Integration of Metabolism

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Hormones and Metabolism

Metabolic effects of insulin

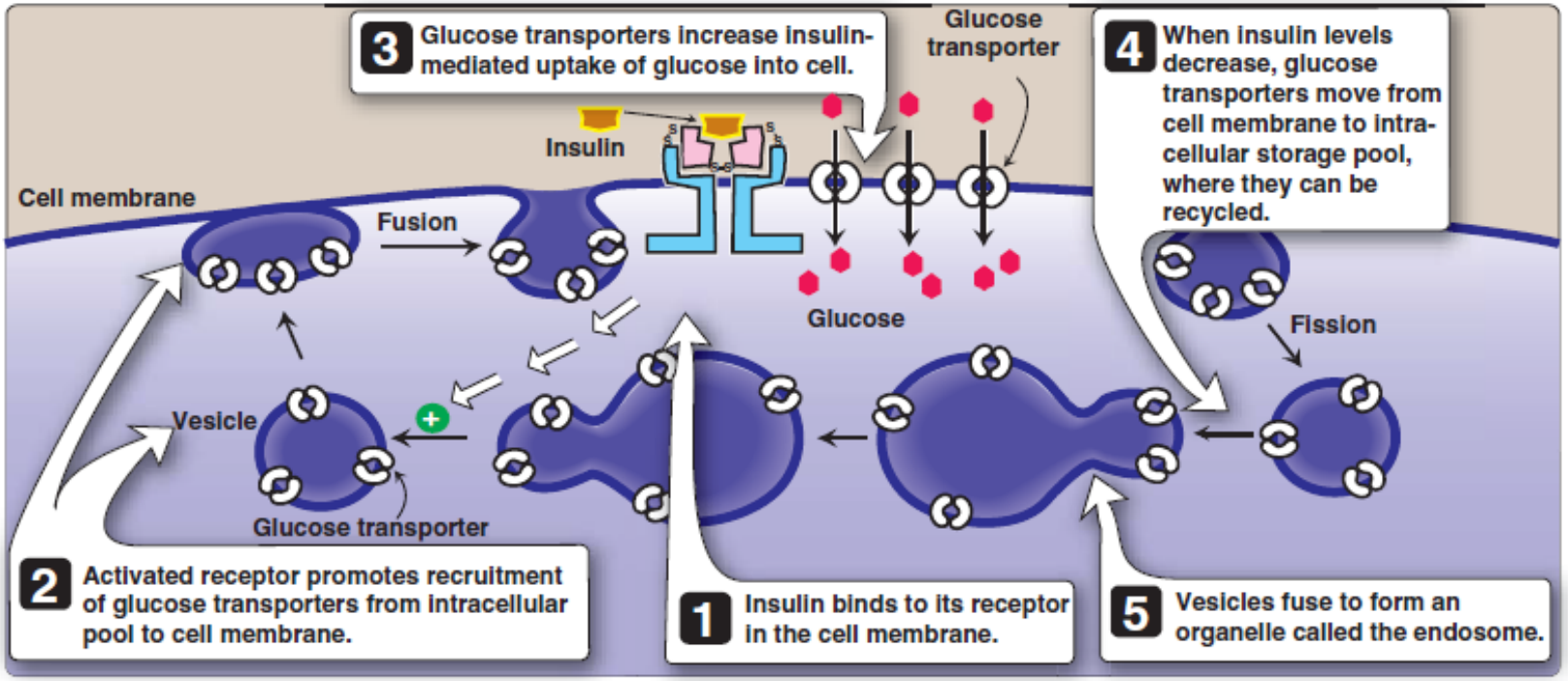


Figure 23.8
Insulin causes the recruitment of glucose transporters (GLUTs) from intracellular stores in skeletal and cardiac muscle and adipose tissue.

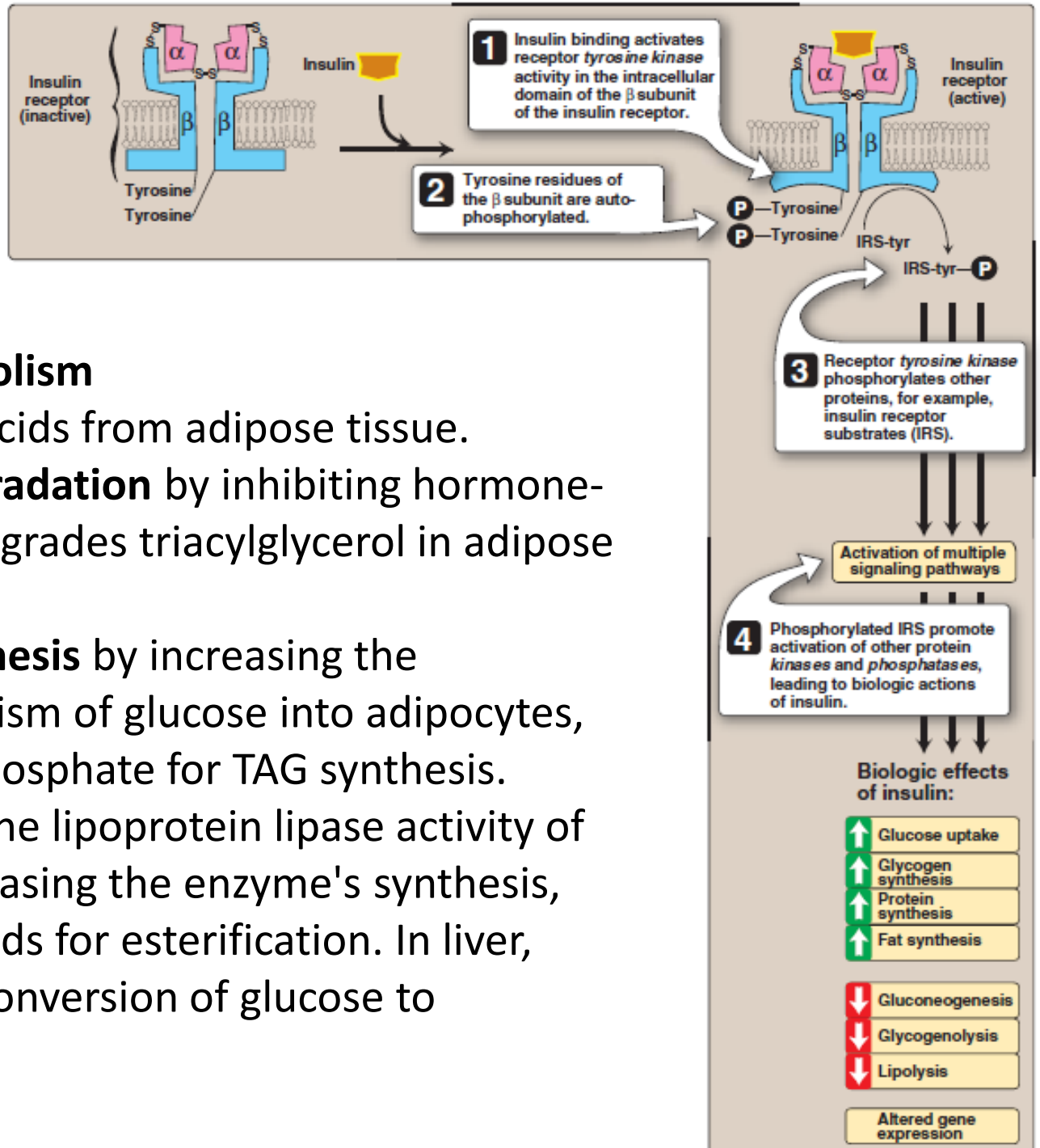
Carbohydrate metabolism

- ✓ Glucose storage mostly in three tissues: liver, muscle, and adipose tissue.
- ✓ ↑ glycogen synthesis in the liver and muscle.
- ✓ ↑ glucose uptake by increasing transporters in muscle and adipose tissue.
- ✓ ↓ glycogenolysis and gluconeogenesis in the liver

Effects on protein synthesis

- ✓ ↑ entry of amino acids into cells and protein synthesis

Metabolic effects of insulin



Effects on lipid metabolism

✓ ↓ release of fatty acids from adipose tissue.

a. Decreased TAG degradation by inhibiting hormone-sensitive lipase that degrades triacylglycerol in adipose tissue.

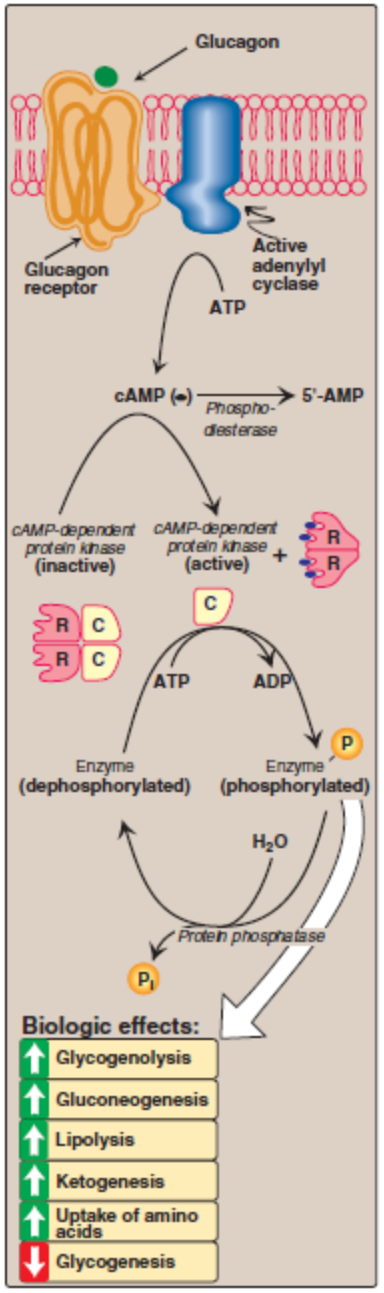
b. Increased TAG synthesis by increasing the transport and metabolism of glucose into adipocytes, providing glycerol 3-phosphate for TAG synthesis. Insulin also increases the lipoprotein lipase activity of adipose tissue by increasing the enzyme's synthesis, thus providing fatty acids for esterification. In liver, insulin promotes the conversion of glucose to triacylglycerols.

Metabolic effects of glucagon

- ✓ Glucagon is a polypeptide (29 aa) hormone secreted by the α cells of the pancreatic islets of Langerhans.
- ✓ Glucagon, along with epinephrine, cortisol, and growth hormone (the "counter-regulatory hormones"), opposes many of the actions of insulin
- ✓ Glucagon receptors are found in hepatocytes but not on skeletal muscle.
- ✓ Glucagon acts to maintain blood glucose levels by activation of hepatic **glycogenolysis** and **gluconeogenesis**.
- ✓ Glucagon secretion is increased by:

1. Low blood glucose.
2. Amino acids derived from a meal containing protein.
3. Epinephrine or norepinephrine.

- ✓ Glucagon secretion is inhibited by elevated blood glucose and by insulin.



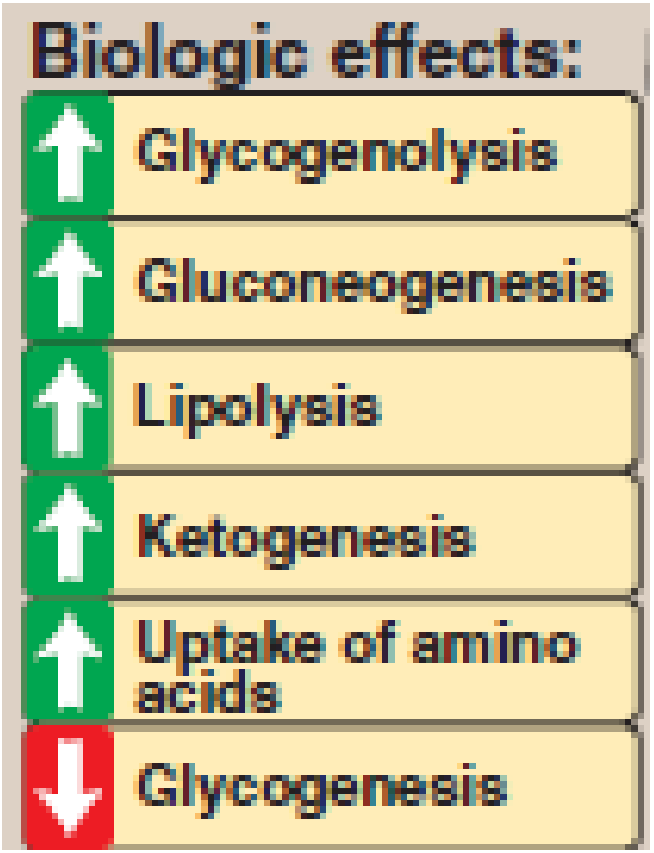
Metabolic effects of glucagon

1. Effects on carbohydrate metabolism: increase in the breakdown of liver (not muscle) glycogen and an increase in gluconeogenesis.

2. Effects on lipid metabolism: Glucagon activates lipolysis in adipose tissue.

The free fatty acids released are taken up by liver and oxidized to acetyl coenzyme A, which is used in ketone body synthesis.

3. Effects on protein metabolism: Glucagon increases uptake of amino acids by the liver, resulting in increased availability of carbon skeletons for gluconeogenesis, thus, plasma levels of amino acids are decreased.



Insulin vs Glucagon

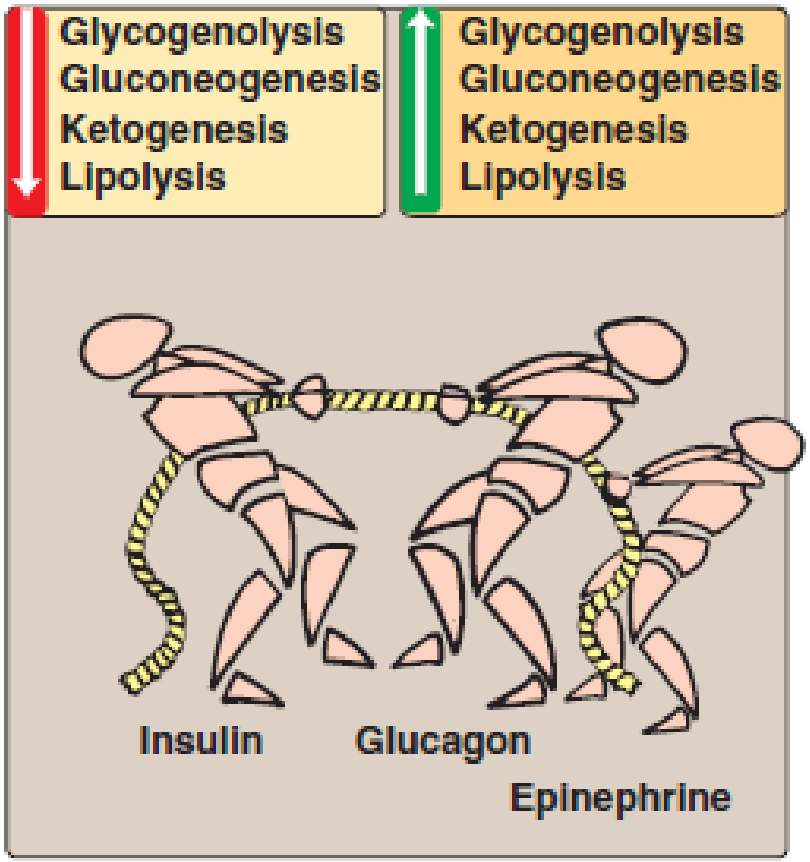
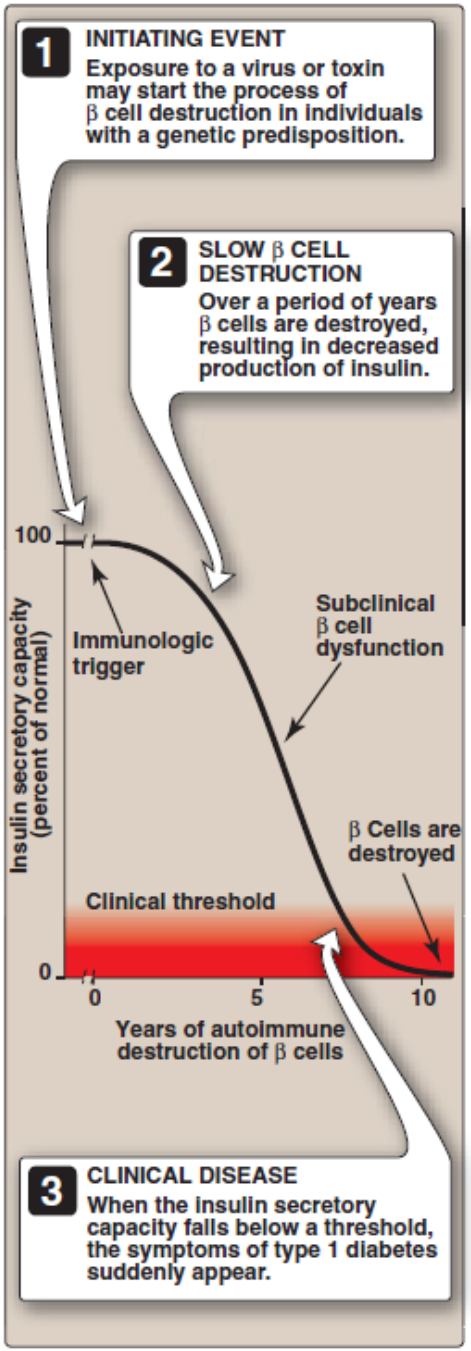


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

Diabetes and Metabolism

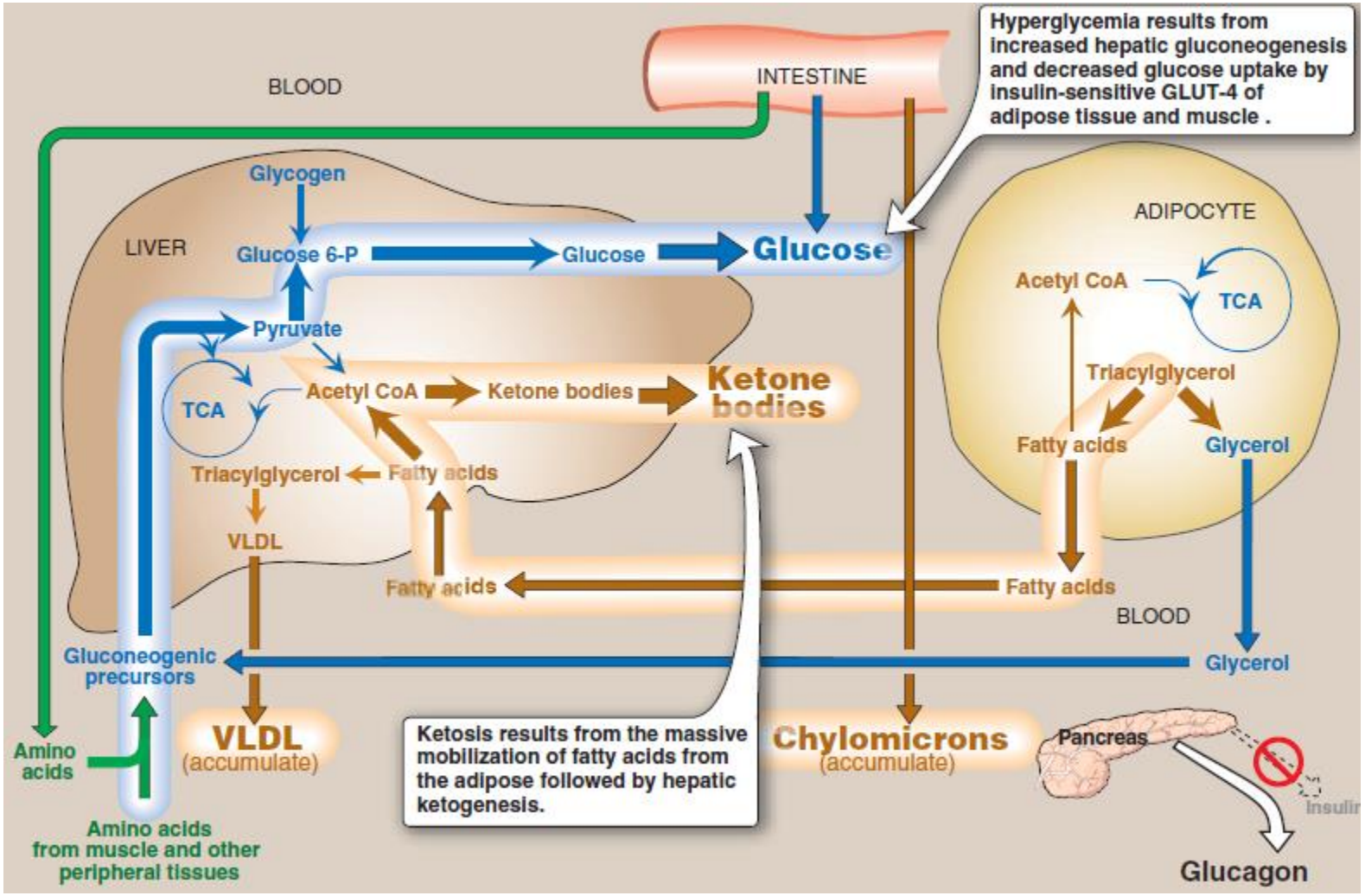
Type I Diabetes Mellitus (DM)

- Insulin deficiency



Metabolic changes in type 1 DM

- The metabolic abnormalities result from an insulin deficiency
- Affects metabolism in three tissues: liver, muscle, and adipose tissue



Metabolic changes in type 1 DM

- Elevated levels of blood glucose and ketones are the hallmarks of untreated type 1
- **Hyperglycemia** due to increased hepatic production of glucose, combined with diminished peripheral utilization (muscle and adipose have the insulin-sensitive GLUT-4)
- **Ketoacidosis** results from increased mobilization of fatty acids from adipose tissue, combined with accelerated hepatic fatty acid β-oxidation and synthesis of 3-hydroxybutyrate and acetoacetate
- **Hypertriacylglycerolemia:** excess fatty acids are converted to TAG, which is packaged and secreted in very-low-density lipoproteins (VLDL)
- ↑ Chylomicrons synthesis because lipoprotein degradation catalyzed by lipoprotein lipase in the capillary beds of muscle and adipose tissue is low in diabetics (synthesis of the enzyme is decreased when insulin levels are low)

Type II Diabetes Mellitus (DM)

- Most common (90%)
- Develops gradually without obvious symptoms
- Polyuria and polydipsia and polyphagia
- A combination of insulin resistance and dysfunctional β cells
- The metabolic alterations are milder than those for type 1, because insulin secretion in type 2, although not adequate, does restrain ketogenesis and blunts the development of diabetic ketoacidosis (DKA)
- Pathogenesis does not involve viruses or autoimmune antibodies.

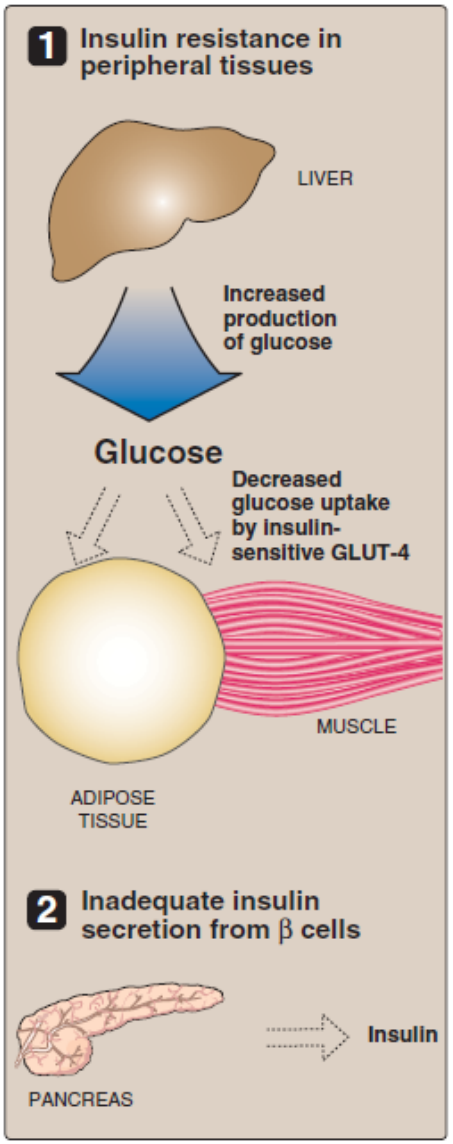


Figure 25.6
Major factors contributing to hyperglycemia observed in type 2 diabetes.

Insulin Resistance (IR)

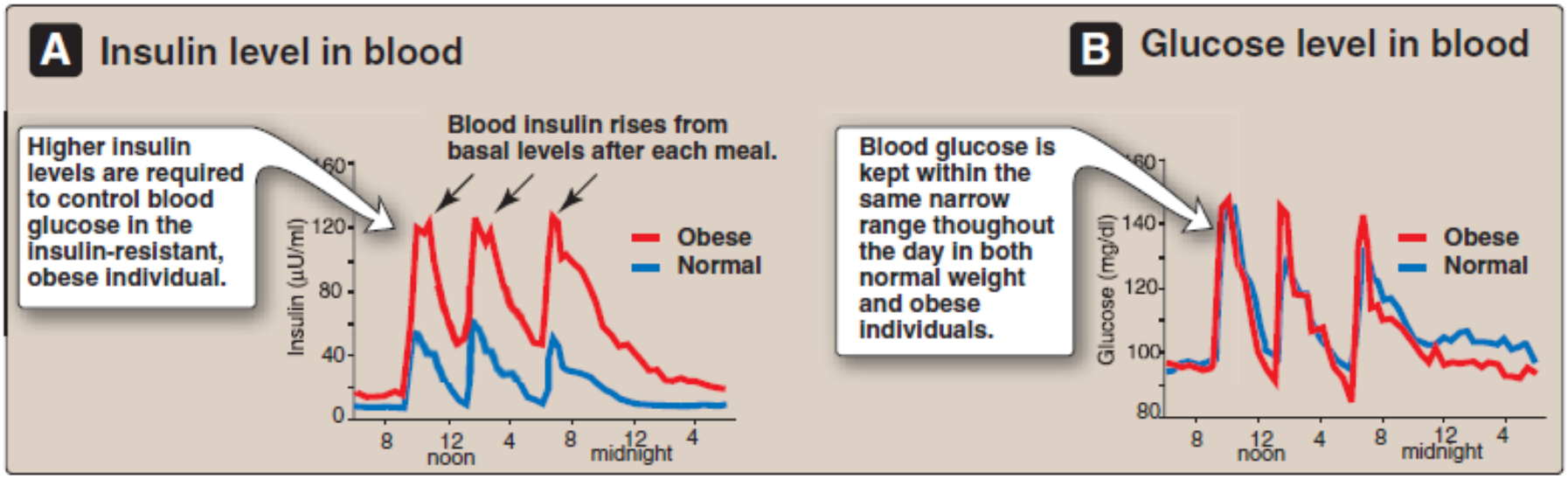


Figure 25.7
Blood insulin and glucose levels in normal weight and obese subjects.

- ✓ IR is the decreased ability of target tissues, such as liver, adipose, and muscle, to respond properly to normal (or elevated) circulating concentrations of insulin.
- ✓ IR is characterized by uncontrolled hepatic glucose production, and decreased glucose uptake by muscle and adipose tissue.
- ✓ Obesity is the most common cause of IR.
- ✓ IR alone will not lead to type 2 diabetes.
- ✓ Type 2 diabetes develops in insulin-resistant individuals who also show impaired β-cell function.

Metabolic changes in type 2 DM

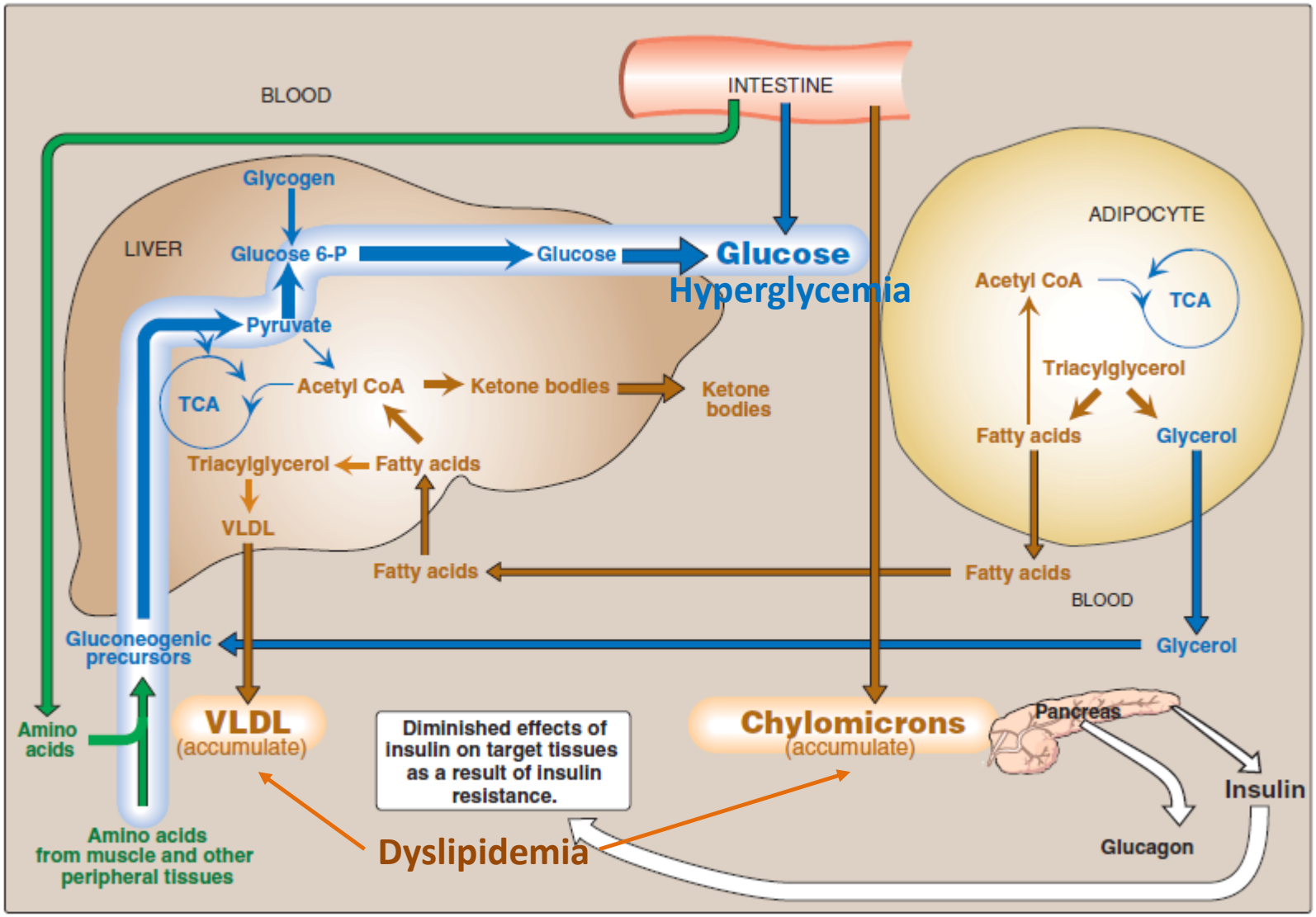


Figure 25.10
Intertissue relationships in type 2 diabetes.

Metabolic changes in type 2 DM

1. Hyperglycemia

- Caused by increased hepatic production of glucose, combined with diminished peripheral use.
- **Ketosis is usually minimal or absent** in type 2 DM because the presence of insulin—even in the presence of IR— diminishes hepatic ketogenesis.

2. Dyslipidemia

- In the liver, fatty acids are converted to **triacylglycerols**, which are packaged and secreted in **VLDL**.
- **↑ Chylomicrons** synthesis from dietary lipids by the intestinal mucosal cells because lipoprotein degradation catalyzed by lipoprotein lipase in adipose tissue is low in diabetics, and the plasma chylomicron and VLDL levels are elevated, resulting in hypertriacylglycerolemia.
- **Low HDL** levels are also associated with type 2 diabetes.

Fasting and Metabolism

OVERVIEW OF FASTING

- Begins if no food is taken after the absorptive period.
- Result from an inability to obtain food, the desire to lose weight rapidly, or clinical situations in which an individual cannot eat, for example, because of trauma, surgery, cancer, or burns.
- In the absence of food, plasma levels of glucose, amino acids, and TAG fall, reducing insulin secretion and increasing glucagon release.
- The nutrient deprivation is a catabolic period characterized by degradation of TAG, glycogen, and protein.

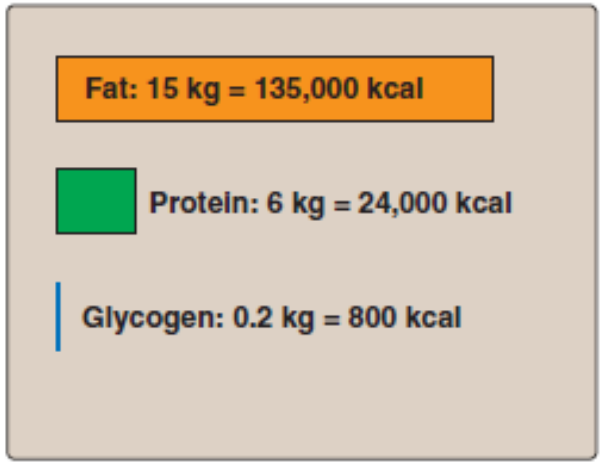


Figure 24.9
Metabolic fuels present in a 70-kg man at the beginning of a fast. Fat stores are sufficient to meet energy needs for about 3 months.

- Priorities:

1) to maintain adequate plasma levels of glucose to supply brain, RBCs, and other glucose-requiring tissues with glucose
2) the need to mobilize fatty acids from adipose tissue, and the synthesis and release of ketone bodies from the liver, to supply energy to all other tissues.

- Although protein is an energy source, each protein also has another function, therefore, only ~1/3 of the body's protein can be used for energy production without fatally compromising vital functions.

Enzyme changes in fasting

- The flow of intermediates through the pathways of energy metabolism is controlled by four mechanisms:

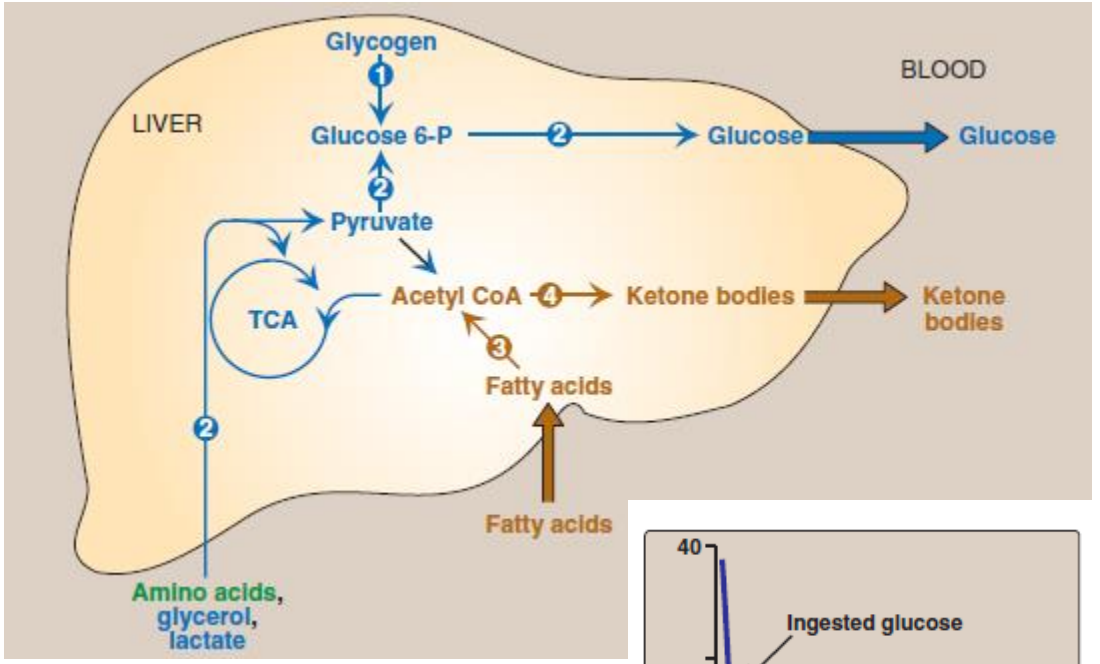
1) the availability of substrates
2) allosteric regulation of enzymes
3) covalent modification of enzymes
4) induction-repression of enzyme synthesis.

- The metabolic changes observed in fasting are generally opposite to those in the absorptive state

- In fasting, substrates are not provided by the diet, but are available from the breakdown of stores and/or tissues.

LIVER IN FASTING

- The primary role of the liver during fasting is to maintain blood glucose through the synthesis and to distribute fuel molecules for use by other organs
- The liver first uses glycogen degradation and then gluconeogenesis to maintain blood glucose levels to sustain energy metabolism of the brain and other glucose-requiring tissues in the fasted (postabsorptive) state.
- Increased fatty acid oxidation as a major source of energy for liver
- Increased synthesis of ketone bodies especially 3-hydroxybutyrate



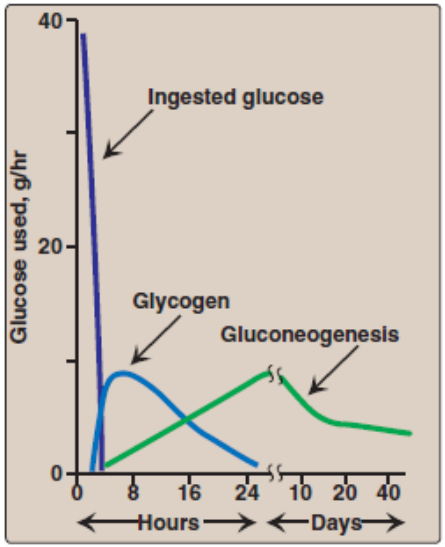
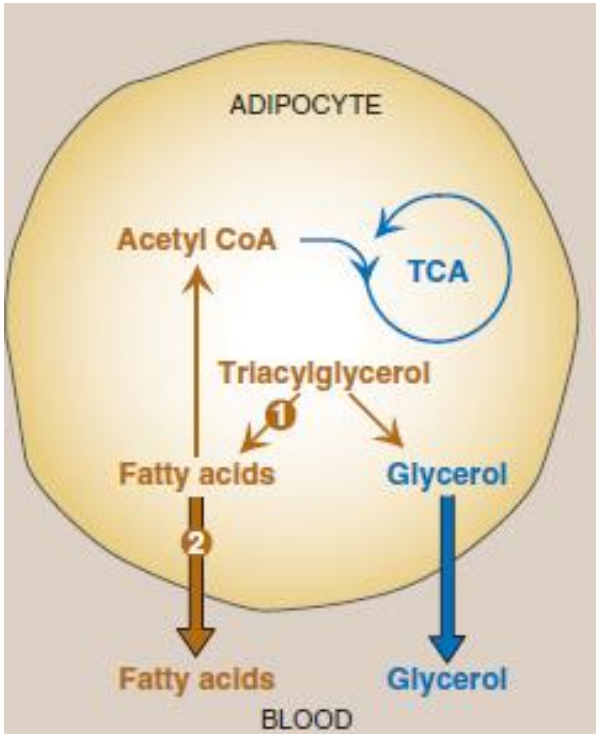


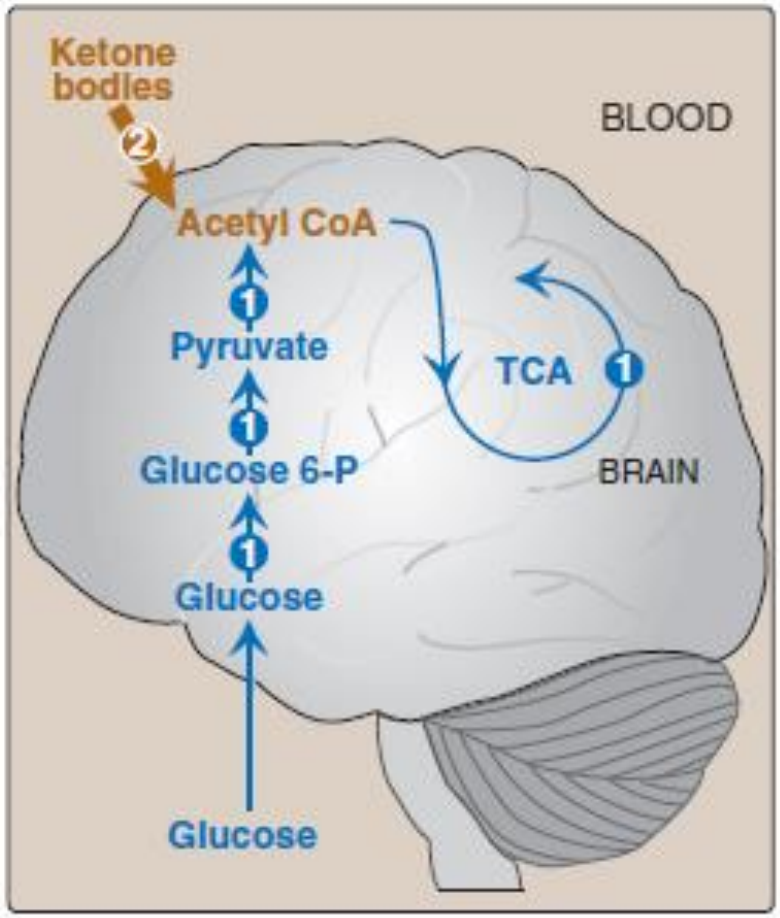
Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

ADIPOSE TISSUE IN FASTING

- Glucose transport by insulin-sensitive GLUT-4 into the adipocyte and its subsequent metabolism are depressed due to low insulin levels. This leads to a decrease in fatty acid and TAG synthesis.
- Increased degradation of TAG by hormone sensitive lipase
- Increased release of hydrolyzed fatty acids from stored TAG into the blood as albumin bound FA to be transported to a variety of tissues for use as fuel.
- The glycerol produced from TAG degradation is used as a gluconeogenic precursor by the liver.



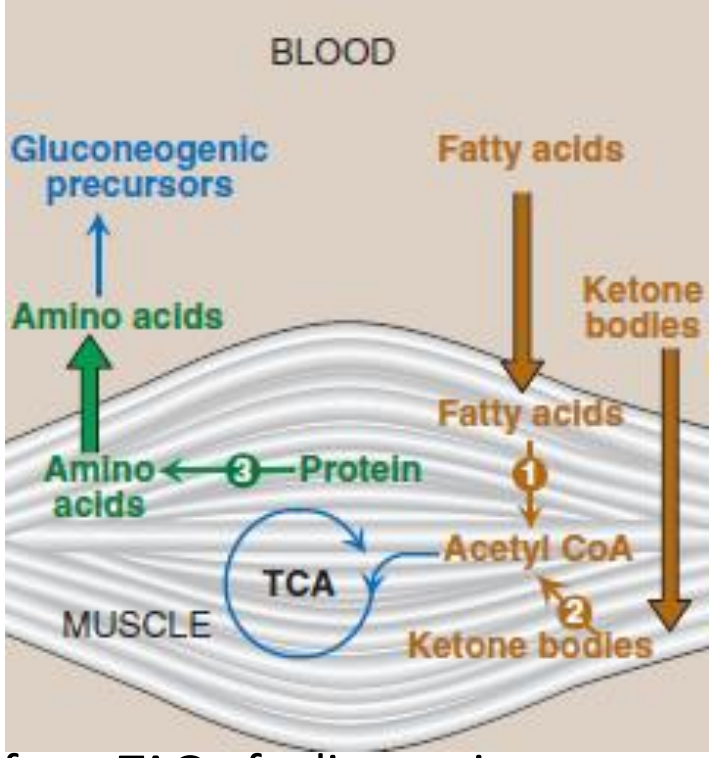
- Decreased uptake of fatty acids since lipoprotein lipase activity of adipose tissue is low during fasting. Consequently, circulating TAG of lipoproteins is not available to adipose tissue.



BRAIN IN FASTING

- During the first days of fasting, the brain continues to use glucose exclusively as a fuel
- Blood glucose is maintained by hepatic gluconeogenesis from glucogenic precursors, such as amino acids from proteolysis and glycerol from lipolysis.
- In prolonged fasting (greater than 2–3 weeks), plasma ketone bodies reach significantly elevated levels, and replace glucose as the primary fuel for the brain reducing the need for protein catabolism for gluconeogenesis and sparing glucose and, thus, muscle protein.

RESTING SKELETAL MUSCLE IN FASTING



- Resting muscle uses fatty acids as its major fuel source.
- Exercising muscle initially uses its glycogen stores as a source of energy.
- During intense exercise, glucose 6-phosphate derived from glycogen is converted to lactate by anaerobic glycolysis
- As glycogen reserves are depleted, free fatty acids from TAG of adipose tissue become the dominant energy source.
- Glucose transport and metabolism are decreased due to low insulin
- During the first 2 weeks of fasting, muscle uses fatty acids from adipose tissue and ketone bodies from the liver as fuels.
- After about 3 weeks of fasting, muscle decreases its use of ketone bodies and oxidizes fatty acids almost exclusively.
- Rapid breakdown of muscle protein during the first few days of fasting to provide AAs (Ala, Gln) for gluconeogenesis in the liver.

KIDNEY IN LONG-TERM FASTING

- Kidney expresses the enzymes of gluconeogenesis, including G-6-phosphatase, and in late fasting about 50% of gluconeogenesis occurs here.
- The Gln released from the muscle's metabolism of branched-chain amino acids is taken up by the kidney and acted upon by renal glutaminase and glutamate dehydrogenase, producing α-ketoglutarate that can be used as a substrate for gluconeogenesis
- Kidney also provides compensation for the acidosis that accompanies the increased production of ketone bodies
- NH3 produced from deamination picks up H+ from ketone body dissociation, and is excreted in the urine as NH4+, decreasing the acid load in the body.
- In long-term fasting, nitrogen disposal occurs in the form of ammonia rather than urea.