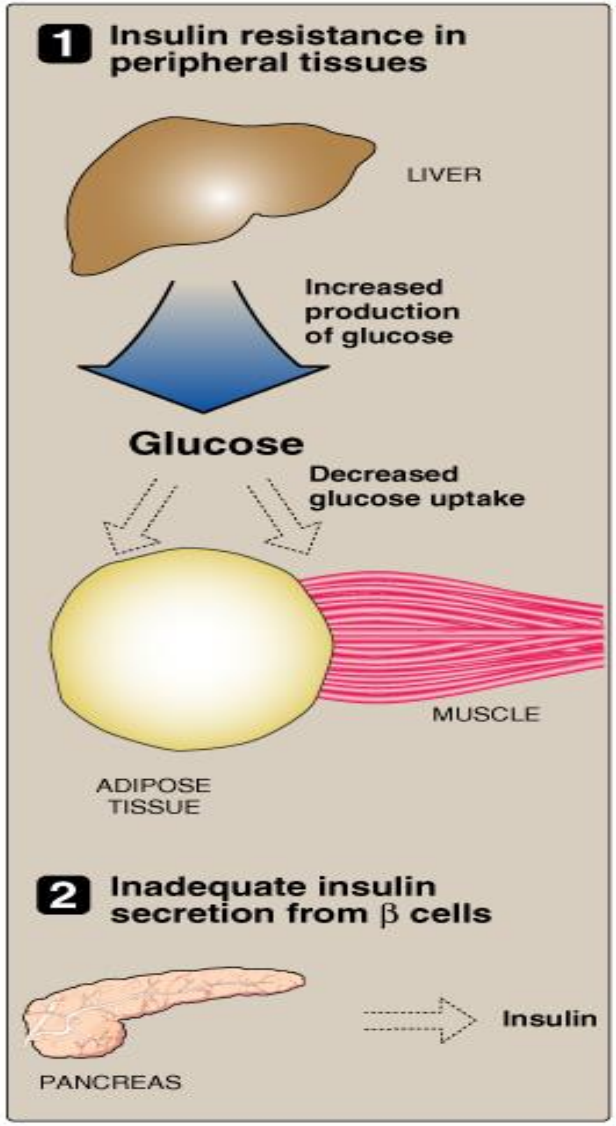


Figure 25.6

Major factors contributing to hyperglycemia observed in type 2 diabetes.

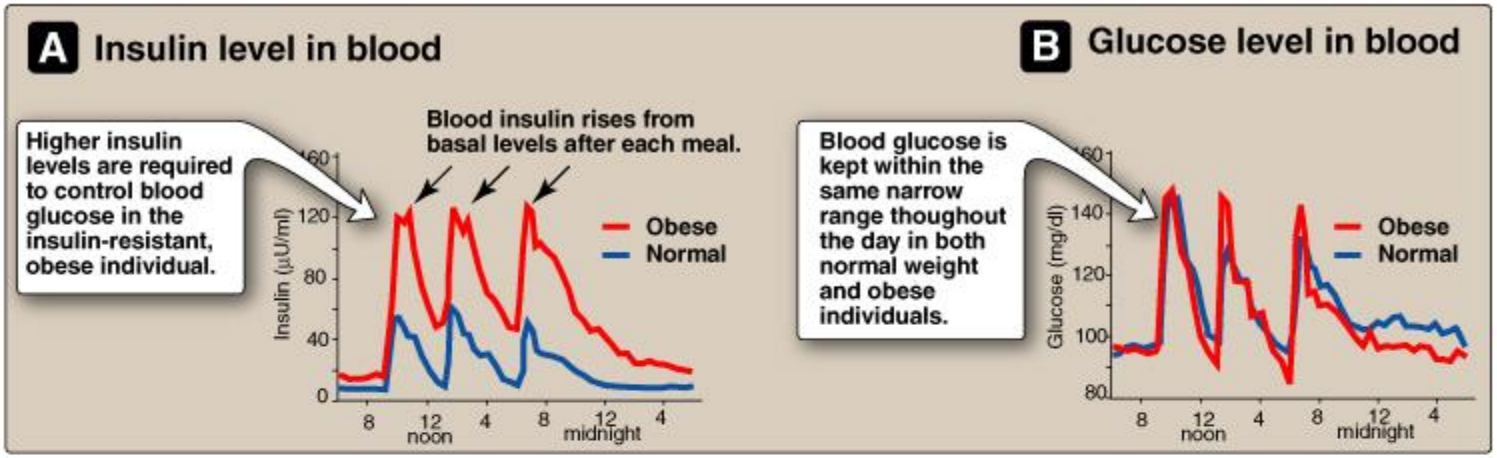


Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.

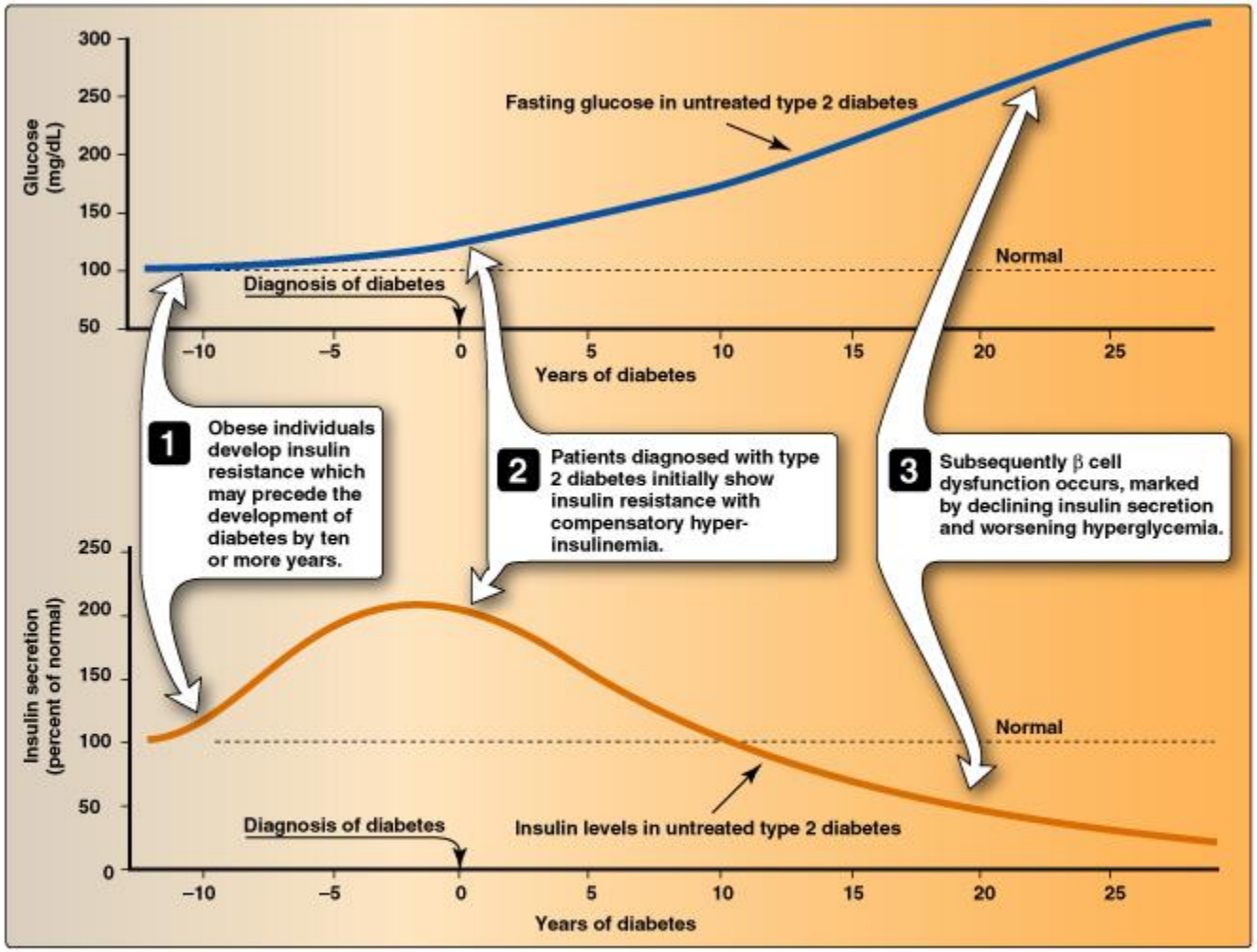


Figure 25.8
Progression of blood glucose and insulin levels in patients with type 2 diabetes.

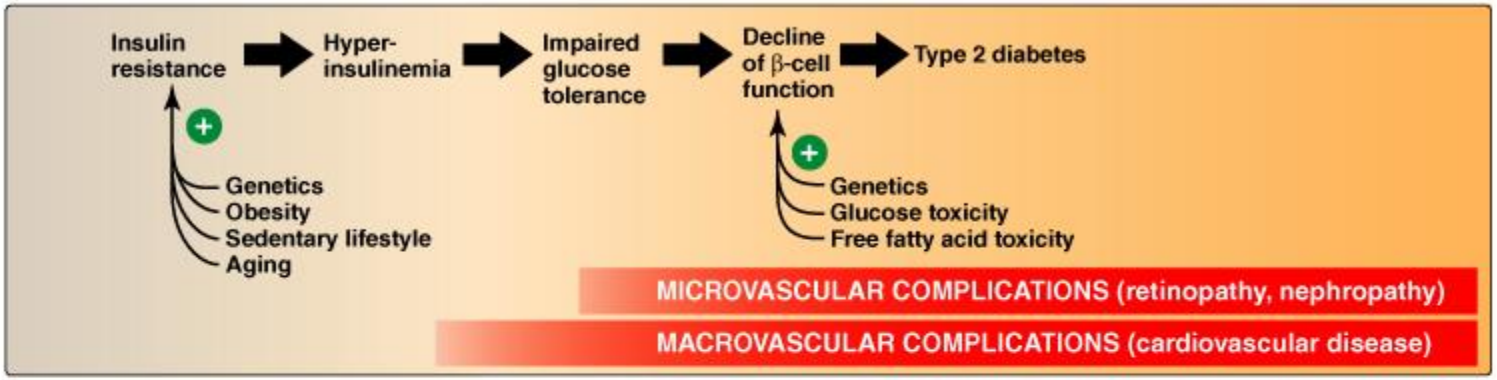


Figure 25.9

Typical progression of type 2 diabetes.

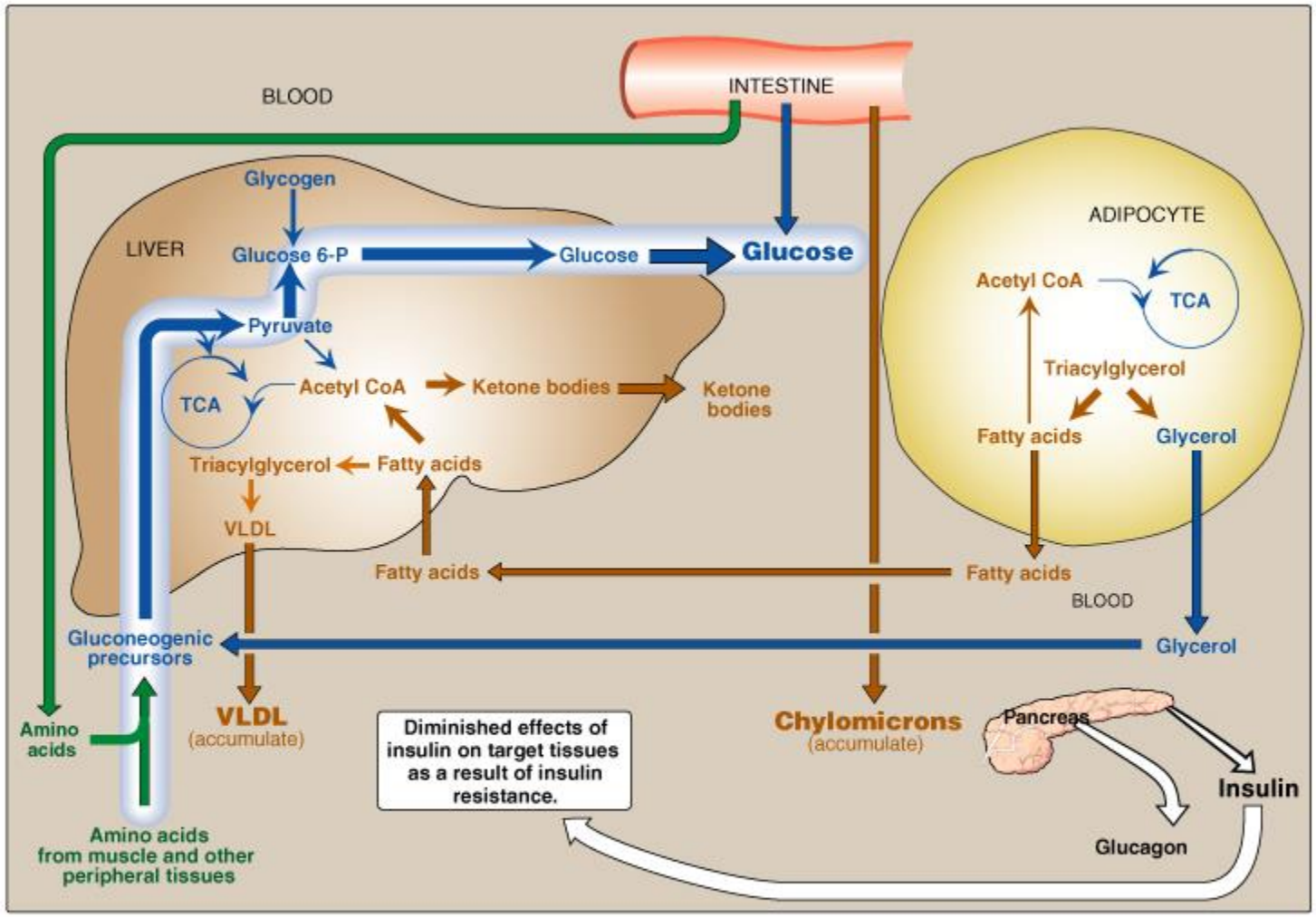
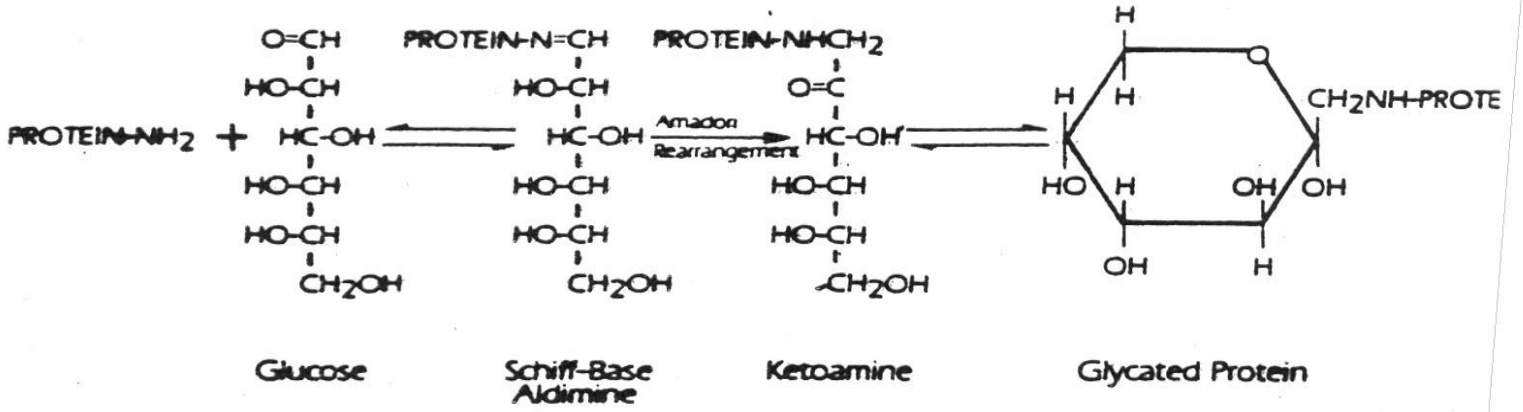


Figure 25.10
Intertissue relationships in type 2 diabetes.

The Glycation Reaction



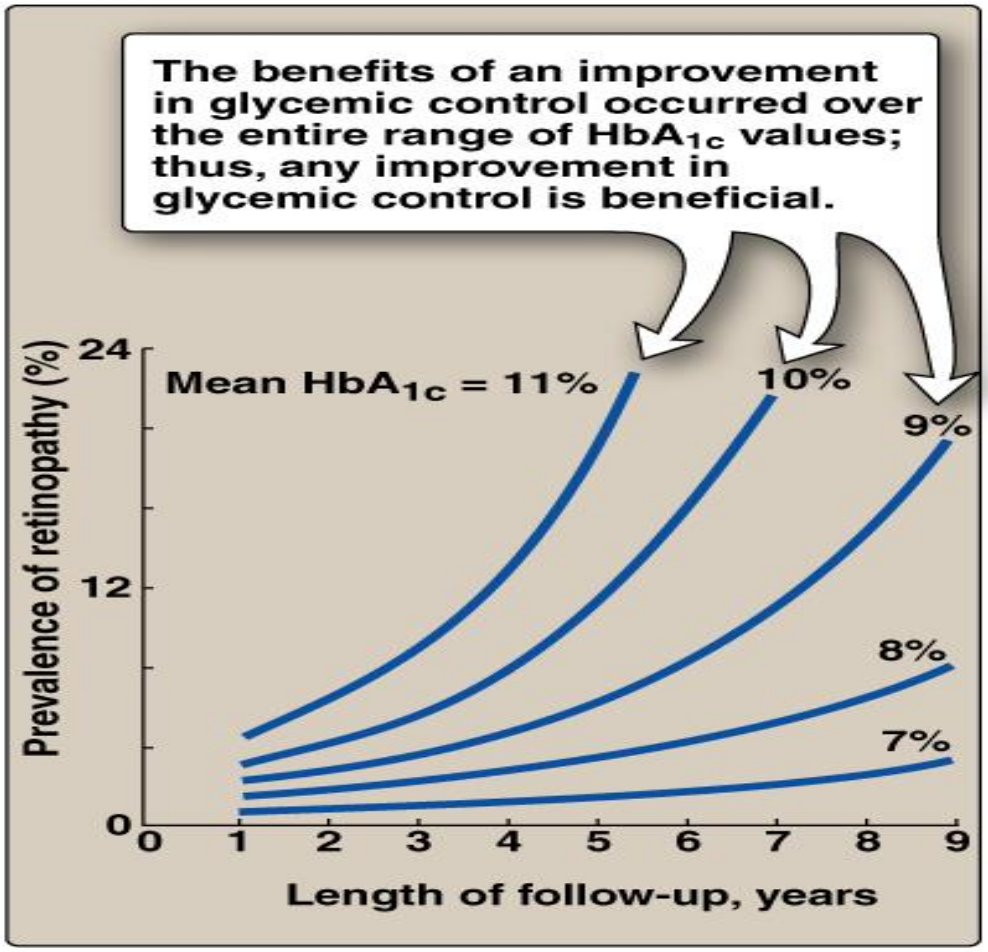


Figure 25.11
Relationship of glycemic control and diabetic retinopathy.

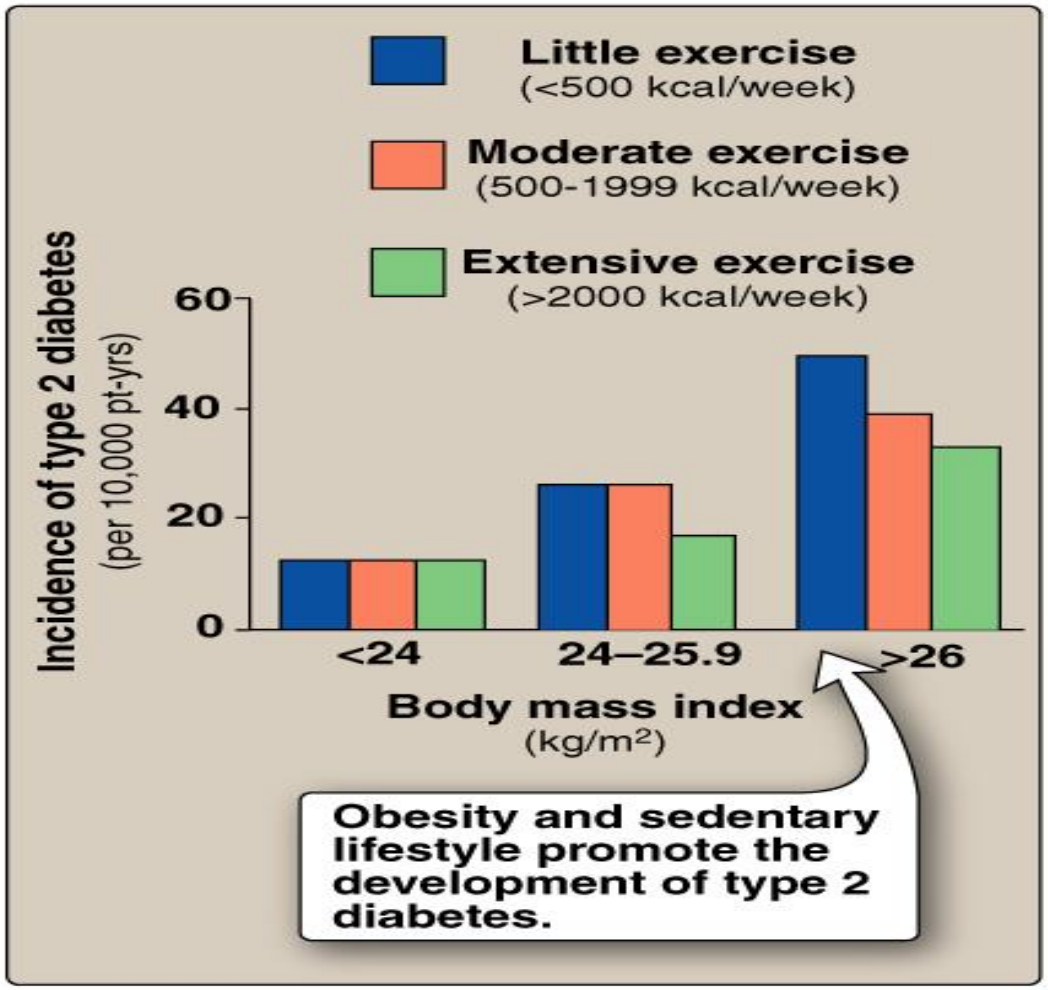


Figure 25.12
Effect of body weight and excercise on the development of type 2 diabetes.