39

Hormonal Regulation of Energy Metabolism

LEARNING OBJECTIVES

Upon completion of this chapter, the student should be able to answer the following questions:

1. Explain the different requirements for and utilization by different cells of fuels during the digestive phase as opposed to the interdigestive and fasting phases.
2. Integrate the structure, synthesis, and secretion of insulin with circulating fuel levels, especially glucose.
3. Utilize the different signaling pathways regulated by insulin to link insulin to its cellular effects at the molecular level.
4. Integrate the structure, synthesis, and secretion of glucagon with the levels of circulating fuels, insulin, and catecholamines.
5. Map out and integrate the actions of insulin on the utilization and storage of glucose, free fatty acids (FFAs), and amino acids (AAs) by hepatocytes, skeletal muscle, and adipocytes during the digestive phase.
6. Map out and integrate the actions of counterregulatory hormones (glucagon, catecholamines) on the utilization of glucose, the sparing of glucose, and the utilization of FFAs and AAs by hepatocytes, skeletal muscle, and adipocytes during the interdigestive and fasting phases.
7. Integrate the changes in fuel utilization and hormonal signaling in hepatocytes during the interdigestive and fasting phases that allow for and promote hepatic glucose production and ketogenesis.
8. Compare signaling pathways that have orexigenic and anorexigenic actions via the hypothalamus.
9. Link several pathologies related to metabolism, especially those caused by the absolute or relative absence of insulin and by obesity.

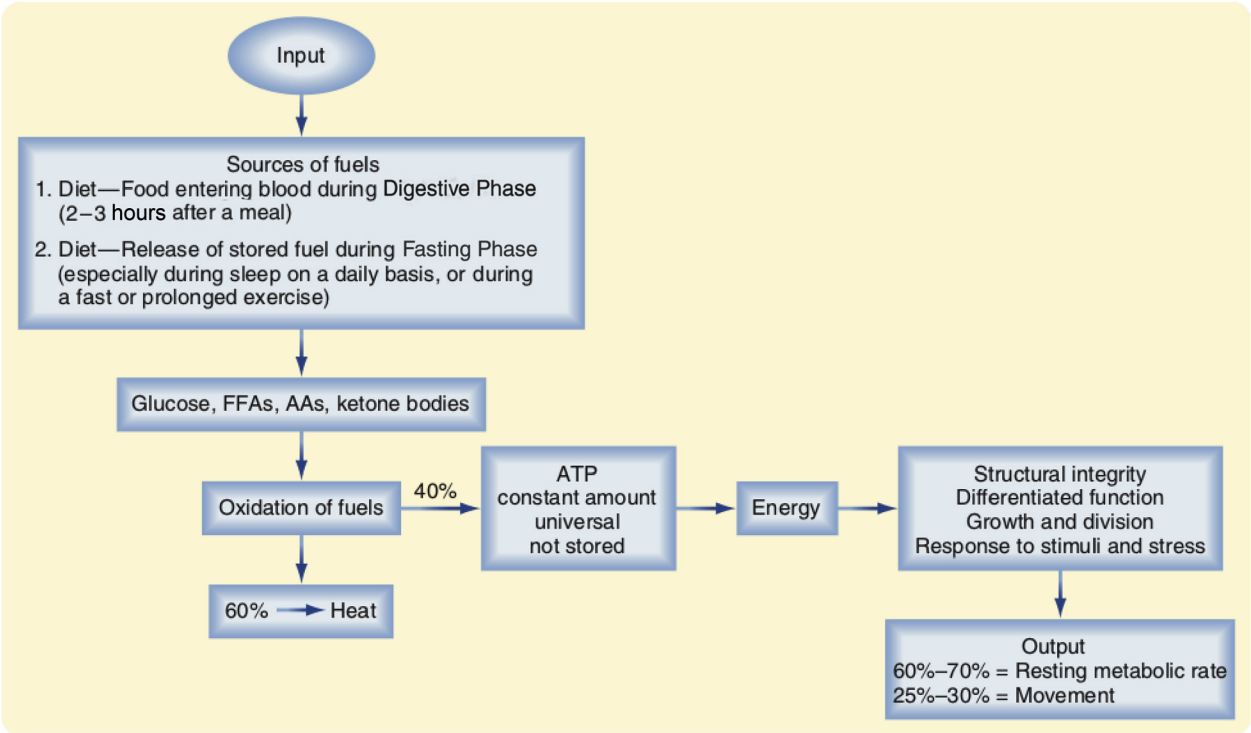
Continual Energy Supply and Demand: The Challenge

There are an estimated 40 trillion cells in the human body, not including the approximately 40 trillion non-human cells that comprise the human microbiome. All these cells must continually perform **work** to stay alive. This work includes maintenance of cellular composition and structural integrity, along with the integrated synthesis and breakdown (i.e., turnover) of macromolecules and organelles. This work also involves the functions of cells that contribute to the human body as a whole (e.g., contraction of the muscle fibers of the diaphragm). Additional work is required of cells when the human body is engaged in a variety of activities, including (but not limited to) manual labor, exercise, and outdoor play; body growth spurt and maturation of the reproductive systems at puberty; pregnancy and breast-feeding; combating an infection or cancer; and the healing of damaged tissues/organs (e.g., healing from surgery). On average, the **resting metabolic rate** of a relaxed, awake, stationary, healthy adult human accounts for about 70% of their total energy expenditure each day (Fig. 39.1).

To perform this work, cells need **fuels,** along with the capability to convert fuels into potential chemical energy in the form of **adenosine triphosphate (ATP).** Cells then convert the energy within ATP into chemical and mechanical work (see Fig. 39.1). This means that the need for ATP is immediate and unending, and consequently all living cells must continually synthesize ATP. In fact, humans produce about the equivalent of their body weight in ATP daily. This places a demand on the body to continually supply fuel in some form to all cells. All fuel originates from the **diet,** but humans do not eat in a nonstop manner all day long. *Thus, the constant cellular demand for fuels to make ATP and perform work is paired with an intermittent ingestion of fuels*. Diet-derived fuels are oxidized for ATP, but in order to maintain ATP production when not eating for a while (e.g., during sleep), some fuels are stored for future use.

In trying to make sense of energy metabolism, it is important to organize one's thinking around the following:

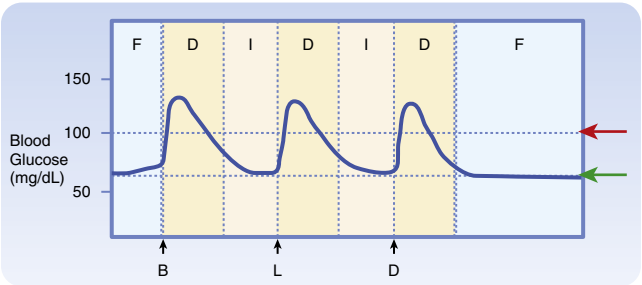
1. *Fuels (Fig. 39.1)*. Our diet includes both monomeric and polymeric forms (the latter are converted into monomeric forms during digestion and absorption) of the following: (1) **monosaccharides,** including **glucose,** fructose, and galactose; (2) **long-chain free fatty acids** (referred to in this chapter as simply **FFAs**); and (3) **amino acids (AAs)**. The fourth general type of fuel is **ketone bodies** (KBs), which are largely absent in the diet. Instead, KBs are produced by hepatocytes via ketogenesis (reaction 14



• **Fig. 39.1** Overview of energy metabolism. *AAs*, amino acids; *FFAs*, free fatty acids.

in Fig. 39.3B), using FFAs and **ketogenic AAs,** both of which become abundant during the Fasting Phase. The diet also includes other fuels such as **ethanol.**

2. *Metabolic Phases.* Metabolic Phases refer to the hourly and daily differences in fuel usage and energy metabolism, which are dictated largely by the abundance or scarcity of certain fuels and orchestrated by phase-specific hormones. In general, there are three metabolic phases (Fig. 39.2): (1) the **Digestive** or **Absorptive Phase,** which occurs during the 2 to 3 hours it takes to digest a meal; (2) the **Interdigestive** or **Postabsorptive Phase,** which normally occurs between meals; and (3) the **Fasting Phase,** which most commonly occurs between the last snack before bedtime and breakfast. (In fact, physicians refer to a blood value as "fasting," e.g., "fasting blood glucose," if the patient abstains from eating after midnight and has blood drawn about 8 AM; **prolonged fasting** and **starvation** are more extreme forms of fasting.) **Physical exertion,** which imposes a heightened energy demand, is another type of metabolic phase that occurs with some frequency and regularity for some individuals. This chapter primarily compares how metabolism differs between the **Digestive Phase** and the **Fasting Phase**, and how different hormones orchestrate these metabolic differences.



• **Fig. 39.2** Blood glucose levels during the three metabolic phases: *D*, Digestive Phase; *F*, Fasting Phase; *I*, Interdigestive Phase. *B*, breakfast; *D*, dinner; *L*, lunch. *Red arrow* indicates the upper limit for normal fasting glucose; *green arrow* indicates the lower limit for normal fasting glucose.

3. *Metabolic actions of hepatocytes, adipocytes, and skeletal myocytes.* All cells are involved in energy metabolism, but these three cell types have a profound impact on whole-body metabolism. During the Digestive Phase, **hepatocytes, skeletal myocytes,** and **adipocytes** function largely independently of each other. In contrast, the actions of these three cell types become highly integrated during the Fasting Phase in order to maintain adequate blood glucose levels while providing alternative energy substrates for each cell type. Key features with respect to metabolism of these three cell types are listed in Table 39.1.
4. *Blood glucose levels.* Cells with no or very few mitochondria (e.g., erythrocytes, lens cells of the eye) are absolutely dependent on glucose for energy. Additionally, the central nervous system (CNS) can only use glucose for ATP production under normal conditions. Thus, in the Interdigestive and Fasting Phases, maintenance of blood glucose above a certain minimal threshold is absolutely necessary to avoid CNS-related symptoms, beginning with those caused by a hypoglycemia-activated autonomic response (e.g., nausea, sweating, cardiac arrhythmias). If

TABLE 39.1 Fate of Fuels During Digestive and Fasting Phases

	Hepatocytes	Adipocytes	Skeletal Myocytes
Glucose, fed phase	• Utilization for ATP • Storage as glycogen • DNL	• Increased uptake by GLUT4 • Utilization for ATP • Utilization for G3P	• Increased uptake by GLUT4 (largest impact on glucose tolerance) • Utilization for ATP • Storage as glycogen
Glucose, fasting phase	• Breakdown of glycogen and release of glucose into blood • New synthesis of glucose from small precursors and release into blood • Use of alternative fuel for ATP	• Decreased uptake by GLUT4 • Use of alternative fuels	• Decreased uptake by GLUT4 • Use of alternative fuels • Breakdown of glycogen and use of glucose intracellularly (no export), especially during exercise
FFA/TG, fed phase	• Make FFAs from glucose by DNL • Esterify FFAs into intrahepatic TG • Uptake of chylomicron remnants	• Lipolysis of chylomicrons and uptake of FFAs • Esterification of FFAs into storage TG • Inhibition of lipolysis of stored TG	• Minimal involvement
FFA/TG, fasting phase	• Utilization for ATP • Utilization to produce KBs • Assembly of TG into VLDL • Secretion of VLDL	• Release of FFAs from TG stores • Utilization for ATP	• Utilization for ATP
AAs, fed phase	• Utilization for multiple anabolic pathways	• Utilization for multiple anabolic pathways	• Utilization for multiple anabolic pathways
AAs, fasting phase	• Utilization for gluconeogenesis • Utilization for ketogenesis	• Proteolysis and release of AAs	• Proteolysis and release of AAs
KBs, fed phase	• Should be absent	• Should be absent	• Should be absent
KBs, fasting phase	• Synthesis from FFAs and some AAs • Cannot be utilized for ATP	• Utilization for ATP	• Utilization for ATP

AA, Amino acid; *ATP*, adenosine triphosphate; *DNL*, de novo lipogenesis; *FFA*, free fatty acid; *G3P*, glycerol-3-phosphate; *KB*, ketone body; *TG*, triglyceride; *VLDL*, very low-density lipoprotein.

blood glucose continues to fall, progression to symptoms caused by neuroglycopenia (e.g., cognitive dysfunction, loss of coordinated motor function, and ultimately even coma and death) can occur. This means that whole-body metabolism during the Interdigestive and Fasting Phases must meet the challenge of maintaining blood glucose above 60 mg/dL (see Fig. 39.2, *green arrow*).

Conversely, blood glucose levels must be maintained below an upper threshold (see Fig. 39.2, *red arrow*). This is because glucose is a fairly reactive molecule. High blood glucose leads to high intracellular glucose in many cells, which, in turn, becomes nonenzymatically covalently linked to proteins and other molecules, thereby disrupting their configuration, half-life, and function (see In The Clinic—Glucotoxicity Within Microvasculature).

5. *Insulin and the counterregulatory hormones.* Metabolism during the Digestive Phase is orchestrated almost entirely by **insulin.** During the Fasting Phase, insulin drops to low levels, and this alone allows for some of the metabolic adaptions during the Fasting Phase. In addition, **glucagon** and **catecholamines** (**epinephrine, norepinephrine**) stimulate metabolic pathways that integrate the body's response to an absence of ingested and absorbed fuels. These hormones are referred to as *counterregulatory hormones* based on their opposition to insulin. Growth hormone (see Chapter 41) and cortisol (see Chapter 43) also contribute somewhat to Fasting-Phase metabolism.

Integrated Overview of Energy Metabolism

The basic objectives of the Digestive Phase (see Table 39.1) include:

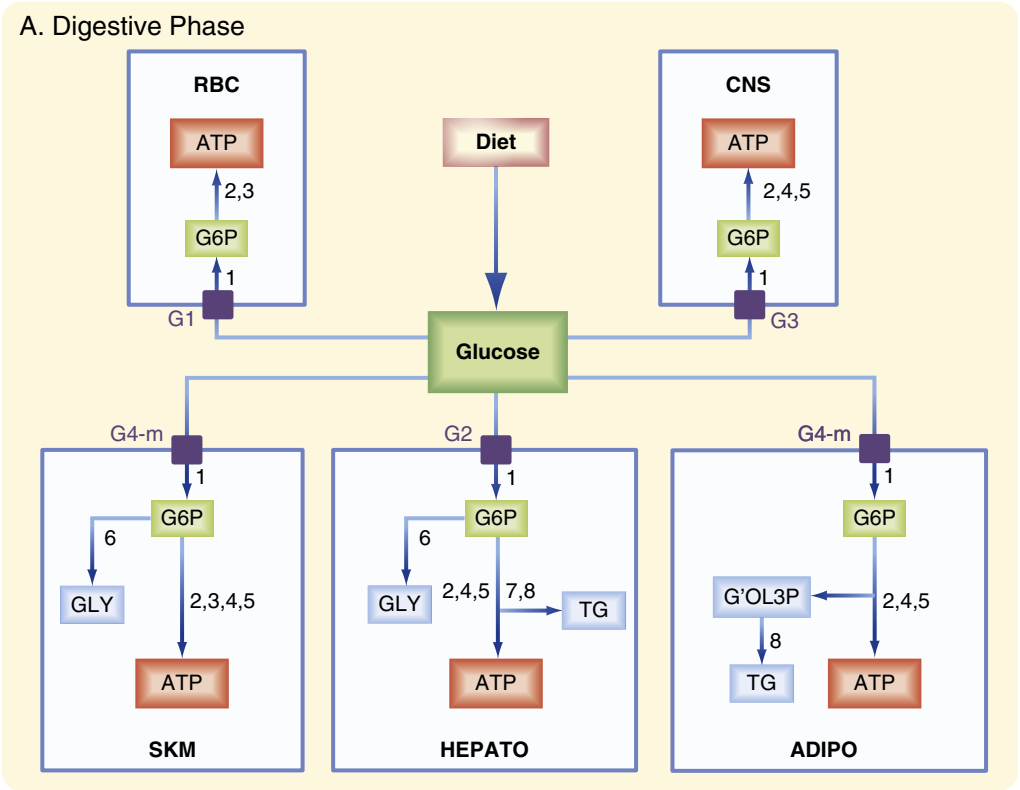
1. **Glucose utilization**, in order to prevent prolonged periods of high blood glucose (Fig. 39.2; *red arrow*).
2. **Synthesis and storage of fuel polymers** (glycogen, triglycerides, proteins) that can be accessed for fuels during the Fasting Phase.
3. **Overall anabolism** to maintain the molecular integrity of cells.

The metabolic pathways that fulfill these objectives are driven by **insulin**, which is the main hormone of the Digestive Phase.

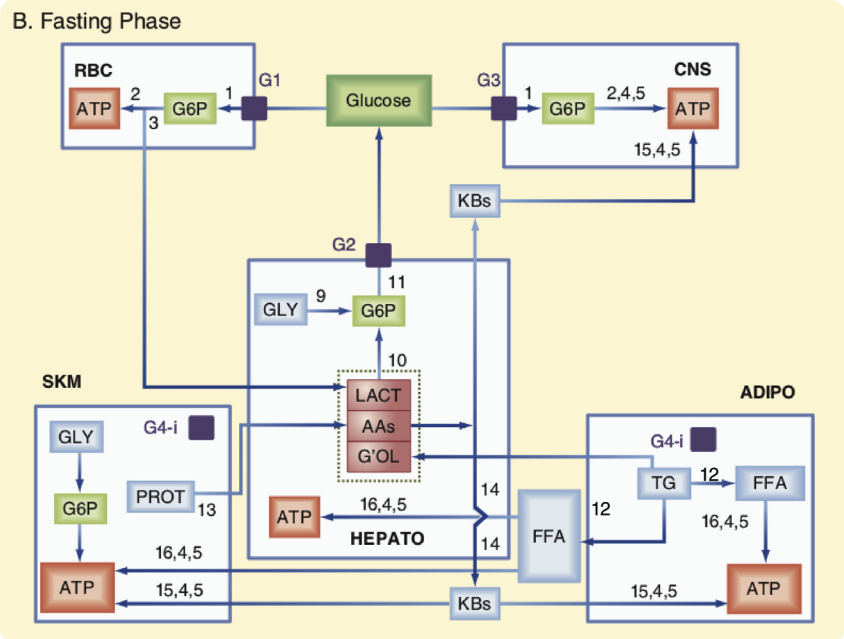
Digestive Phase

During the Digestive Phase, absorbed fuels are partitioned and used for different purposes. **Glucose** is the primary fuel used for energy (i.e., ATP production) during the Digestive Phase (refer to Fig. 39.3A for enzymatic pathways). Glucose is considered a universal fuel in that most cells can perform the following:

1. Import glucose via bidirectional facilitative GLUT transporters (G1, G2, G3, and G4).
2. "Trap" and "activate" imported glucose by converting glucose into glucose-6-phosphate (G6P) through the activity of one or more hexokinases (Pathway 1). G6P cannot pass through GLUT transporters ("trapping") and is now a substrate for several enzymatic pathways ("activation").
3. Metabolize G6P to pyruvate via the glycolytic pathway, which yields a small amount of ATP without requiring mitochondria or O_2 (Pathway 2). Cells without mitochondria ferment pyruvate to lactate (Pathway 3) and export lactate to the ECF. In contrast, most cells import pyruvate into mitochondria, convert it to acetyl CoA by pyruvate dehydrogenase, and then condense acetyl CoA with oxaloacetate to form citrate. Citrate is cycled through the tricarboxylic acid (TCA) cycle back to oxaloacetate (Pathway 4). This metabolism of pyruvate through the TCA cycle releases CO_2 as waste and generates guanosine triphosphate (GTP) along with flavin adenine dinucleotide hydride ($FADH_2$) and nicotine adenine dinucleotide hydride (NADH). $FADH_2$ and NADH are used by the electron transport system and oxidative phosphorylation to ultimately generate relatively large amounts of ATP through a process that is absolutely dependent on O_2 (Pathway 5).



• **Fig. 39.3 A,** Overview of glucose utilization during the Digestive Phase. GLUT transporters: *G1*, GLUT1; *G2*, GLUT2; *G3*, GLUT3; *G4-m*, functional GLUT4 localized to cell membrane. Cell types: *ADIPO*, adipocyte; *CNS*, central nervous system neurons and glia; *HEPATO*, hepatocyte; *RBC*, red blood cell; *SKM*, skeletal myocyte. Metabolites: *G6P*, glucose-6-phosphate; *GLY*, glycogen; *G'OL3P*, glycerol-3-phosphate; *TG*, triglyceride. Metabolic reactions/pathways: *1*, hexokinase/glucokinase; *2*, glycolysis; *3*, lactate dehydrogenase; *4*, TCA cycle ± pyruvate dehydrogenase; *5*, oxidative phosphorylation; *6*, glycogen synthesis; *7*, de novo lipogenesis; *8*, esterification of FFAs to G'OL3P to form TG. **B,** Overview of energy metabolism during the Fasting Phase. GLUT transporters: see legend for Fig. 39.3A, plus: *G4-I*, inactive GLUT4 with intracellular localization. Cell types: see legend for Fig. 39.3A. Metabolites: see legend for Fig. 39.3A, plus: *AAs*, amino acids; *FFA*, free fatty acid; *G'OL*, glycerol; *KBs*, ketone bodies; *LACT*, lactate; *PROT*, protein. Metabolic reactions/pathways: see legend for Fig. 39.3A, plus: *9*, glycogenolysis; *10*, gluconeogenesis; *11*, G-6-phosphatase; *12*, lipolysis; *13*, proteolysis; *14*, ketogenesis; *15*, ketolysis; *16*, β-oxidation.



• **Fig. 39.3 cont'd**

IN THE CLINIC

Glucotoxicity Within Microvasculature

The endothelium of the microvasculature of the kidney and retina, as well as the endothelium of the vasa nervosum of the autonomic nervous system, is particularly sensitive to hyperglycemia. Chronically high blood glucose results in pathologically high intracellular levels of glucose in these endothelial cells, resulting in altered protein and lipid structure, oxidative stress, and altered signaling pathways. These insults, collectively referred to as **glucotoxicity,** cause pathological changes in intracellular and membrane components as well as in secreted molecules that either signal and/or make up the extracellular matrix. Indeed, glucotoxicity is the root cause of the **nephropathy, retinopathy, and peripheral neuropathy** that occur in poorly controlled diabetes mellitus. Therefore, whole-body metabolism during all metabolic phases must meet the challenge of minimizing the magnitude and duration of the rise in blood glucose associated with ingestion of a meal and must maintain blood glucose below a safe maximal threshold of 100 mg/dL during all other times. Fasting blood glucose between 100 and 124 mg/dL is indicative of **impaired glucose tolerance,** and values at 125 mg/dL and above are evidence of **diabetes mellitus.**

Glucose is consumed by erythrocytes and the brain continually throughout all metabolic phases. In contrast, **hepatocytes**, **skeletal myocytes,** and **adipocytes** primarily use glucose during the Digestive Phase. Insulin stimulates glycolysis and entry of pyruvate (end product of glycolysis) into the TCA cycle and oxidative phosphorylation for ATP production in hepatocytes, skeletal myocytes, and adipocytes (see Table 39.1).

Hepatocytes express the **GLUT2** isoform of the glucose transporter, which is not regulated by insulin for its insertion into the cell membrane. In contrast, skeletal myocytes and adipocytes express the **GLUT4** isoform. Newly synthesized GLUT4 exists in an intracellular inactive state with GLUT4 storage vesicles (G4-i in Fig. 39.3B). Insulin induces translocation and insertion of these GLUT4-rich vesicles into the cell membrane, where GLUT4 can function as an active glucose transporter (G4-m in Fig. 39.3A).

After its phosphorylation to G6P by glucokinase, hepatocytes convert some of the imported glucose into the storage form, **glycogen,** during the Digestive Phase (Fig. 39.3A, Pathway 6). Similarly, skeletal muscle converts some of the G6P from imported glucose into glycogen. Hepatocytes can only store a finite amount of glucose as glycogen. Hepatocytes also convert excess glucose into FFAs through the process of **de novo lipogenesis (DNL;** Pathway 7**).** These FFAs are typically esterified to **glycerol-3-phosphate** (G3P) to form **triglyceride (TG;** Pathway 8), which accumulates as **intrahepatic TG** during the Digestive Phase. As discussed later for insulin signaling, an excessive accumulation of intrahepatic TG (i.e., fatty liver, hepatic steatosis) can result in insulin resistance.

During the Digestive Phase, AAs are used in multiple anabolic pathways to regenerate degraded molecules, including other AAs, proteins, nucleotides and nucleic acids, glutathione, and complex lipids.

FFAs represent the most efficient fuel type in terms of ATP molecules made per carbon of fuel. However, utilization of FFAs competes effectively with glucose utilization in the mitochondria. High FFA levels during the Digestive Phase would promote a greater magnitude and duration of the glucose surge, thereby contributing to hyperglycemia. Thus, most of the FFAs in an average meal are prevented from entering the circulation by their reesterification into TG and packaging into **chylomicrons** within the intestinal

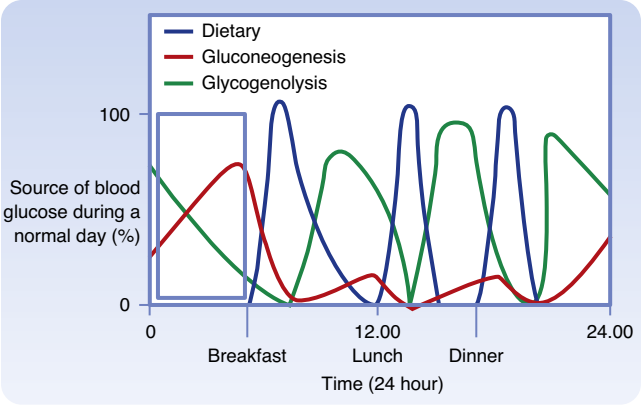
enterocyte. Chylomicrons are secreted, enter lymphatic vessels and then the blood, and supply adipocytes with FFAs to be stored as TG for use during the Fasting Phase (discussed in more detail later).

Fasting Phase

The basic objectives of the Fasting Phase include:

1. **Glucose production** that maintains blood glucose levels above the lower normal limit (Fig. 39.2; *green arrow*). Glucose production is achieved through glycogenolysis and gluconeogenesis in hepatocytes and kidney (see Table 39.1).
2. **Glucose sparing**, which involves a general decrease in the uptake of glucose by cells, especially by skeletal muscle, and the utilization of FFAs, AAs, and KBs (instead of glucose) for ATP production by most cells. This also helps to maintain adequate blood glucose levels during the Fasting Phase (Fig. 39.2; *green arrow*).
3. **Overall catabolism**, with the breakdown of polymers into alternate forms of fuel. The metabolic pathways that achieve these objectives are driven by glucagon (liver, adipose tissue), and catecholamines and intracellular metabolic signals (e.g., increased Ca^{2+}, increased AMP/ATP ratio). Note also that decreased anabolism reduces cellular ATP needs.

Hepatic glucose production is based on two metabolic pathways (refer to Fig. 39.3B). The first is the rapid catabolic process of **glycogenolysis** (Pathway 9). Hepatocytes express the enzyme **glucose-6-phosphatase (G6Pase)** (Pathway 11), allowing them to convert G6P back to glucose, which can then exit the cell through a bidirectional GLUT2 transporter. Release of glucose derived from glycogenolysis is relatively short lived because the liver glycogen supply becomes exhausted by about 8 hours. The second metabolic contribution to hepatic glucose production during the Fasting Phase is the gradual pathway of **gluconeogenesis** (Pathway 10). The onset of gluconeogenesis during fasting is slower than glycogenolysis, but gluconeogenesis continues essentially nonstop throughout a Fasting Phase (Fig. 39.4). Gluconeogenesis requires 3-carbon precursors, especially **lactate, "gluconeogenic" AAs,** and **glycerol.** How are these precursors supplied during the Fasting Phase? Lactate is continually produced by erythrocytes. Lactate is also produced by glycolytic skeletal muscle fibers during exercise (exercise tends to occur more frequently during the Interdigestive and Fasting Phases as opposed to "on a full stomach"), although much of this lactate is utilized by aerobic skeletal muscle and cardiac muscle during exercise. But additionally, the overall anabolism of the Digestive Phase switches over to a general **catabolism** during the Fasting Phase (see Fig. 39.3B). TGs within adipocytes undergo **lipolysis** to FFAs and glycerol (Pathway 12), and there is a general net **proteolysis** with the release of AAs during the Fasting state, especially from muscle (Pathway 13). The glycerol and gluconeogenic AAs are released from cells and circulate to the liver, where they are subsequently used for gluconeogenesis



• **Fig. 39.4** Relative contributions of the three sources of blood glucose relative to meals and time of day. The *inset box* stresses replacement of glycogenolysis with gluconeogenesis during the fasting phase (i.e., sleep). (Adapted from Baynes JW, Dominiczak JH [eds]. *Medical Biochemistry.* 3rd ed. Philadelphia: Mosby/Elsevier; 2009.)

(Pathway 10). Thus, gluconeogenesis requires an integration of catabolic pathways in adipocytes and skeletal myocytes with anabolic gluconeogenesis in hepatocytes. Gluconeogenesis eventually supplants glycogenolysis and can continue as long as precursors flow into the liver.

Glucose sparing represents the other general process that contributes to maintenance of adequate blood glucose levels during the Fasting Phase. *Glucose sparing* means the switching of fuel utilization from glucose to a **nongluconeogenic fuel** in most cell types, but especially in skeletal muscle, which represents the potentially largest single consumer of glucose. First, the uptake of glucose by skeletal muscle and adipocytes is greatly reduced because the GLUT4 transporter isoform exists in intracellular vesicles and this in an inactive state (G4-i in Fig. 39.3B) during the Fasting Phase. Thus, alternative fuels need to be delivered to skeletal muscle and adipocytes.

The nongluconeogenic fuels (i.e., cannot be used for gluconeogenesis by the liver) are **FFAs** and **KBs.** FFAs are primarily released from adipocytes (Pathway 12) but are also released after packaging of intrahepatic TGs into very low-density lipoproteins (VLDLs) by hepatocytes (discussed later). FFAs are then converted via multiple rounds of β-oxidation (Pathway 16) to acetyl CoAs. KBs are produced via ketogenesis (Pathway 14) in hepatocytes from acetyl CoA, which in turn originates primarily from FFAs and **ketogenic AAs,** both of which become abundant during the Fasting Phase. KBs are converted back to acetyl CoA via ketolysis (Pathway 15) in nonhepatic cell types. Thus, glucose sparing depends on catabolic adipocyte metabolism, which results in lipolysis of stored TGs and release of FFAs. FFAs are imported by hepatocytes, which use FFAs to produce acetyl CoA. Protein degradation in skeletal muscle and other tissues also makes certain AAs available for ketogenesis. High levels of intramitochondrial acetyl CoA in the hepatocyte not only provides ample carbons for ATP synthesis but serves to: (1) inhibit conversion of pyruvate to acetyl CoA, (2) promote conversion of pyruvate to

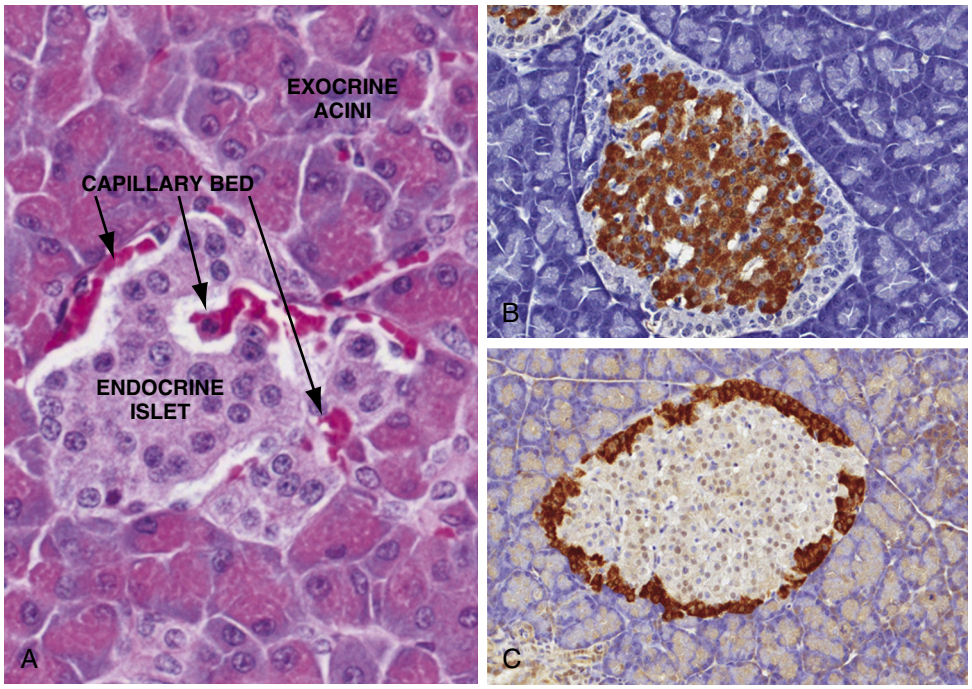
oxaloacetate for gluconeogenesis, and (3) promote synthesis of KBs (see Fig. 39.3B). After several days of fasting, the CNS can start using KBs for energy, thereby further sparing glucose for erythrocytes. Many other cell types with mitochondria use KBs along with FFAs for ATP production, especially skeletal muscle. Note however that hepatocytes only carry out ketogenesis, but not ketolysis, as this would form a futile cycle.

The hormones that drive glycogenolysis, gluconeogenesis, lipogenesis, and hepatic ketogenesis as well as VLDL production by the liver during the Fasting Phase are glucagon and catecholamines. In the presence of low glucose, insulin levels fall, and that removes the inhibition by insulin of the secretion of another pancreatic hormone, **glucagon.** Thus, diminished blood glucose causes a rise in the circulating **glucagon-to-insulin ratio.** Hepatocytes are the primary target organ of glucagon, which directly drives glycogenolysis (Pathway 9), gluconeogenesis (Pathway 10), ketogenesis (Pathway 14), and FFA oxidation (Pathway 16). Hepatocytes also express β_2- and α_1-adrenergic receptors so that norepinephrine from sympathetic innervation and epinephrine from the adrenal medulla (see Chapter 43) can reinforce the actions of glucagon. Adipocytes also express the glucagon receptor, as well as the β_2- and β_3-adrenergic receptors that respond to catecholamines in response to hypoglycemia, exertion, or certain stresses. Skeletal muscle is not a target of glucagon but does respond to catecholamines stimulation through β_2-adrenergic receptors. Skeletal muscle is very responsive to intracellular **signals,** such as **Ca^{++}**, which increases during physical exertion/movement, and to an increase in the **adenosine monophosphate (AMP):ATP ratio,** which activates **AMP kinase.**

Finally, it is important to understand that the pathways upregulated during the Fasting Phase are opposed by insulin-dependent pathways that are most active during the Digestive Phase (discussed later). Thus, **attenuation of insulin signaling** also contributes to the ability of hepatocytes, skeletal myocytes, and adipocytes to display an integrated response to the metabolic challenges of the Fasting Phase.

Pancreatic Hormones Involved in Metabolic Homeostasis During Different Metabolic Phases

The islets of Langerhans constitute the **endocrine pancreas** (Fig. 39.5A). Approximately 1 million islets making up about 1% to 2% of the pancreatic mass are spread throughout the **exocrine pancreas** (see Chapter 27). The islets are composed of several cell types, each producing a different hormone. Beta cells make up about three-fourths of the cells of the islets and produce the hormone **insulin** (see Fig. 39.5B). **Alpha cells** account for about 10% of islet cells and secrete **glucagon** (see Fig. 39.5C). Other endocrine cell types reside within islets, but their respective hormone products are of marginal or unclear importance and thus will not be discussed further.

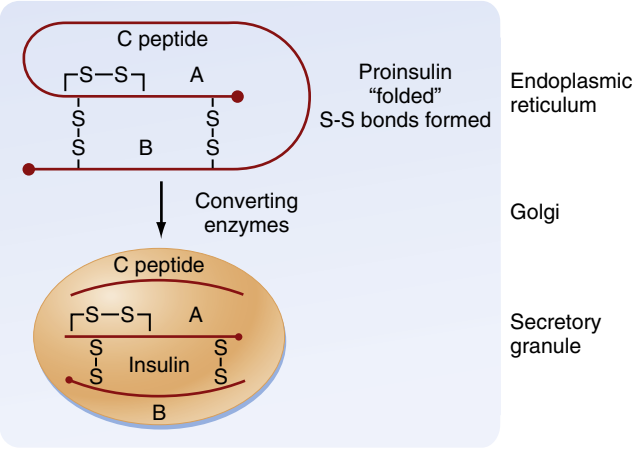


• **Fig. 39.5** The islets of Langerhans (endocrine pancreas) from rat. **A,** Pancreas histology showing exocrine acini where digestive enzymes are produced to be delivered to the duodenum via the pancreatic duct, and an endocrine islet where insulin and glucagon are produced and delivered to the circulation upon uptake by a rich capillary bed. **B,** Staining of endocrine islet for insulin within beta cells; these are the most numerous cell type and are primarily located centrally within the islet. **C,** Staining of endocrine islet for glucagon with alpha cells; these are much less numerous than beta cells and are primarily located along the periphery of the islet.

Blood flow to the islets is somewhat autonomous from blood flow to the surrounding exocrine pancreatic tissue. Blood flow through the islets passes from beta cells, which predominate in the center of the islet, to alpha and delta cells, which predominate in the periphery (see Fig. 38.5B-C). Consequently, the first cells affected by circulating insulin are the alpha cells, in which insulin inhibits glucagon secretion.

Insulin

Insulin is the primary anabolic hormone that dominates regulation of metabolism during the Digestive Phase. Insulin is a protein hormone that belongs to the gene family that includes **insulin-like growth factors I and II (IGF-I, IGF-II)** and **relaxin.** Insulin is synthesized as preproinsulin, which is converted to proinsulin as the hormone enters the endoplasmic reticulum. **Proinsulin** is packaged in the Golgi apparatus into membrane-bound secretory granules. Proinsulin contains the AA sequence of insulin plus the **C (connecting) peptide.** The proteases that cleave proinsulin (proprotein convertases) are packaged with proinsulin within secretory vesicles. Proteolytic processing clips out the C peptide and generates the mature hormone, which consists of two chains, an α chain and a β chain, connected by two disulfide bridges (Fig. 39.6). A third disulfide bridge is contained within the α chain. Insulin is stored within secretory granules as zinc-bound crystals. Upon stimulation, the granule's contents are released to the outside of the cell by exocytosis. Equimolar amounts of mature insulin and C peptide are released, along with small amounts of proinsulin. C peptide has no known biological activity but is useful in assessing endogenous insulin production. C peptide is more stable in blood than insulin (making it easier to assay) and helps distinguish endogenous insulin production from injected insulin, insofar as the latter has been purified from C peptide.



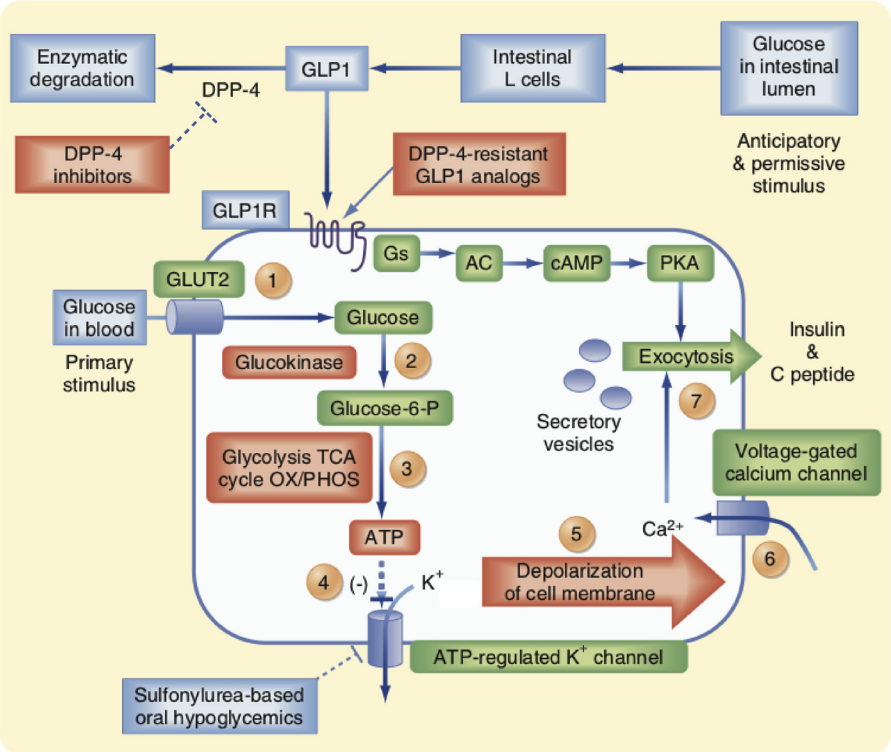
• **Fig. 39.6** Proinsulin is processed by prohormone convertases into a mature insulin molecule with two peptide strands linked by H-bonds and a C peptide. Both are secreted in equimolar ratios. (From White BA, Porterfield SP [eds]. *Endocrine and Reproductive Physiology.* 4th ed. Philadelphia: Mosby/Elsevier; 2013.)

Insulin has a short half-life of about 5 minutes and is cleared rapidly from the circulation. It is degraded by **insulin-degrading enzyme (IDE;** also called *insulinase*) in the liver, kidney, and other tissues. Because insulin is secreted into the **hepatic portal vein,** it is exposed to liver IDE before it enters the peripheral circulation. About half the insulin is degraded before leaving the liver. Thus, peripheral tissues are exposed to significantly less serum insulin concentrations than the liver. **Recombinant human insulin** and **insulin analogs** with different characteristics of speed of onset and duration of action and peak activity are now available. Serum insulin levels normally begin to rise within 10 minutes after ingestion of food and reach a peak in 30 to 45 minutes. The higher serum insulin level rapidly lowers blood glucose to baseline values.

Glucose is the primary stimulus of insulin secretion ("steps" in glucose-stimulated insulin secretion (GSIS) described in the discussion that follows refer to Fig. 39.7). Entry of glucose into beta cells is facilitated by the **GLUT2 transporter** (Step 1). Once glucose enters the beta cell, it is phosphorylated to **G6P** by the low-affinity hexokinase **glucokinase** (Step 2). Glucokinase is referred to as the **"glucose sensor"** of the beta cell because the rate of glucose entry is correlated with the rate of glucose phosphorylation, which in turn is directly related to insulin secretion. Metabolism of G6P through glycolysis, the TCA cycle, and oxidative phosphorylation by beta cells increases the intracellular ATP:ADP ratio (Step 3) and closes an **ATP-sensitive K^+ channel** (Step 4). This results in depolarization of the beta cell membrane (Step 5), which opens **voltage-gated Ca^{++} channels** (Step 6). Increased intracellular [Ca^{++}] activates microtubule-mediated exocytosis of insulin/proinsulin-containing secretory granules (Step 7).

Ingested glucose has a greater effect on insulin secretion than *injected glucose*. This phenomenon, called the **incretin effect,** is due to stimulation by glucose of **incretin hormones** from the gastrointestinal tract. One clinically relevant incretin hormone is **glucagon-like peptide 1 (GLP-1),** which is released by **L cells** of the ileum in response to glucose in the ileal lumen (Fig. 39.7). As a hormone, GLP-1 enters the circulation and ultimately binds to the Gs-coupled **GLP1 receptor** (GLP1R) on beta cells. This GLP1R/Gs/adenylyl cyclase/protein kinase A (PKA) signaling pathway amplifies the intracellular effects of Ca^{++} on insulin secretion. GLP-1 is rapidly degraded in the circulation by **dipeptidyl peptidase 4 (DPP-4).**

Several AAs and vagal (parasympathetic) cholinergic innervation via muscarinic receptor 3 (MR3) also stimulate insulin through increasing intracellular [Ca^{++}] (Fig. 39.8). Insulin secretion is primarily dampened by sympathetic autonomic regulation through **α_2-adrenergic receptors**. Binding of **norepinephrine** or **epinephrine** to relatively abundant α_2-adrenergic receptors decreases cyclic adenosine monophosphate (cAMP), thereby dampening insulin secretion (see Fig. 39.8). Adrenergic inhibition of insulin serves to protect against hypoglycemia, especially during exercise. Beta cells also express Gs-coupled β_2-adrenergic receptors



• **Fig. 39.7** Glucose is the primary stimulus of insulin secretion and is enhanced by sulfonylurea drugs as well as GLP-1 analogs/DPP-4 inhibitors. See text for explanation of numbered steps in glucose-stimulated insulin secretion (GSIS).

IN THE CLINIC

Oral and Injectable Hypoglycemic Drugs

The ATP-sensitive K^+ channel is an octameric protein complex that contains four ATP-binding subunits called **SUR subunits.** These subunits are bound by **sulfonylurea drugs,** which also close the K^+ channel and are widely used as oral hypoglycemics to treat hyperglycemia in patients with partially impaired beta cell function (see Fig. 39.7). Hypoglycemia is a significant side effect of sulfonylurea drugs if used in excess or incorrectly in combination with other drugs, owing to inappropriately high release of insulin.

Both **DPP-4–resistant analogs of GLP-1** and **inhibitors of DPP-4** are currently approved for treatment of patients with type 2 DM with some beta cell function. Importantly these drugs are **permissive** to the actions of glucose on the beta cell and thus only weakly increase insulin secretion in the absence of glucose. Thus GLP-1 analogs induce hypoglycemia much less frequently than sulfonylurea drugs.

IN THE CLINIC

MODY and Beta Cell Transcription Factors

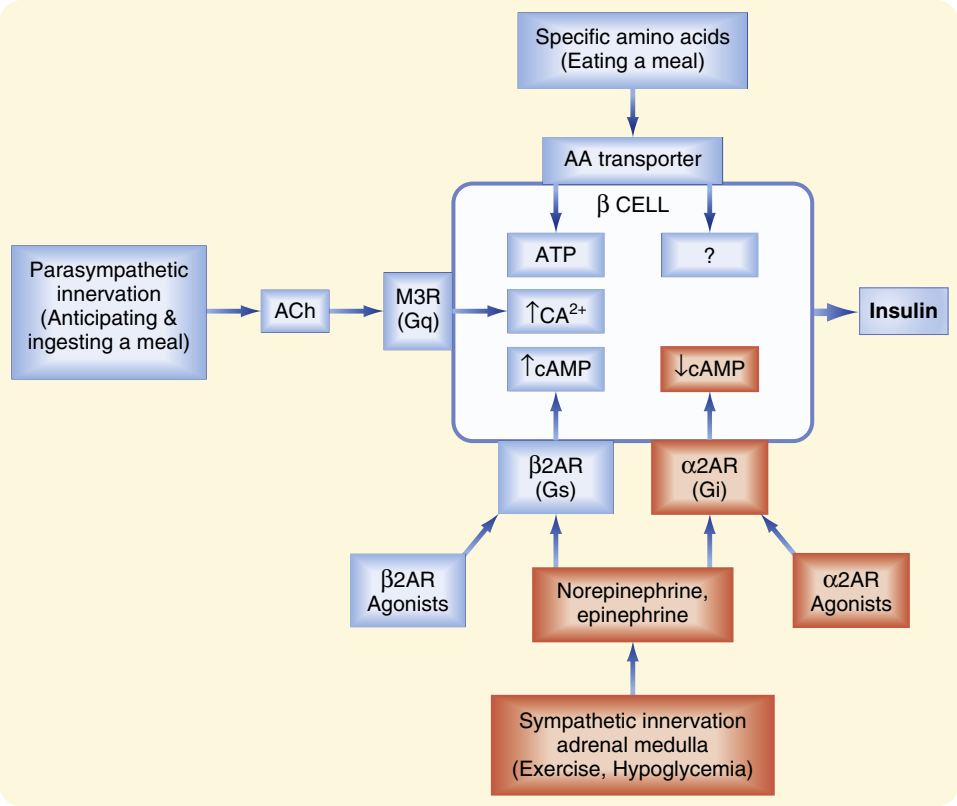
Insulin gene expression and islet cell biogenesis are dependent on several transcription factors specific to the pancreas, liver, and kidney. These transcription factors include **hepatocyte nuclear factor 4α (HNF-4α), HNF-1α, insulin promoter factor 1 (IPF-1), HNF-1β, and neurogenic differentiation 1/beta cell E-box trans-activator 2 (NeuroD1/β_2).** A heterozygous null mutation of one of these factors results in progressively inadequate production of insulin and **maturity-onset diabetes of the young (MODY)** before the age of 25. MODY is characterized by nonketotic hyperglycemia, often asymptomatic, that begins in childhood or adolescence. In addition to the five transcription factors, mutations in **glucokinase** also give rise to MODY.

at a low level that normally play a minor role in promoting insulin secretion (Fig. 39.8).

Insulin Receptor

The **insulin receptor (InsR)** is a member of the **receptor tyrosine kinase *(RTK)*** gene family (see Chapter 3). Most of the actions of insulin on metabolism involve activation of the protein kinase Akt, which in turn has pleiotropic actions on cell metabolism.

The InsR is expressed on the cell membrane as a homodimer, with each monomer containing a tyrosine kinase domain on the cytosolic side (see Fig. 39.9A). Binding of insulin to the receptor induces cross-phosphorylation of the subunits. These phosphotyrosine residues are then bound by the **insulin receptor substrate (IRS) proteins** (i.e., IRS proteins are "recruited" to the InsR). The IRS proteins themselves are phosphorylated by the InsR on specific tyrosines, which then recruits **phosphoinositide-3-kinase (PI3K)** to the IRS protein bound to the InsR (see Fig. 39.9B). PI3K converts



• **Fig. 39.8** Secondary regulators of insulin secretion. See text for explanation of abbreviations.

phosphoinositol-4,5-bisphosphate (PIP2) to **phosphoinositol-3,4,5-trisphosphate (PIP3).** PIP3 is an informational lipid that recruits proteins to the membrane. In this pathway, PIP3 recruits **Akt protein kinase** to the cell membrane where it becomes activated. This pleiotropic Akt protein kinase signaling pathway orchestrates the numerous metabolic actions of insulin in hepatocytes, skeletal muscle, and adipocytes, including (see Fig. 39.9C):

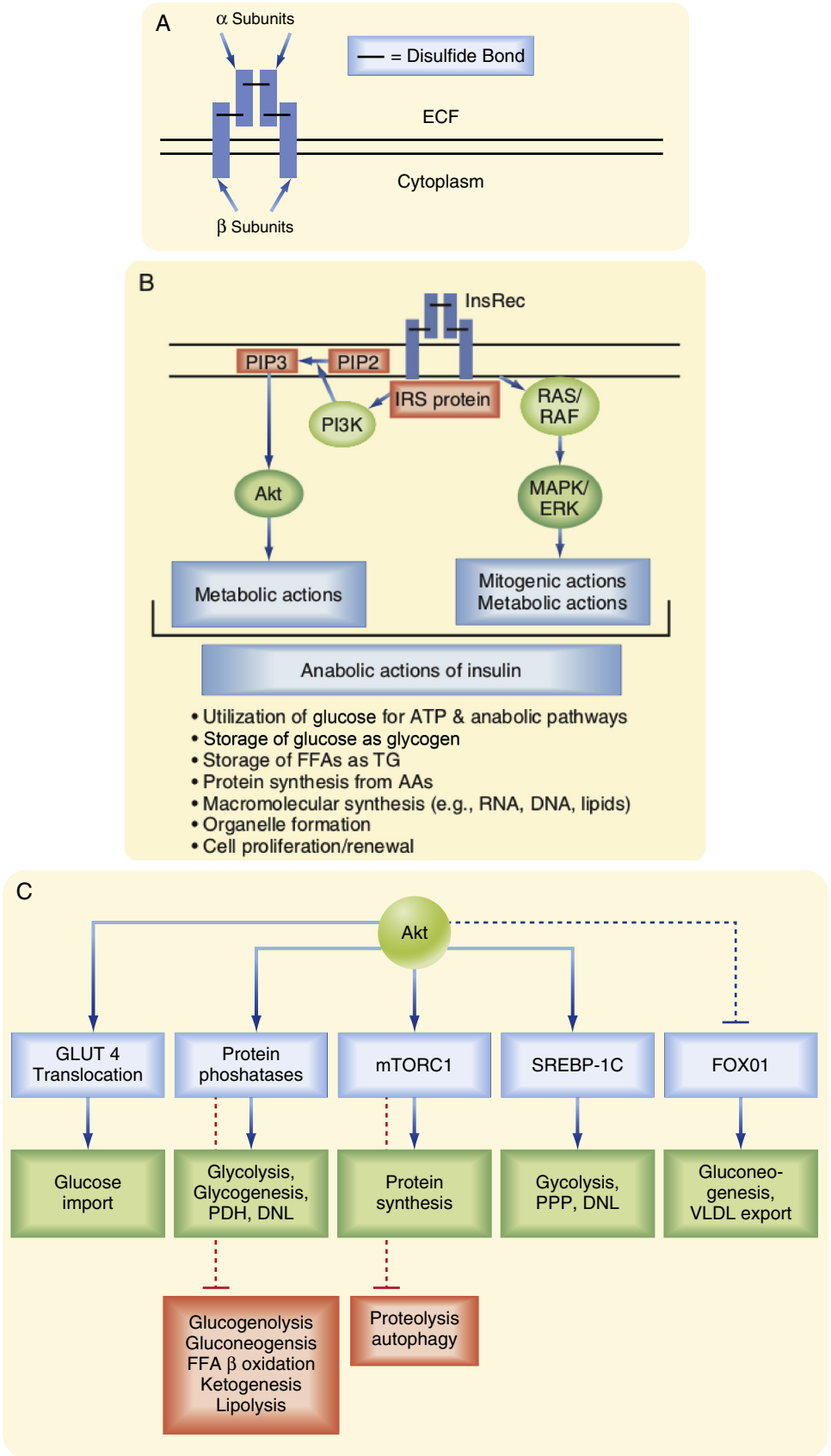
1. *Translocation* of the **GLUT4 glucose transporter** to the cell membrane, thereby allowing import of glucose into **skeletal myocytes** and **adipocytes.**
2. *Activation* of multiple **protein phosphatases,** which in turn regulate the activity of multiple metabolic enzymes in all insulin target cells.
3. *Activation* of the protein complex **mechanistic target of rapamycin complex 1 (mTORC1),** which promotes protein synthesis and may inhibit proteasomal-mediated protein degradation in insulin target cells.
4. *Activation* of the transcription factor **sterol response element–binding protein 1 (SREBP1).** SREBP1 is especially important for insulin effects on the liver, where it orchestrates glycolysis and **de novo lipogenesis (DNL)** for production of phospholipids, FAs, and TGs from excessive ingested glucose and fructose. InsR/Akt signaling stimulates SREBP1 directly as well as indirectly through activation of mTORC1, which also activates SREBP1. SREBP1 also induces the enzyme that catalyzes the first reaction in the oxidative arm of the **pentose phosphate pathway (PPP).** This reaction generates the coenzyme NADPH, which is required co-factor for the DNL pathway.
5. *Inactivation* of the transcription factor **FOXO1.** Akt-mediated phosphorylation of FOXO1 promotes nuclear exclusion of FOXO1. In the absence of insulin/Akt signaling, FOXO1 induces expression of genes encoding gluconeogenic enzymes and proteins involved in hepatic VLDL assembly and export.

All these actions of Akt will be discussed in more detail later. The InsR also promotes **proliferation/renewal** of some target cells through the **Ras/Raf/mitogen-activated protein kinase (MAPK) pathway** (see Fig. 39.9B). The MAPK pathway also participates in some metabolic regulation.

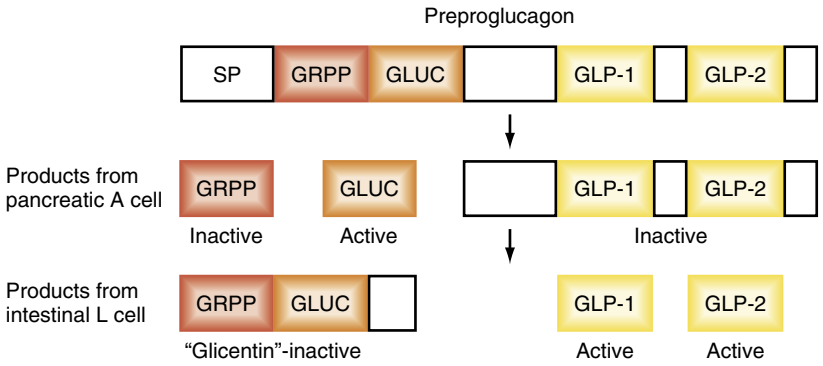
Glucagon

Glucagon is the primary **counterregulatory hormone** that increases blood glucose levels, primarily through its effects on liver glucose output. Glucagon also enhances intramitochondrial fatty acid oxidation and ketogenesis in hepatocytes.

Glucagon is a member of the secretin gene family. The precursor **preproglucagon** harbors the AA sequences for glucagon, **GLP-1,** and **GLP-2** (Fig. 39.10). Preproglucagon is proteolytically cleaved in the alpha cell in a cell-specific manner to produce the peptide glucagon. Glucagon circulates in an unbound form and has a short half-life of about 6 minutes. The predominant site of glucagon degradation is the liver, which degrades as much as 80% of circulating



• **Fig. 39.9** **A,** Structure of dimerized insulin receptor in cell membrane. **B,** Simplified diagram of the Akt kinase and MAPK pathways downstream of the InsR. **C,** Summarized actions of insulin/InsR-activated Akt kinase.



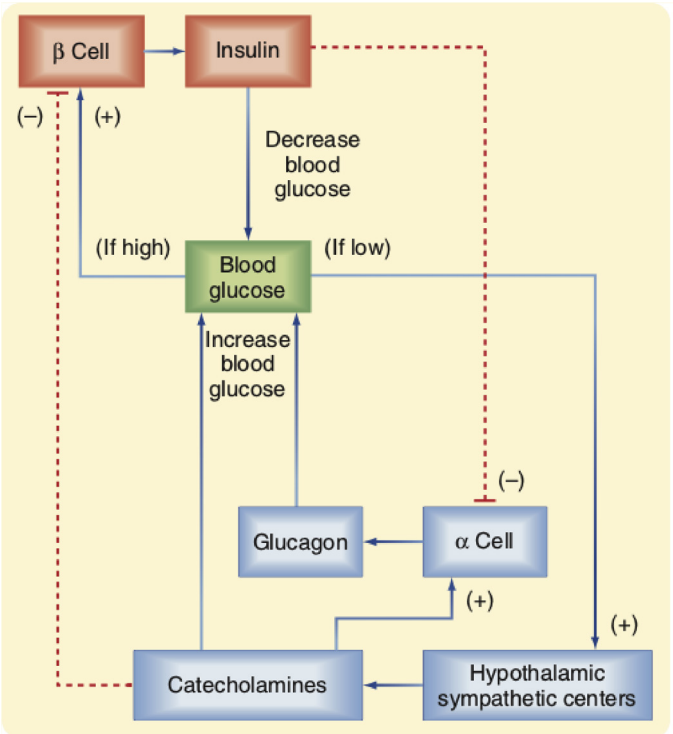
• **Fig. 39.10** Divergent proteolytic cleavage patterns of the proglucagon molecule. GLP, Glucagon-like peptide; *GLUC*, glucagon; *GRPP*, glucagon-related polypeptide.

glucagon in one pass. Because glucagon enters the hepatic portal vein and is carried to the liver before reaching the systemic circulation, a large portion of the hormone never reaches the systemic circulation. The liver is the primary target organ of glucagon, with lesser effects on adipocytes. Skeletal muscle does not express the glucagon receptor.

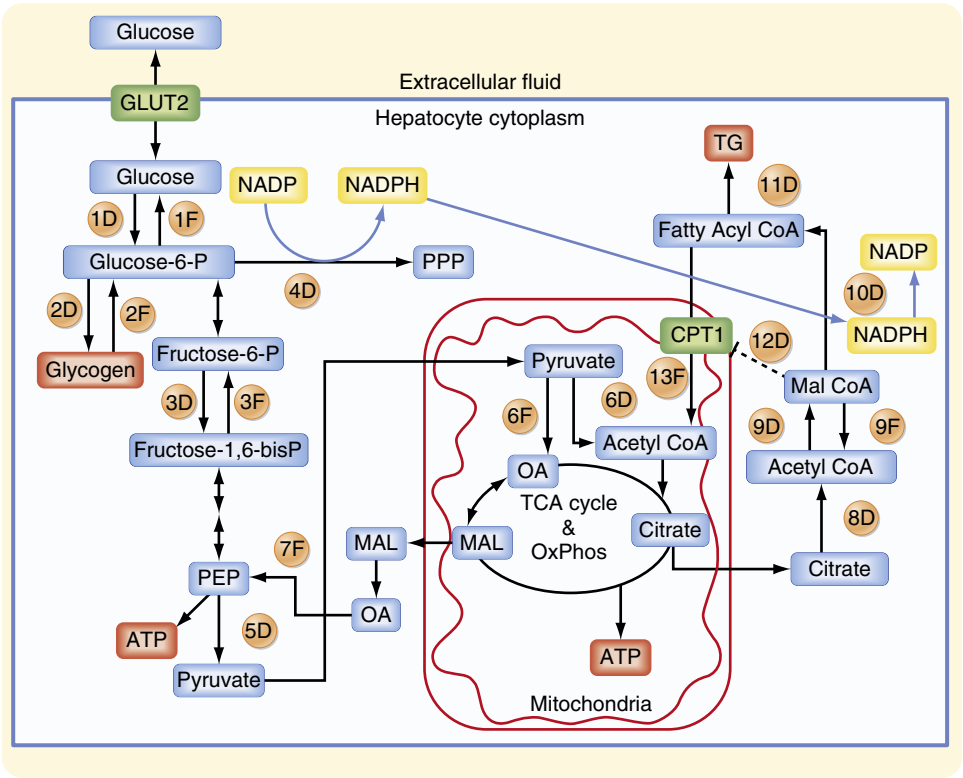
The glucagon receptor is a Gs-linked G protein–coupled receptor that increases adenylyl cyclase activity and thus cAMP levels. Glucagon exerts many rapid actions through PKA signaling. Glucagon also exerts some transcription effects through phosphorylation and activation of transcription factors such as CREB (cAMP response element–binding) protein.

The **insulin-glucagon ratio** determines the net effect of metabolic pathways on blood glucose. A major stimulus for secretion of glucagon is a decline in blood glucose. Insulin inhibits glucagon secretion, so low blood glucose has an indirect effect on glucagon secretion through removal of inhibition by insulin (Fig. 39.11). Some recent evidence also indicates that low glucose has a direct effect on alpha cells to increase glucagon secretion.

Circulating catecholamines, which inhibit secretion of insulin from β cells via **α_2-adrenergic** receptors, stimulate secretion of glucagon from α cells via **β_2-adrenergic receptors** (see Fig. 39.11). Serum AAs also promote secretion of glucagon. This means a protein meal will increase postprandial levels of both insulin and glucagon (which protects against hypoglycemia), whereas a carbohydrate meal stimulates only insulin.



• **Fig. 39.11** Integrated regulation of blood glucose by insulin and the counterregulatory factors glucagon and catecholamines (norepinephrine, epinephrine).



• **Fig. 39.12** Metabolic pathways in hepatocytes during Digestive ("D" numbers) and Fasting ("F" numbers) Phases. Reactions/pathways: *1D*, glucokinase; *1F*; G6Pase; *2D*, glycogen synthesis; *2F*, glycogenolysis; *3D*, phosphofructokinase 1; *3F*, fructose-1,6-bisphosphatase; *4D*, glucose-6-phosphate dehydrogenase; *5D*, pyruvate kinase; *6D*, pyruvate dehydrogenase; *6F*, pyruvate carboxylase; *7F*, phosphoenolpyruvate carboxykinase; *8D*, ATP-citrate lyase; *9D*, acetyl CoA carboxylase; *9F*, malonyl CoA decarboxylase; *10D*, fatty acid synthase; *11D*, esterification and formation of TG; *12D,* inhibition by malonyl CoA *(Mal CoA)* of fatty acyl CoA transporter, carnitine/palmitoyl transporter 1 *(CPT1)* on outer mitochondrial membrane; *13F*, movement of fatty acyl CoA into mitochondrion through CPT1 (and CPT2) and beta-oxidation to acetyl CoA.

Catecholamines: Epinephrine and Norepinephrine

The other major counterregulatory factors are the catecholamines **epinephrine** and **norepinephrine.** Epinephrine is the primary product of the **adrenal medulla** (see Chapter 43), whereas norepinephrine is released from **postganglionic sympathetic nerve endings** (see Chapter 11). Catecholamines are released in response to decreased glucose concentrations, various forms of stress, and exercise. Decreased glucose levels (i.e., hypoglycemia) are primarily sensed by neurons in the CNS, which initiate an integrated sympathetic response through the hypothalamus. The direct metabolic actions of catecholamines are mediated primarily by **α_1-, β_2-, and β_3-adrenergic receptors** located on muscle, adipose, and liver tissue (see later). Like the glucagon receptor, β-adrenergic receptors (β_2 and β_3) increase intracellular cAMP.

Hormonal Regulation of Specific Metabolic Reactions and Pathways

This section discusses the main pathways in hepatocytes, skeletal myocytes, and adipocytes that contribute to integrated metabolism. For even more detailed description, the student is referred to biochemistry textbooks.

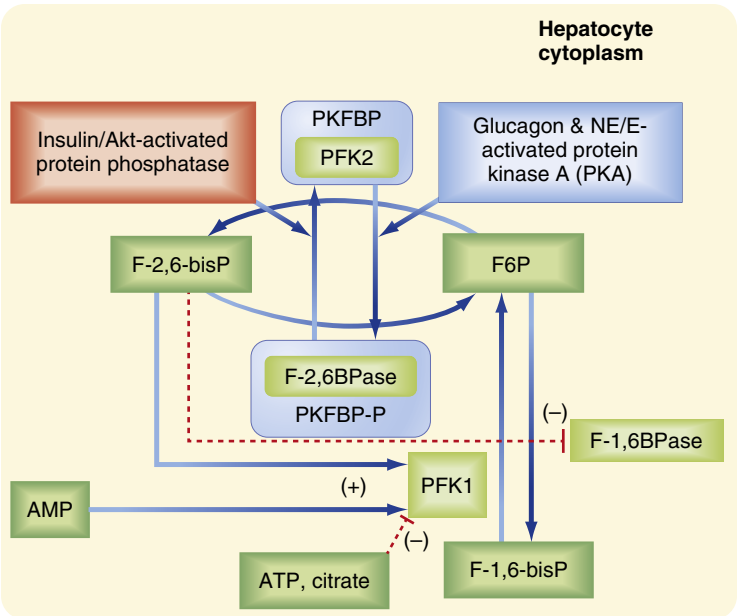
Hepatocyte Metabolism: Digestive vs. Fasting Phases

Some of the key metabolic steps regulated by **insulin and glucagon (and catecholamines)** in the **liver** are as follows (refer to Fig. 39.12 for numbered pathways; "D" denotes Digestive Phase, "F" denotes Fasting Phase):

1. *Trapping vs. releasing intracellular glucose*. Although glucose enters hepatocytes through insulin-independent GLUT2 transporters, insulin increases hepatic retention and utilization of glucose by increasing expression of **glucokinase** (Pathway 1D). Insulin increases glucokinase gene expression through increased expression and activation of the transcription factor **sterol regulatory element–binding protein 1C (SREBP1C),** which acts as a "master switch" in the fed state to coordinately increase levels of several enzymes involved in glucose utilization and de novo lipogenesis (DNL; see Fig. 39.9C). Hepatocytes also express the enzyme glucose-6-phosphatase (G6Pase; Pathway 1F), which converts G6P back to glucose, which can then exit the hepatocyte

via the GLUT2 transporter. Insulin prevents the futile cycle of glucose phosphorylation-dephosphorylation by repressing gene expression of the enzyme **G6Pase.** The transcription factor FOXO1 stimulates gene expression of G6Pase. Insulin-activated Akt kinase phosphorylates and inactivates FOXO1 (Fig. 39.9C). During the Fasting Phase, FOXO1 is active and promotes G6Pase expression, whereas SREBP1C is inactive and does not stimulate glucokinase expression. The reciprocal regulation of SREBP1C and FOXO1 is thus regulated primarily by the presence or absence of insulin.

2. *Glycogen synthesis vs. breakdown.* Insulin indirectly increases glycogen synthesis through increased expression of glucokinase because high levels of G6P allosterically increase **glycogen synthase** activity. Through stimulation of specific protein phosphatases, insulin promotes dephosphorylation and thereby activation of **glycogen synthase** (Fig. 39.12, Pathway 2D). Insulin also prevents the futile cycle of glycogen synthesis to glycogenolysis through phosphatase-mediated inhibition of **glycogen phosphorylase** (Pathway 2F). Glucagon-activated PKA phosphorylates phosphorylase kinase, which in turn phosphorylates and activates glycogen phosphorylase and glycogenolysis during the Fasting Phase (Pathway 2F).
3. *Increasing glycolysis.*
   A. **Activating phosphofructokinase 1 (PFK1) and inhibiting fructose-2,6-bisphosphatase.** Insulin increases the activity of **PFK1**, which phosphorylates fructose-6-phosphate (F6P) to fructose-1,6-bisphosphate (Pathway 3D). This reaction is referred to as the "commitment" reaction for glycolysis. Insulin also inhibits the reverse reaction, as catalyzed by the gluconeogenic enzyme **fructose-1,6-bisphosphatase** (Pathway 3F). Insulin regulates these two enzymes through an indirect two-step mechanism that is diagramed in Fig. 39.13. This mechanism involves the *bifunctional* enzyme called PKFBP, that catalyzes two opposite reactions: 1, a **phosphofructokinase-2 (PFK2)** and a **fructose-2,6-bisphosphatase (F-2,6-BPase**). Insulin/Akt-activated protein phosphatases promote dephosphorylation of PKFBP, thereby activating the kinase function (PKF2) and lessening the phosphatase function (F-2,6BPase). This phosphorylates F6P to **fructose-2,6-bisphosphate (F-2,6-bisP).** F-2,6-bisP, in turn, binds to and allosterically activates PFK1, thereby driving glycolysis. F-2,6-bisP also competitively inhibits fructose-1,6-bisphosphatase (F-1,6BPase), thereby blocking the futile cycle of F6P to fructose-1,6-bisphosphate to F6P (Fig. 39.13).
   B. **Activating pyruvate kinase (PK).** PK catalyzes the irreversible conversion of phosphoenolpyruvate (PEP) to pyruvate (see Pathway 5D in Fig. 39.12). Again, insulin/Akt kinase activation of a protein phosphatase dephosphorylates PK, which activates the enzyme. Insulin also increases *PK* gene expression through SREBP1C. Finally, fructose-1,6-bisphosphate (product of Pathway 3D) allosterically activates PK. In contrast, glucagon and catecholamines promote PK phosphorylation, thereby inhibiting this last step in glycolysis, during the Fasting Phase.
4. *Activating pyruvate dehydrogenase (PDH) complex.* PDH complex converts pyruvate to acetyl CoA, which can



• **Fig. 39.13** Insulin and counterregulatory hormone regulation of phosphofructokinase 1 (*PFK1*; reaction 3D in Fig. 39.12) and fructose-1,6-bisphosphatase (*F1,6BPase*; reaction 3F in Fig. 39.12) through changing the activity of the bifunctional enzyme phosphofructokinase 2/fructose-2,6-bisphosphatase *(PKFBP)* and thus the levels of the allosteric regulatory metabolite fructose-2,6-bisphosphate *(F-2,6-bisP)*. *F6P*, Fructose-6-phosphate.

then enter the TCA cycle upon condensation with oxaloacetate (OA) to form citrate (Fig. 39.12, Pathway 6D). Insulin increases PDH complex activity through Akt kinase activation of PDH complex phosphatase, which in turn dephosphorylates and activates PDH complex

5. *Increasing synthesis of intrahepatic TG.* During the Digestive Phase, some **acetyl CoA** is transferred from the mitochondria to the cytosol in the form of **citrate,** which is then converted back to acetyl CoA and oxaloacetate by the cytosolic enzyme **ATP-citrate lyase** (Pathway 8D). Insulin increases ATP-citrate lyase gene expression through transcription factor SREBP1C. Once in the cytoplasm, acetyl CoA can enter fatty acid synthesis. The first step involves conversion of **acetyl CoA** to **malonyl CoA** by the enzyme **acetyl-CoA carboxylase** (Pathway 9D). Insulin stimulates acetyl-CoA carboxylase gene expression through the transcription factor SREBP1C. Insulin also promotes dephosphorylation of acetyl-CoA carboxylase, which activates the enzyme. Malonyl CoA is converted to the 16-carbon fatty acid **palmitoyl CoA** by repetitive additions of acetyl groups (contributed by malonyl CoA) by the **fatty acid synthase (FASN) complex** (Pathway 10D). *FASN* gene expression is enhanced by insulin through the transcription factor SREBP1C. Insulin also stimulates glycerol phosphate–fatty acyl transferases that esterify FFAs to G3P to form intrahepatic TG (Pathway 11D).

   Palmitate synthesis requires the coenzyme **NADPH.** A major source of NADPH is the **pentose phosphate pathway** (PPP; see Fig. 39.12). The first reaction converts G6P to 6-phosphogluconolactone by the enzyme **glucose-6-phosphate dehydrogenase (G6PD;** Step 4D**).** Insulin increases *G6PD* gene expression through the transcription factor SREBP1C.

   By activating steps that lead to generation of malonyl CoA, insulin indirectly inhibits oxidation of FFAs. Malonyl CoA inhibits the activity of CPT-I, which transports FFAs from the cytosol into the mitochondria (Pathway 12D). As a result, FFAs that are synthesized by DNL cannot be transported into mitochondria, where they would undergo β-oxidation (Pathway 13F). Thus, increased malonyl CoA prevents the futile cycle of FFA synthesis to FFA oxidation.

   FFAs are converted to TGs by the liver (Pathway 11D) and are either stored in the liver or transported to adipose tissue and muscle in the form of VLDL (see later). Insulin acutely promotes degradation of the VLDL apoprotein apoB-100. This keeps the liver from secreting VLDL during a meal when the blood is rich with chylomicrons from the GI tract. Thus, the lipid made in response to insulin during a meal is released as VLDL during the Interdigestive and Fasting Phases and provides an important source of energy to skeletal and cardiac muscle.

6. *Activation vs. inhibition of the gluconeogenic enzymes pyruvate carboxylase (PC) and phosphoenolpyruvate carboxykinase (PEPCK).* Pyruvate can also be converted to OA by PC (Pathway 6F). However, this reaction is indirectly inhibited by insulin in several ways. First, insulin activates PDH as just discussed, thereby diverting pyruvate away from the PC reaction. Additionally, PC is allosterically activated by high levels of intramitochondrial acetyl CoA. Insulin keeps intramitochondrial levels of acetyl CoA low by activation of cytosolic DNL, which promotes removal of acetyl CoA via citrate from the mitochondria. Another key mechanism is to prevent β-oxidation of FFAs within the mitochondria, which generates high levels of acetyl CoA. By stimulating DNL, insulin also increases levels of cytosolic malonyl CoA, which inhibits transport of FFAs into the mitochondria (Pathway 12D). Also, inhibitory actions of insulin on glucagon secretion and on lipolysis of TG within adipocytes prevent release of FFAs by adipose tissue and their import into hepatocytes.

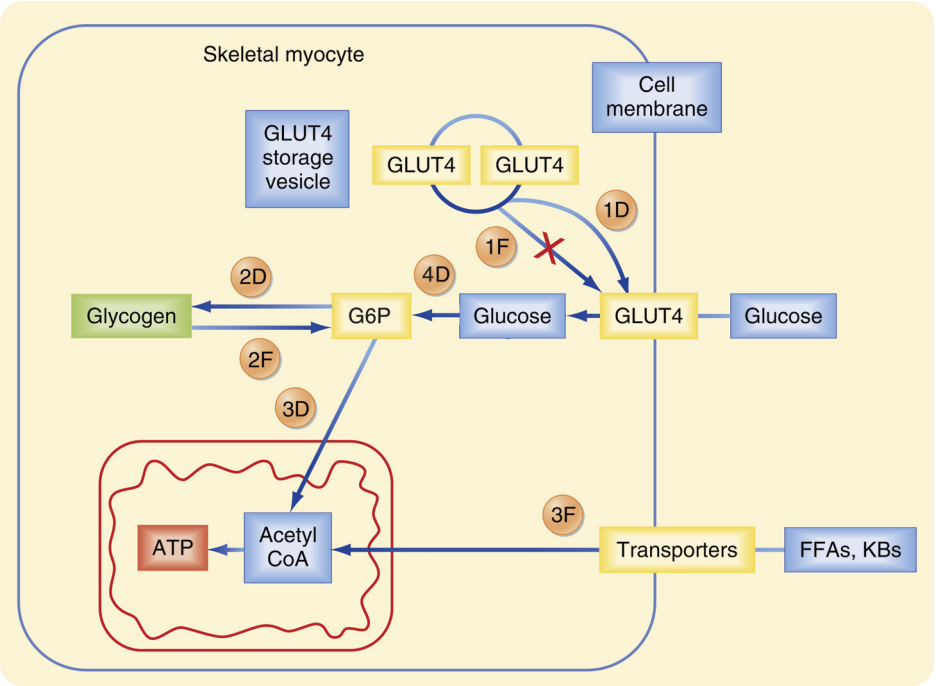
   In contrast, during the Fasting Phase, low insulin coupled with high glucagon and/or catecholamines stimulate release of FFAs from adipocytes (see later), which increases the flow of FFAs into hepatocytes. Glucagon also phosphorylates and activates the enzyme malonyl decarboxylase, which converts malonyl CoA back to acetyl CoA (Pathway 9F). Enhanced malonyl CoA decarboxylase, along with generally low DNL due to low insulin, reduces malonyl CoA levels and thus removes the inhibition on the CPT1 transporter. This allows FFAs to enter the mitochondria and undergo β-oxidation (Pathway 13F), generating high levels of intramitochondrial acetyl CoA, thereby activating PC (Pathway 6F) and also allosterically inhibiting PDH (Pathway 6D). The enzymes involved in β-oxidation are activated by PKA signaling. Glucagon also activates the transcription factor PPARα, which further induces expression of enzymes involved in β-oxidation. Fibrate drugs activate PPARα, promoting oxidation of intrahepatic TG and ameliorating insulin resistance.

   Cytosolic pyruvate can be generated by way of a multistep process that involves PC (Pathway 6F), conversion of oxaloacetate (OA) to malate (MAL), transfer of MAL out of the mitochondria, conversion to back to OA, and then to cytosolic pyruvate. Pyruvate can then enter the gluconeogenic pathway after conversion to phosphoenolpyruvate (PEP) via the action of phosphoenolpyruvate carboxykinase (PEPCK; Pathway 7F). Insulin represses gene expression of the gluconeogenic enzyme **PEPCK**. PEPCK is primarily regulated at the level of transcription, which partly explains the slow onset of gluconeogenesis during the Fasting Phase. Similar to its actions on G6Pase, FOXO1 stimulates transcription of PEPCK during the Fasting Phase, and insulin/Akt kinase signaling inactivates FOXO1 during the Digestive Phase. Glucagon and catecholamines also increase *PEPCK* gene expression through PKA-CREB signaling during the Fasting Phase. So, pyruvate can generate glucose in hepatocytes in a pathway that involves four irreversible and highly regulated reactions: PC (Reaction 6F), PEPCK

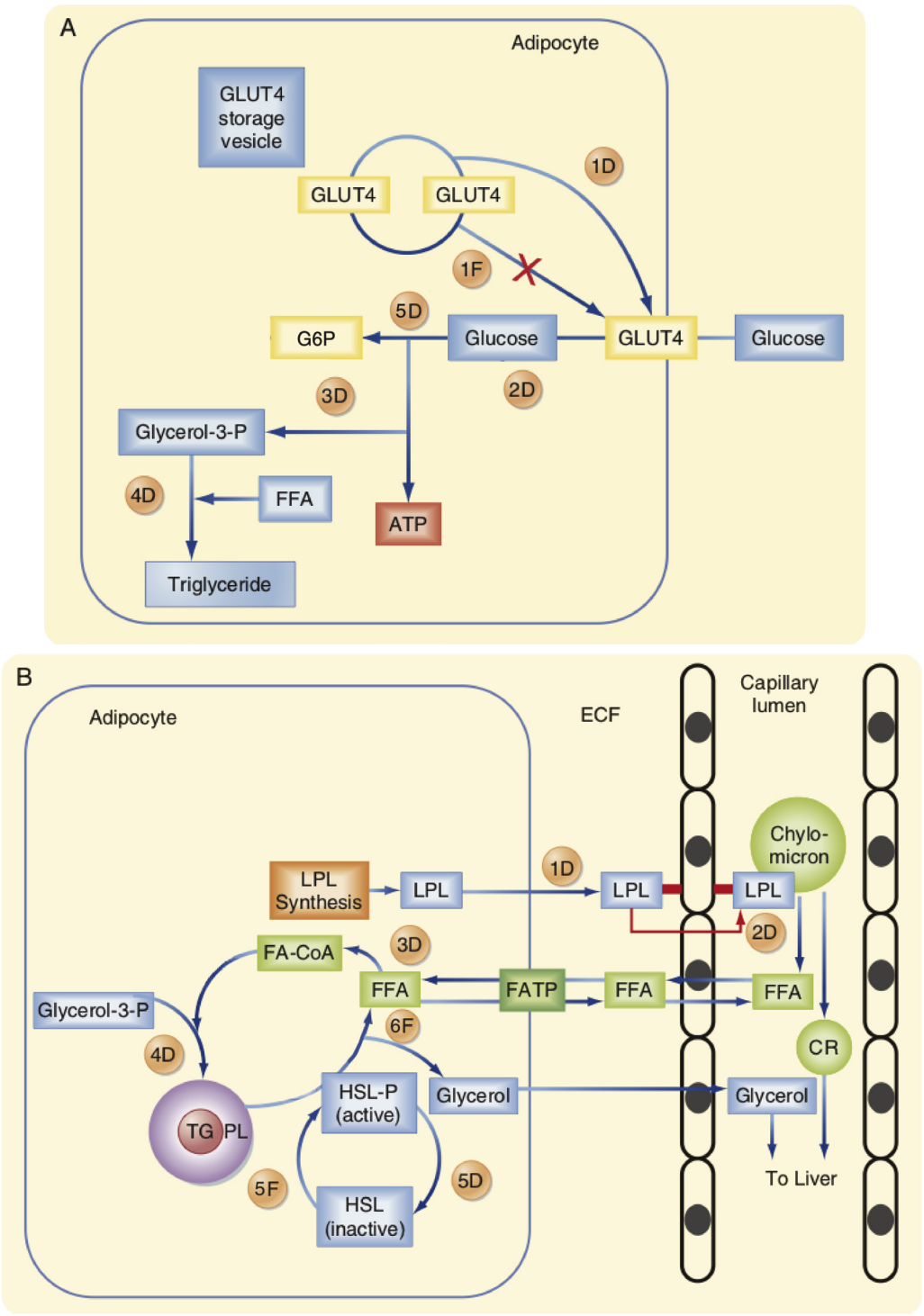
(Reaction 7F), F-1,6-BPtase (Reaction 3F), and G6Ptase Reaction 1F).

Skeletal Muscle and Adipose Tissue Metabolism: Digestive vs. Fasting Phases

1. *Skeletal muscle* (Fig. 39.14). **Glucose tolerance** refers to the ability of an individual to minimize the increase in blood glucose concentration after a meal during the Digestive Phase. A primary way by which insulin promotes glucose tolerance is activation of glucose transporters in skeletal muscle. Insulin stimulates translocation of preexisting intracellular **GLUT4 transporter-containing vesicles** to the cell membrane (Pathway 1D). Skeletal muscle expresses a high affinity isoform of hexokinase that effectively converts glucose to glucose-6-P (Pathway 4D). Note that muscle does not express glucose-6-phosphatase, and thus cannot contribute directly to blood glucose.
   Insulin also promotes storage of glucose in muscle as glycogen (Pathway 2D) and promotes oxidation of glucose through glycolysis, PDH, TCA, and OxPhos (Pathway 3D/F). During the Fasting Phase, low insulin results in a low number of GLUT4 transporters at the membrane (reaction 1F), so these cells consume less glucose (**glucose sparing**). Skeletal muscle fibers break down stored glycogen for use within that fiber (Pathways 2F and 3D). Skeletal muscle fibers with mitochondria augment the use of FFAs from adipocytes and KBs from hepatocytes (Pathways 3F). Skeletal myocytes do not express glucagon receptors. Uptake of FFAs and KBs and their oxidation for ATP is largely upregulated by intracellular Ca^{++} levels and a high AMP:ATP ratio, as well as adrenergic stimulation.
2. *Adipocytes→ glucose* (Fig. 39.15A). Insulin also stimulates GLUT4-dependent uptake of glucose. Adipocytes also expresses a hexokinase that effectively converts glucose to glucose-6-P (Pathway 5D), and, like muscle, does not express glucose-6-phosphatase.
   Insulin stimulates subsequent glycolysis in adipose tissue (Pathways 1D and 2D). Adipose tissue uses glycolysis for energy needs but also for generating G3P (Pathway 3D), which is required for esterification of FFAs into TGs (Pathway 4D). During the Fasting Phase, insulin is low, so GLUT4 movement to the cell membrane is blocked (Pathway 1F).
3. *Adipocytes → FFAs and TG* (see Fig. 39.15B). Insulin stimulates expression of **lipoprotein lipase** (**LPL**) within adipocytes and its migration to the apical side of endothelia in adipose capillaries (Pathway 1D). This action of insulin allows LPL to extract FFAs from chylomicrons within adipose tissue capillary beds (Pathway 2D). The chylomicron remnants (CRs; discussed later) are removed by the liver. Insulin also stimulates activation of imported FFAs by their conversion to fatty acyl CoAs (Pathway 3D). As discussed earlier, insulin stimulates glycolysis in adipocytes, which generates the G3P required for reesterification of FFAs with glycerol-3-P into TGs (Pathway



• **Fig. 39.14** Metabolism in skeletal muscle during digestive ("D" reactions) vs. fasting ("F" reactions) phases. Reactions/pathways: *1D*, translocation of GLUT4 transporter to cell membrane; *1F*, loss of translocation of GLUT4 transporter to cell membrane; *4D*, conversion of glucose to G-6-P; *2D*, glycogen synthesis; *2F*, glycogenolysis; *3D*, glycolysis and lactate dehydrogenase, or pyruvate dehydrogenase/TCA cycle/oxidative phosphorylation (OxPhos), depending on muscle fiber type; *3F*, β-oxidation of FFAs or ketolysis followed by the TCA cycle and OxPhos.



• **Fig. 39.15 A,** Glucose metabolism in an adipocyte during Digestive ("D" pathways) and Fasting ("F" pathways) phases. Reactions/pathways: *1D* and *1F*, insertion or lack thereof of GLUT4 transporters into cell membrane (see Fig. 39.14 legend); *5D*, conversion of glucose to G-6-P; *2D*, glycolysis, pyruvate dehydrogenase/TCA cycle/OxPhos; *3D*, glycerol-3-phosphate dehydrogenase; *4D*, esterification of FFAs to G3P to form triglyceride. **B,** Lipid metabolism in adipocyte during Digestive ("D" pathways) and Fasting ("F" pathways) phases. Reactions/pathways: *1D*, synthesis of lipoprotein lipase *(LPL)* and LPL secretion into subcapillary space, binding to GPI-anchored protein *(thick red line),* and migration to luminal side of capillary endothelial cell; *2D*, lipolysis of chylomicron TG and releasing free FFA (after digestion, chylomicron remnant *(CR)* is cleared from circulation by liver); *3D*, activation of imported FFAs by transfer to acetyl CoA to form fatty acyl CoA; *4D*, esterification of fatty acyl CoAs to G3P to form TG); *5D*, dephosphorylation and inactivation of hormone-sensitive lipase *(HSL)*, thereby promoting storage of TG; *5F*, phosphorylation and activation of HSL, which contributes to complete lipolysis of TG; *6F*, final step in TG lipase by monoglyceride lipase releases FFA and glycerol.

4D). TG droplets in adipocytes are coated by perilipins (PL). Insulin directly inhibits **hormone-sensitive lipase** (**HSL**; Pathway 5D), thereby promoting storage of FFAs as opposed to their release. During the Fasting Phase, glucagon and catecholamines phosphorylate and activate HSL (Pathway 5F), thereby promoting release of FFAs and glycerol from stored TG (Pathway 6F). In the absence of insulin these two products of lipolysis are exported into the blood.

Protein Metabolism in All Hormone Target Cells: Digestive vs. Fasting Phases

Insulin promotes protein synthesis in muscle and adipose tissue by stimulating AA uptake and mRNA translation. Insulin also inhibits proteolysis. Although the liver uses AAs for ATP synthesis, insulin also promotes synthesis of proteins during the Digestive Phase and attenuates the activity of urea cycle enzymes in the liver. Glucagon and catecholamines activate proteasomal degradation of proteins and release of AAs during the Fasting Phase.

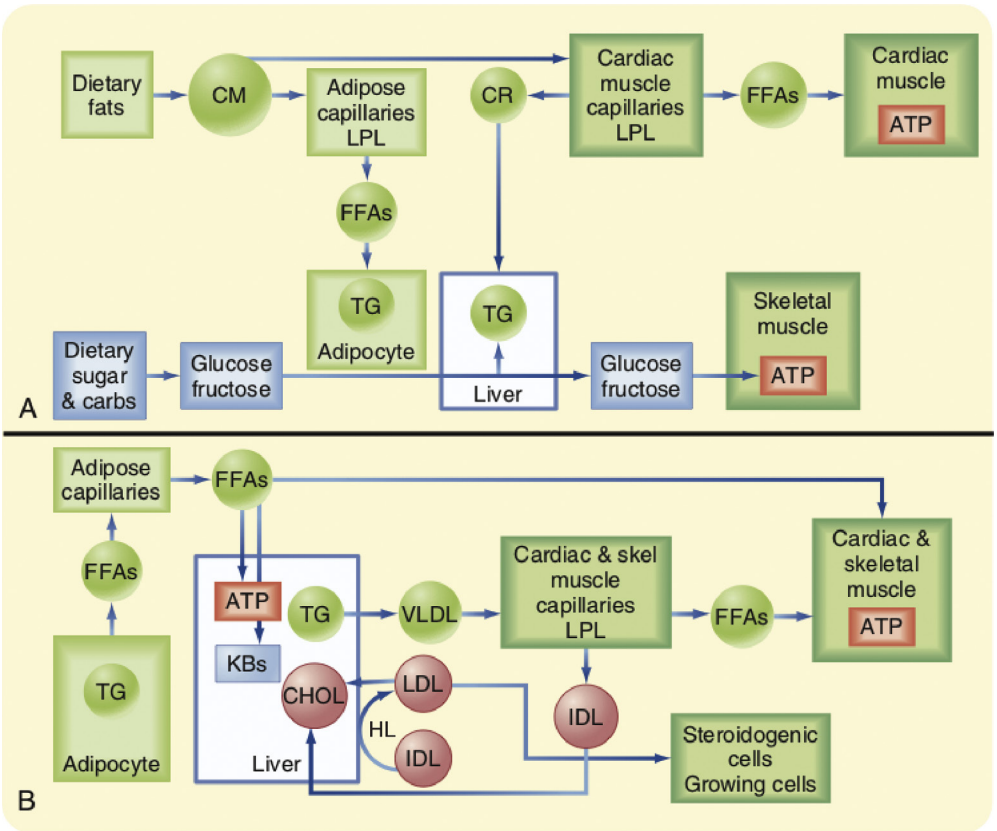
Metabolic Roles of Lipoproteins: Digestive vs. Fasting Phases

This section provides an overview of lipoprotein metabolism, as depicted in Fig. 39.16. For more details, please consult a biochemistry textbook.

FFAs circulate in the blood primarily bound to **albumin.** However, TG, free cholesterol, cholesterol esters, phospholipids, and some lipid-soluble vitamins, all of which are hydrophobic and would partition into the membranes of endothelial cells instead of circulating, are transported through blood within lipid aggregations (i.e., a mix of the above) bound by specific apoproteins. These lipid-protein complexes are referred to as **lipoproteins.** The **TG-rich lipoproteins** are **chylomicrons** and **VLDL** and primarily function to deliver FFAs (as TG) to skeletal and cardiac muscle for energy and to adipocytes for storage. The **cholesterol-rich lipoproteins** include **low-density lipoprotein (LDL)** and **high-density lipoprotein (HDL),** which deliver cholesterol to proliferating cells, steroidogenic cells, and bile-producing hepatocytes. HDL also removes excess cholesterol (i.e., from macrophage-engulfed dead cells) from the periphery. There are also **"remnants"** of lipoproteins that have their lipid cargo partially digested and then cleared from the circulation by the liver.

Digestive Phase: Chylomicrons and Chylomicron Remnants (Fig. 39.16A)

TGs in a meal are enzymatically digested to FFAs and 2-monoglycerides within the lumen of the intestine. Intestinal enterocytes import both of these lipids and reesterify them to form TGs. TGs, along with fat-soluble vitamins, cholesterol, cholesterol esters, and phospholipids, are complexed with the protein **ApoB48** to form **chylomicrons.** Chylomicrons are



• **Fig. 39.16** Role of lipoproteins in energy metabolism. **A,** Digestive phase. **B,** Fasting phase.

secreted, move into lymphatics, and then ultimately enter the circulation. While in the blood, other apoproteins such as **ApoE** and **ApoC2** are transferred to the chylomicrons from HDL particles (one function of HDL is to provide a circulating reservoir of various apoproteins). This converts nascent chylomicrons into mature chylomicrons.

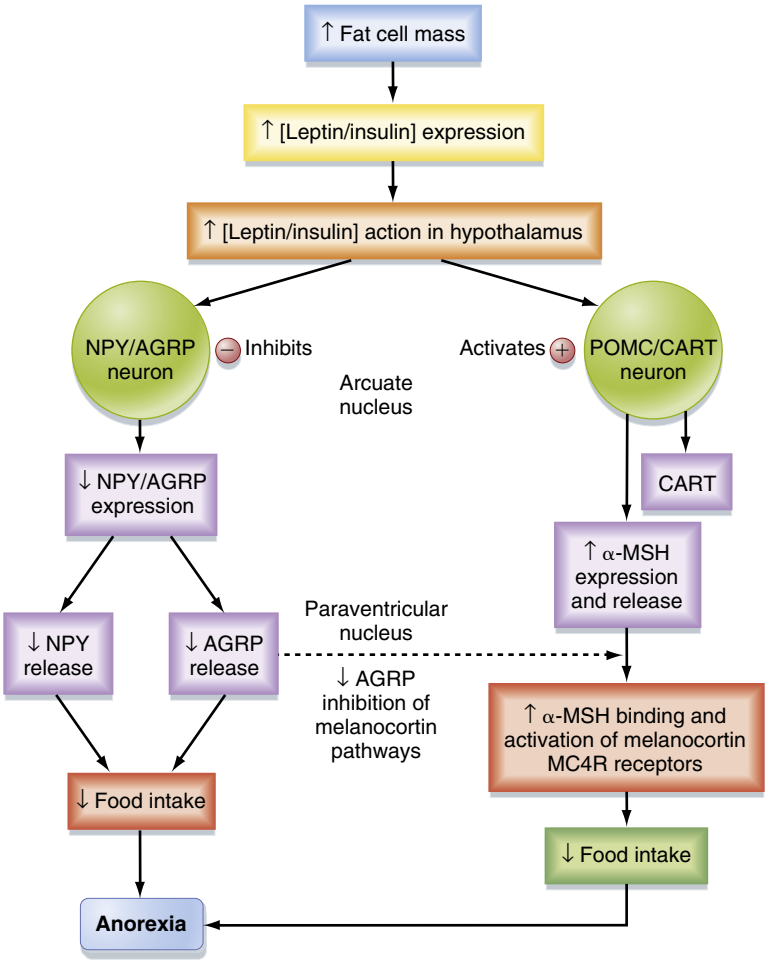
When chylomicrons enter the capillaries of adipose tissue during the Digestive Phase, they are partially digested by **lipoprotein lipase (LPL).** LPL is synthesized by adipocytes and secreted into the subendothelial space. LPL then binds to an endothelial membrane GPI-anchored protein, which transports LPL to the luminal (apical) surface of the capillary endothelial cell. Once in this position, LPL molecules come into contact with chylomicrons. ApoC2 within chylomicrons is an activator of LPL dimerization and activity. FFAs are released from chylomicrons by LPL-mediated lipolysis of TG. (See earlier discussion and Fig. 39.15B for an explanation of the processing of FFAs to stored TG within adipocytes.)

LPL is also expressed in cardiac and skeletal muscle. Cardiac muscle preferentially uses FFA for energy and obtains most FFAs from lipoprotein particles (Fig. 39.16). Thus, cardiac muscle also extracts FFA from chylomicrons during the Digestive Phase. The activity of LPL in cardiomyocytes is highly regulated by local factors such as the local concentration of FFAs within the coronary capillary beds. LPL activity in skeletal muscle is relatively low during the Digestive Phase.

After lipolytic digestion within adipose and cardiac muscle capillary beds, chylomicrons are converted to smaller, denser **chylomicron remnants (CRs)** that now have reduced TG content. CR particles are able to penetrate the tunica intima of blood vessels at sites with endothelial dysfunction and thus are atherogenic. Because they still have ApoE protein associated with them, they can bind to one of several membrane receptors that recognize ApoE. Bound CRs are then endocytosed by hepatocytes (see Fig. 39.16). Remaining FFAs that are released after endocytosis of CRs are reesterified into intrahepatic TG.

Fasting Phase: VLDL, IDL, and LDL (Fig. 39.16B)

The source of circulating TG during the Fasting Phase is primarily the liver (see Fig. 39.16). During the Digestive Phase, intrahepatic TGs accumulate from DNL and from endocytosed CRs. Intrahepatic TG, along with other lipids including cholesterol and cholesterol esters, is exported by hepatocytes as **VLDL.** VLDL particles are assembled as lipids complexed to the **ApoB100 protein.** Expression of ApoB100, along with other components involved in VLDL assembly, is stimulated by transcription factor **FOXO1.**



• **Fig. 39.17** Leptin and hypothalamic centers involved in regulation of appetite. See text for explanations of abbreviations.

FOXO1, in turn, is inhibited by the insulin signaling pathway. This means that hepatic VLDL production is minimal during the time when blood is rich in chylomicrons. During the Fasting Phase, insulin levels are low, so FOXO1 activity is high, and VLDL assembly and secretion resumes. Once VLDL particles enter the circulation, they accept other apoproteins (e.g., ApoE, ApoC2) and become mature VLDL.

Adipocytes display low LPL activity during the Fasting Phase, in part owing to low insulin levels. However, cardiomyocytes and skeletal myocytes express LPL, which digests VLDL and provides FFA to these muscle cell types during the Fasting Phase. Lipolytic extraction of some FFAs from VLDL generates a remnant particle called **intermediate-density lipoprotein (IDL).** IDL circulates to the liver, where it is processed in one of two ways (see Fig. 39.16). About half of the IDL binds to one of several **ApoE-recognizing receptors** on hepatocytes, undergoes receptor-mediated endocytosis, and is digested in endolysosomes. Released lipids can be reassembled into VLDL particles and returned to the circulation to provide fuel for cardiac and skeletal muscle as the Fasting Phase progresses. The other half of the IDL undergoes further digestion from the hepatocyte-specific LPL-related enzyme **hepatic lipase (HL).** HL extracts most of the remaining TG in the IDL, forming the final remnant of VLDL, namely **LDL.** LDL is TG poor but cholesterol rich. It should be noted that both mature chylomicrons and VLDL can receive additional cholesterol from HDL while in the circulation through the action of **cholesterol ester transport protein (CETP)**, so cholesterol content of the remnant particles (ChyR, IDL, and LDL) can vary. In any case the LDL particle is a small, dense, cholesterol-rich particle that is potentially very atherogenic in the face of endothelial damage. LDL particles are safely imported into cells through the **LDL receptor.** It should be noted that in the conversion of IDL to LDL, the **ApoE protein** disassociates from the particle. This means that only ApoB100 receptors can remove LDL from the blood. In contrast to the multiple ApoE receptors, only one receptor, the LDL receptor, can recognize and bind ApoB100. Thus, loss or decrease of a functional LDL receptor has significant clinical consequences (see At the Cellular Level box). LDL receptor is expressed on **proliferating cells,** including some cancer cells, which need to synthesize new cell membranes. LDL receptor is also expressed on **steroidogenic cells,** which use cholesterol to make steroid hormones. The major site of LDL uptake is the **liver,** which secretes cholesterol as well as cholesterol-based **bile acids,** as bile into the biliary tree. Some cholesterol is excreted by the intestines. Other cholesterol by-products (e.g., steroid hormones) are excreted primarily at the kidney.

AT THE CELLULAR LEVEL

SREBP2 was discovered as a transcription factor that resides in the membrane of the endoplasmic reticulum (ER). In the presence of high intracellular cholesterol, SREBP2 is held in the ER by a lipid-sensing protein called *SCAP* (SREBP cleavage–activating protein). In response to depleted sterols, SCAP escorts SREBP2 to the Golgi, where SREBP is cleaved sequentially by proteases and released into the cytoplasm. SREBP2 then translocates to the nucleus and increases the transcription of genes involved in synthesis and uptake of cholesterol. A more recently discovered member of this transcription factor family is **SREBP1C,** which is highly expressed in adipose and liver. In contrast to SREBP2, SREBP1C stimulates genes involved in synthesis of FA and TG. Regulation of SREBP1C occurs at the transcriptional level of the *SREBP1C* gene, with cleavage induced by polyunsaturated fatty acids and activation by the MAPK pathway.

Peroxisome proliferation activator receptors (PPARs) belong to the nuclear hormone receptor superfamily that also includes steroid hormone receptors and thyroid hormone receptors. PPARs heterodimerize with the **retinoid X receptors (RXRs).** Unlike steroid and thyroid hormone receptors, PPARs bind to ligands in the micromolar range (i.e., with lower affinity). PPARs bind saturated and unsaturated fatty acids as well as natural and synthetic prostanoids. **PPARγ** is highly expressed in adipose tissue and at a lower level in skeletal muscle and liver. Its natural ligands include several polyunsaturated fatty acids. PPARγ regulates genes that promote fat storage. It also synergizes with SREBP1C to promote differentiation of adipocytes from preadipocytes. Tissue-specific knockout of PPARγ in mice and PPARγ-dominant negative mutations in humans give rise to **lipodystrophy** (i.e., lack of white adipose tissue), which leads to deposits of TG in muscle and liver (called *steatosis*), insulin resistance, diabetes, and hypertension. The **thiazolidinediones** are exogenous ligands for PPARγ. Although they promote weight gain, moderate levels of thiazolidinediones significantly improve insulin sensitivity. PPARγ also stimulates secretion of **adiponectin,** which promotes oxidation of lipids in muscle and fat and thereby improves insulin sensitivity. **PPARα** is abundantly expressed in liver and to a lesser extent in skeletal and cardiac muscle and kidney. PPARα promotes uptake and oxidation of FFAs. Thus, PPARα is an antisteatotic molecule. The **fibrates** are exogenous ligands of PPARα and are used to reduce TG deposits in muscle and liver, thereby improving insulin sensitivity. A third member, **PPARδ,** similarly promotes fatty acid oxidation in adipose and muscle tissue. PPARδ promotes development of slow-twitch oxidative muscle fibers and increases muscle stamina. PPARδ has a positive effect on lipoprotein metabolism by increasing production of ApoA apoproteins and the number of HDL particles.

Another family of lipid-sensing transcription factors is the **liver X receptor (LXR)** family, which is composed of LXRα and LXRβ. LXRα is expressed primarily in adipose tissue, liver, intestine, and kidney, whereas LXRβ is ubiquitously expressed. LXRs are related to PPARs in that they are members of the nuclear hormone receptor family and heterodimerize with RXR. LXRs are cholesterol sensors. In high-cholesterol conditions, LXRs upregulate expression of ATP-binding cassette (ABC) proteins. In the face of excess cholesterol, LXRs also increase ABC protein expression in the gastrointestinal tract, which promotes efflux of cholesterol from enterocytes to the lumen for excretion. Mutations in these transporters (ABCG5 and ABCG8) cause **sitosterolemia,** characterized by excessive absorption of cholesterol and plant sterols. In the liver, LXRs promote conversion of cholesterol to bile acids for excretion or to cholesterol esters for storage. In the latter action, LXRs increase SREBP1C expression, thereby increasing the fatty acyl CoAs needed for esterification.

IN THE CLINIC

Diabetes mellitus is a disease in which insulin levels or responsiveness of tissues to insulin (or both) is insufficient to maintain normal levels of plasma glucose. Although the diagnosis of diabetes is based primarily on plasma glucose, diabetes also promotes imbalances in circulating levels of lipids and lipoproteins (i.e., **dyslipidemia**). Major symptoms of diabetes mellitus include hyperglycemia, polyuria, polydipsia, polyphagia, muscle wasting, electrolyte depletion, and ketoacidosis (in T1DM). With normal fasting (i.e., no caloric intake for at least 8 hours), plasma glucose levels should be below 110 mg/dL. A patient is considered to have impaired glucose control if fasting plasma glucose levels are between 110 and 126 mg/dL, and the diagnosis of diabetes is made if fasting plasma glucose exceeds 126 mg/dL on two successive days. Another approach to the diagnosis of diabetes is the oral glucose tolerance test. After overnight fasting the patient is given a bolus of glucose (usually 75 g) orally, and blood glucose levels are measured at 2 hours. A 2-hour plasma glucose concentration greater than 200 mg/dL on two consecutive days is sufficient to make the diagnosis of diabetes. The diagnosis of diabetes is also indicated if the patient has symptoms associated with diabetes and has a nonfasting plasma glucose level greater than 200 mg/dL.

Diabetes mellitus is currently classified as **type 1 (T1DM)** or **type 2 (T2DM).** T2DM is by far the more common form and accounts for 90% of diagnosed cases. However, T2DM is usually a progressive disease that remains undiagnosed in a significant percentage of patients for several years. T2DM is often associated with visceral obesity and lack of exercise—indeed, obesity-related T2DM is reaching epidemic proportions worldwide. Usually there are multiple causes for the development of T2DM in a given individual that are associated with defects in the ability of target organs to respond to insulin (i.e., **insulin resistance**), along with some degree of **beta cell deficiency.** Insulin sensitivity can be compromised at the level of the InsR or at the level of postreceptor signaling. T2DM appears to be the consequence of insulin resistance, followed by reactive hyperinsulinemia, but ultimately by **relative hypoinsulinemia** (i.e., inadequate release of insulin to compensate for the end-organ resistance) and **beta cell failure.**

The underlying causes of Insulin Resistance differ among patients. Three major underlying causes of obesity-induced insulin resistance are:

1. *Decreased ability of insulin to increase GLUT4-mediated uptake of glucose, especially by skeletal muscle.* This function, which is specifically a part of **glucometabolic regulation by insulin,** may be due to excessive accumulation of TG in muscle in obese individuals. Excessive caloric intake induces hyperinsulinemia. Initially this leads to excessive glucose uptake into skeletal muscle. Just as in the liver, excessive calories in the form of glucose promote lipogenesis and, through generation of malonyl CoA, repression of fatty acyl CoA oxidation. Byproducts of fatty acid and TG synthesis (e.g., diacylglycerol, ceramide) may accumulate and stimulate signaling pathways (e.g., protein kinase C–dependent pathways) that antagonize signaling from the InsR or IRS proteins, or both. Thus, insulin resistance in the skeletal muscle of obese individuals may be due to **lipotoxicity.**
2. *Decreased ability of insulin to repress hepatic glucose production.* The liver makes glucose by glycogenolysis in the short term and by gluconeogenesis in the long term. The ability of insulin to repress key hepatic enzymes in both these pathways is attenuated in insulin-resistant individuals. Insulin resistance in the liver may also be due to lipotoxicity in obese individuals (e.g., **fatty liver** or **hepatic steatosis**). Visceral adipose tissue is likely to affect insulin signaling at the liver in several ways, in addition to the effects of lipotoxicity. For example, visceral adipose tissue releases the cytokine **tumor necrosis factor (TNF)-α,** which has been shown to antagonize insulin signaling pathways. Also, TG in visceral adipose tissue has a high rate of turnover (possibly because of rich sympathetic innervation), so the liver is exposed to high levels of FFAs, which further exacerbates hepatic lipotoxicity.
3. *Inability of insulin to repress hormone-sensitive lipase or increase LPL in adipose tissue (or both).* High HSL and low LPL are major factors in the dyslipidemia associated with insulin resistance and diabetes. Although the factors that resist the actions of insulin on HSL and LPL are not completely understood, there is evidence for increased production of paracrine diabetogenic factors in adipose tissue, such as TNF-α. The dyslipidemia is characterized as hypertriglyceridemia with large TG-rich VLDL particles produced by the liver. Because of their high TG content, large VLDLs and IDLs are digested very efficiently, thereby giving rise to small, dense LDL particles that are very atherogenic. In addition, HDL takes on excess TG in exchange for cholesterol esters, which appears to shorten the circulating half-life of HDL and ApoA proteins. Thus, there are lower levels of HDL particles, which normally play a protective role against vascular disease.

T1DM is characterized by destruction of beta cells, almost always by an autoimmune mechanism. T1DM is also termed *insulin-dependent diabetes mellitus.* Characteristics of T1DM are:

1. People with T1DM need exogenous insulin to maintain life and prevent ketosis; virtually no pancreatic insulin is produced.
2. There is pathological damage to the pancreatic beta cells. Insulitis with pancreatic mononuclear cell infiltration is a characteristic feature at the onset of the disorder. Cytokines may be involved in the early destruction of the pancreas.
3. People with T1DM are prone to ketoacidosis.
4. Ninety percent of cases begin in childhood, mostly between 10 and 14 years of age. This common observation led to application of the term *juvenile diabetes* to the disorder. This term is no longer used because T1DM can arise at any time of life, although juvenile onset is the typical pattern.
5. Islet cell autoantibodies are frequently present around the time of onset. If T1DM is induced by a virus, the autoantibodies are transient. Occasionally antibodies will persist long term, particularly if they are associated with other autoimmune disorders. About 50% of T1DM is related to problems with the major histocompatibility complex on chromosome 6. It is correlated with an increased frequency of certain human leukocyte antigen (HLA) alleles. The HLA types DR3 and DR4 are most commonly associated with diabetes.

Leptin and Energy Balance

White adipose tissue (WAT) is composed of several cell types. The TG-storing cell is called the **adipocyte.** These cells develop from preadipocytes during gestation in humans. This process of adipocyte differentiation, which may continue throughout life, is promoted by several transcription factors. One of these factors is SREBP1C, which is activated by lipids as well as insulin and several growth factors and cytokines. Another important transcription factor in WAT is **PPARγ.** Activated PPARγ promotes expression of genes involved in TG storage. Thus, an increase in food consumption leads to activation of SREBP1C and PPARγ, which increase the differentiation of preadipocytes into small adipocytes and upregulation of enzymes within these cells to allow storage of excess fat.

Leptin

Adipose tissue produces multiple paracrine and endocrine factors. **Leptin** is an adipocyte-derived protein that signals information to the hypothalamus about the degree of adiposity and nutrition, which in turn controls eating behavior and energy expenditure. Leptin-deficient mice and humans become morbidly obese. These findings originally raised hope that leptin therapy could be used to combat morbid obesity. However, administration of leptin to individuals who suffer from diet-induced obesity does not have a significant anorectic or energy-consuming effect. In fact, obese individuals already have elevated endogenous circulating levels of leptin and appear to have developed **leptin resistance.**

Leptin has an important role in liporegulation in peripheral tissues. Leptin protects peripheral tissues (e.g., liver, skeletal muscle, cardiac muscle, beta cells) from accumulation of too much lipid by directing storage of excess caloric intake into adipose tissue. This action of leptin, though opposing the lipogenic actions of insulin, contributes significantly to maintenance of insulin sensitivity (as defined by insulin-dependent glucose uptake) in peripheral tissues. Leptin also acts as a signal that the body has sufficient energy stores to allow reproduction and to enhance erythropoiesis, lymphopoiesis, and myelopoiesis. For example, in women suffering from anorexia nervosa, leptin levels are extremely low and result in low ovarian steroids, amenorrhea (lack of menstrual bleeding), anemia from low red blood cell production, and immune dysfunction.

Structure, Synthesis, and Secretion

Leptin, a 16-kDa protein secreted by mature adipocytes, is structurally related to cytokines. Thus, it is sometimes referred to as an **adipocytokine.** Circulating levels of leptin have a direct relationship with adiposity and nutritional status. Leptin output is increased by insulin, which prepares the body for correct partitioning of incoming nutrients. Leptin is inhibited by fasting and weight loss and by lipolytic signals (e.g., increased cAMP and β_3-agonists).

Diet-induced obesity, advanced age, and T2DM are associated with leptin resistance. Thus, mechanisms that turn off leptin signaling are potential therapeutic targets.

Energy Storage

The amount of energy stored by an individual is determined by caloric intake and calories expended as energy per day. In many individuals, input and output are in balance, so weight remains relatively constant. However, the abundance of inexpensive high-fat, high-carbohydrate food, along with more sedentary lifestyles, is currently contributing to a pandemic of obesity and the pathological sequelae of obesity, including T2DM and cardiovascular disease.

The preponderance of stored energy consists of fat, and individuals vary greatly in the amount and percentage of body weight that is accounted for by adipose tissue. About 25% of the variance in total body fat appears to be due to genetic factors. A genetic influence on fat mass is supported by (1) the tendency for the body mass of adopted children to correlate better with that of their biological parents than with that of their adoptive parents; (2) the greater similarity of adipose stores in identical (monozygotic) twins, whether reared together or apart, than in fraternal (dizygotic) twins; (3) the greater correlation between gains in body weight and abdominal fat in identical twins than in fraternal twins when they are fed a caloric excess; and (4) the discovery of several genes that cause obesity.

In addition, the gestational environment has a profound effect on body mass of the adult. The effect of maternal diet on the weight and body composition of offspring is called **fetal programming.** Low birth weights correlate with increased risk for obesity, cardiovascular disease, and diabetes. These findings suggest that the efficiency of fetal metabolism has plasticity and can be altered by the in utero environment. The development of a "thrifty" metabolism would be advantageous to an individual born to a mother who received poor nutrition and into a life that meant chronic undernourishment.

Body Mass Index

A measure of adiposity is the body mass index (BMI). The BMI of an individual is calculated as:

Equation 39.1

$$\text{BMI} = \text{Weight}\,(\text{kg}) / \text{Height}\,(\text{m})^2$$

The BMI of healthy lean individuals ranges from 20 to 25. A BMI greater than 25 indicates that the individual is overweight, whereas a BMI higher than 30 indicates obesity. The condition of being overweight or obese is a risk factor for multiple pathologies, including insulin resistance, dyslipidemia, diabetes, cardiovascular disease, and hypertension.

WAT tissue is divided into subcutaneous and intra-abdominal (visceral) depots. Intra-abdominal *WAT* refers primarily to omental and mesenteric fat and is the smaller of the two depots. These depots receive different blood supplies that are drained in a fundamentally different way in that venous return from intra-abdominal fat leads into the hepatic portal system. Thus, intra-abdominally derived

FFAs are mostly cleared by the liver, whereas subcutaneous fat is the primary site for providing FFAs to muscle during exercise or fasting. Regulation of intra-abdominal and subcutaneous adipose tissue also differs. Abdominal fat is highly innervated by autonomic neurons and has a greater turnover rate. Furthermore, these two depots display differences in hormone production and enzyme activity.

Men tend to gain fat in the intra-abdominal depot **(android [apple-shaped] adiposity),** whereas women tend to gain fat in the subcutaneous depot, particularly in the thighs and buttocks **(gynecoid [pear-shaped] adiposity).** Clearly an excess of abdominal fat poses a greater risk factor for the pathologies mentioned earlier. Thus, another indicator of body composition is circumference of the waist (measured in inches around the narrowest point between the ribs and hips when viewed from the front after exhaling) divided by the circumference of the hips (measured at the point where the buttocks are largest when viewed from the side). This **waist-hip ratio** may be a better indicator of body fat than BMI, especially as it relates to risk for development of diseases. A waist-hip ratio of greater than 0.95 in men or 0.85 in women is linked to a significantly higher risk for development of diabetes and cardiovascular disease.

Central Mechanisms Involved in Energy Balance

In recent years, numerous hormones and neuropeptides have been implicated in both chronic and acute regulation of appetite, satiety, and energy expenditure in humans. One simplified model involves two peptide hormones, **leptin** and **insulin** (see Fig. 39.17), already discussed. Leptin acts on at least two neuron types in the arcuate nucleus of the hypothalamus. In the first, leptin represses production of **neuropeptide Y (NPY),** a very potent stimulator of food-seeking behavior (energy intake) and an inhibitor of energy expenditure. Norepinephrine, another appetite stimulator, co-localizes with NPY in some of these neurons. At the same time, leptin represses production of agouti-related peptide (AGRP), an endogenous antagonist that acts on MC4R, a hypothalamic receptor for the anorexigenic peptide α-melanocyte–stimulating hormone (α-MSH), which inhibits food intake. In another type of arcuate neuron, leptin stimulates production of proopiomelanocortin (POMC) products, one of which is α-MSH, and production of cocaine-amphetamine–regulated transcript (CART), both of which inhibit food intake. Thus, leptin decreases food consumption and increases energy expenditure by simultaneously inhibiting NPY and the α-MSH antagonist AGRP and by stimulating α-MSH and CART (see Fig. 39.17). These second-order neuropeptides are transmitted to and interact with receptors in neurons of the paraventricular hypothalamic nucleus ("satiety" neurons) and lateral hypothalamic nucleus ("hunger" neurons). In turn these hypothalamic neurons generate signals that coordinate feeding behavior and autonomic nervous system activity (especially sympathetic outflow) with diverse endocrine actions on thyroid gland function, reproduction, and growth.

Another regulator of food intake and body energy stores is **melanin-concentrating hormone (MCH).** This neuropeptide increases food seeking and adipose tissue by antagonizing the satiety effect of α-MSH downstream from the interaction of α-MSH with its MC4R receptor. The probable importance of this molecule is demonstrated by the fact that it is the only regulator whose ablation by gene knockout actually results in leanness.

To maintain overall energy homeostasis, the system must also balance specific nutrient intake and expenditure—for example, carbohydrate intake with carbohydrate oxidation. This may account for some specificity in neuropeptide and neurotransmitter responses to meals. Serotonin produces satiety after ingestion of glucose. Gastrointestinal hormones such as cholecystokinin and GLP-1 produce satiety by humoral effects, but their local production in the brain may participate in nutrient and caloric regulation. The recently discovered hormone **ghrelin** is an acylated peptide with potent orexigenic activity that arises in cells of the oxyntic glands in the stomach. Plasma levels of ghrelin rise in humans in the 1 to 2 hours that precede their normal meals. Plasma levels of ghrelin fall drastically to minimum values about 1 hour after eating. Ghrelin appears to stimulate food intake by reacting with its receptor in hypothalamic neurons that express NPY.

Key Concepts

1. Cells make ATP to meet their energy needs. ATP is made by glycolysis and by the TCA cycle coupled to oxidative phosphorylation.
2. Cells can oxidize carbohydrate (primarily in the form of glucose), AAs, and FFAs to make ATP. Additionally, the liver makes KBs for other tissues to oxidize for energy in times of fasting.
3. Some cell types are limited in the energy substrates they can oxidize for energy. The brain is normally exclusively dependent on glucose for energy. Thus, blood glucose must be maintained above 60 mg/dL for normal autonomic and CNS function. Conversely, inappropriately high levels of glucose (i.e., fasting glucose > 100 mg/dL) promote glucotoxicity and thereby lead to the long-term complications of diabetes.
4. The endocrine pancreas produces the hormones insulin, glucagon, somatostatin, gastrin, and pancreatic polypeptide.
5. Insulin is an anabolic hormone that is secreted in times of excess nutrient availability. It allows the body to use carbohydrates as energy sources and store nutrients.
6. Major stimuli for insulin secretion include increased serum glucose and some AAs. Activation of cholinergic (muscarinic) receptors also increases insulin secretion, whereas activation of α_2-adrenergic receptors inhibits insulin secretion. The gastrointestinal tract releases

incretin hormones that stimulate pancreatic insulin secretion. GLP-1 is particularly potent in augmenting glucose-dependent stimulation of insulin secretion (GSIS). GLP-1 is degraded by dipeptidyl peptidase (DPP)-4. DPP-4–resistant GLP-1 analogs and inhibitors of DPP-4 are currently used to increase GSIS in patients with type 2 diabetes.

7. Insulin binds to the insulin receptor (InsR), which is linked to multiple pathways that mediate the metabolic (Akt kinase) and growth effects (MAPK) of insulin.
8. During the digestive phase, insulin acts on the liver to promote trapping of glucose as G6P. Insulin also increases glycogenesis, glycolysis, and de novo lipogenesis (DNL) in the liver. Insulin inhibits gluconeogenesis, glycogenolysis, and assembly of lipids into VLDL.
9. Insulin increases GLUT4-mediated glucose uptake in muscle and adipose tissue.
10. Insulin increases glycogenesis, glycolysis, and in the presence of caloric excess, lipogenesis in muscle.
11. Insulin increases glycolysis and generation of G3P in adipocytes. Insulin induces expression of LPL and its transport to the luminal side of capillary endothelial cells. Insulin promotes uptake and activation of FFAs and esterification of fatty acyl CoAs to G3P to form TG, and it decreases hormone-sensitive lipase activity in adipocytes.
12. Insulin increases AA uptake and protein synthesis in skeletal muscle but also essentially all insulin target cells. Insulin/Akt kinase signaling activates mTORC1 and S6K to promote synthesis of ribosomal proteins and proteins involved in mRNA translation, as well as other types of proteins. Insulin inhibits proteasomal degradation of protein.
13. Glucagon is a catabolic counterregulatory hormone. Its secretion increases during periods of food deprivation, and it acts to mobilize nutrient reserves. It also mobilizes glycogen, fat, and even protein.
14. Glucagon is released in response to decreased serum glucose (and therefore decreased insulin) and increased serum AA levels and β-adrenergic signaling.
15. Glucagon binds to the glucagon receptor, which is linked to PKA-dependent pathways. The primary target organ for glucagon is the liver. Glucagon increases liver glucose output by increasing glycogenolysis and gluconeogenesis. It increases β-oxidation of fatty acids and ketogenesis.
16. Glucagon regulates hepatic metabolism both by regulation of gene expression and through post-translational PKA-dependent pathways.
17. The major counterregulatory factors in muscle and adipose tissue are the adrenal hormone epinephrine and the sympathetic neurotransmitter norepinephrine. These two factors act through β_2- and β_3-adrenergic receptors to increase cAMP levels. Epinephrine and norepinephrine enhance glycogenolysis and fatty acyl oxidation in muscle and increase hormone-sensitive lipase in adipose tissue.
18. Diabetes mellitus is classified as type 1 (T1DM) and type 2 (T2DM). T1DM is characterized by destruction of pancreatic beta cells, and exogenous insulin is required for treatment. T2DM can be due to numerous factors but is usually characterized as insulin resistance coupled to some degree of beta cell deficiency. Patients with T2DM may require exogenous insulin at some point to maintain blood glucose levels.
19. Obesity-associated T2DM is currently at epidemic proportions worldwide and is characterized by insulin resistance due to lipotoxicity, hyperinsulinemia, and inflammatory cytokines produced by adipose tissue. T2DM is often associated with obesity, insulin resistance, hypertension, and coronary artery disease. This constellation of risk factors is referred to as the *metabolic syndrome*.
20. Major symptoms of diabetes mellitus include hyperglycemia, polyuria, polydipsia, polyphagia, muscle wasting, electrolyte depletion, and ketoacidosis (in T1DM).
21. The long-term complications of poorly controlled diabetes are due to excess intracellular glucose (glucotoxicity), especially in the retina, kidney, and peripheral nerves. This leads to retinopathy, nephropathy, and neuropathy.
22. Adipose tissue has an endocrine function, especially in terms of energy homeostasis. Hormones produced by adipose tissue include leptin and adiponectin. Leptin acts on the hypothalamus to promote satiety.