The Endocrine Pancreas and Control of Blood Glucose 9.4

Learning Objectives

- List three hormones and their cell types that secrete them in the islets of Langerhans of the pancreas
- Describe the chemical structure of insulin in terms of its polypeptide chains
- Explain how increased plasma [glucose] causes insulin release
- Explain the mechanism of oral hypoglycemic agents on insulin release
- Describe the mechanism by which insulin increases peripheral glucose uptake
- Summarize the effects of insulin on carbohydrate, fat, and protein metabolism
- Indicate the major physiological stimulus for glucagon release
- Describe the mechanism of glucagon stimulation of liver glycogenolysis
- Describe the mechanism of glucagon stimulation of liver gluconeogenesis
- Explain why diabetics must cut back on their insulin when they exercise
- Describe the levels of glucagon and insulin after a meal and during fasting

THE PANCREAS HAS BOTH EXOCRINE AND ENDOCRINE FUNCTIONS

The pancreas lies between the greater curvature of the stomach and the duodenum. It consists mostly of **acinar glands** that secrete pancreatic juice that is carried by ducts into the duodenum where the exocrine pancreatic secretion neutralizes stomach acid and provides enzymes for digestion. About 1% of the pancreatic mass makes up the **islets of Langerhans**, which are endocrine glands. There are about a million islets distributed throughout the acinar tissue, set off from the acinar pancreas by a connective tissue sheath (see Figure 9.4.1). The islets contain four distinct cells types. The β cells make up about 60% of the islet population and secrete **insulin**. This hormone is the most important hormone in regulating carbohydrate and lipid metabolism. The α cells make up 25% of the islet population and secrete **glucagon**, which increases blood glucose by increasing its formation by gluconeogenesis and glycogenolysis. Insulin is secreted during times of nutrient abundance, and it promotes metabolic fuel storage. Glucagon is secreted during times of nutrient deficit, and it mobilizes metabolic fuel stores.

About 10% of the islet cells are δ cells that secrete **somatostatin**. Among its other actions as a growth hormone antagonist, somatostatin suppresses insulin release. The remaining islet cells, F cells, secrete **pancreatic polypeptide**.

β *CELLS* SYNTHESIZE INSULIN AS A PROHORMONE AND SECRETE INSULIN AND C PEPTIDE 1:1

Like many secreted proteins, insulin is synthesized as a preproinsulin, 110 amino acids long. The signal sequence is cleaved to form proinsulin, 86 amino acids long, which is further processed to form the A and B chains of insulin, and C peptide. The B chain corresponds to amino acids 1–30 of proinsulin; the A chain corresponds to amino acids 64–86, and the peptide connecting the two gives rise to the C peptide after two pairs of basic amino acids are cleaved off. The A and B chains are held together by two disulfide links. The relationship between the A, B, and C chains is shown in Figure 9.4.2.

Both mature insulin and the C peptide are stored in secretory granules and released into the portal blood upon stimulation of the β cells. The portal blood travels to the liver prior to entering the systemic circulation. The liver removes 50–60% of the insulin before it reaches the systemic circulation, so systemic levels of insulin do not indicate the rate of insulin secretion. However, C peptide is not cleared by the liver but instead is excreted by the kidney with a plasma half-life of about 30 min. The half-life of circulating insulin is only about 5 min. Because of these differences, circulating C peptide is a better indicator of β cell function, but it does not reflect rapidly changing rates of insulin secretion.

HIGH PLASMA GLUCOSE STIMULATES INSULIN SECRETION

Glucose has a molecular weight of 180 and cannot easily penetrate lipid bilayers. It enters β cells by facilitated

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FIGURE 9.4.1 Diagrammatic representation of a histological section of pancreatic tissue showing exocrine and endocrine cells. The islets of Langerhans are separated from the exocrine tissue by a connective tissue sheath. The islets contain several distinct cell types that secrete distinct hormones.

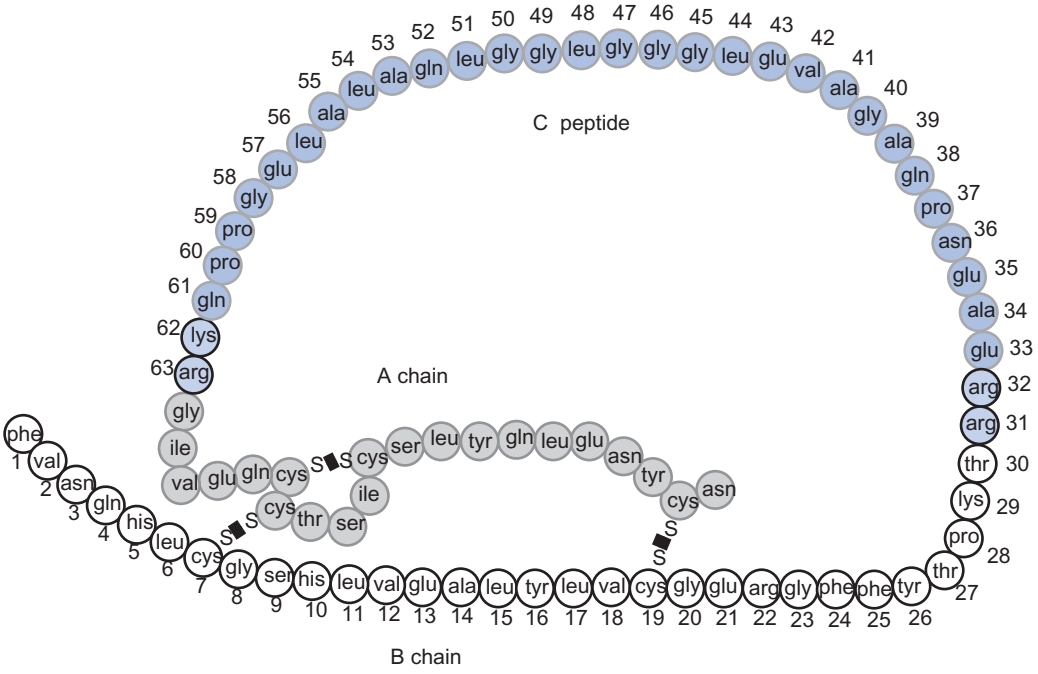

FIGURE 9.4.2 Amino acid sequence of proinsulin, showing the cleavage points that produce the A and B chain. The B chain contains amino acids 1–30 (white circles); the A chain contains amino acids 64–84 (gray circles). The A and B chain are linked by two disulfide bonds, and there is an additional disulfide bond within the A chain. The C peptide is produced by cleaving two pairs of basic amino acids from both ends of the connecting peptide (blue circles with dark outlines). The C peptide is secreted in a 1:1 molar ratio with insulin upon stimulation of the β cells (blue circles).

diffusion using the GLUT2 carrier. **Glucokinase** converts cytoplasmic glucose to glucose-6-phosphate. This is the rate-limiting step in glycolysis and therefore the enzyme serves as a **glucose sensor** for the β cell. As plasma glucose increases, cytoplasmic glucose increases and the rate of glycolysis increases, producing a local increase in cytoplasmic ATP concentrations. ATP inhibits an ATP-sensitive K^+ channel (K_{ATP}), so that increasing ATP blocks the channel, reducing K^+ efflux and reducing an outward current. This depolarizes the cell.

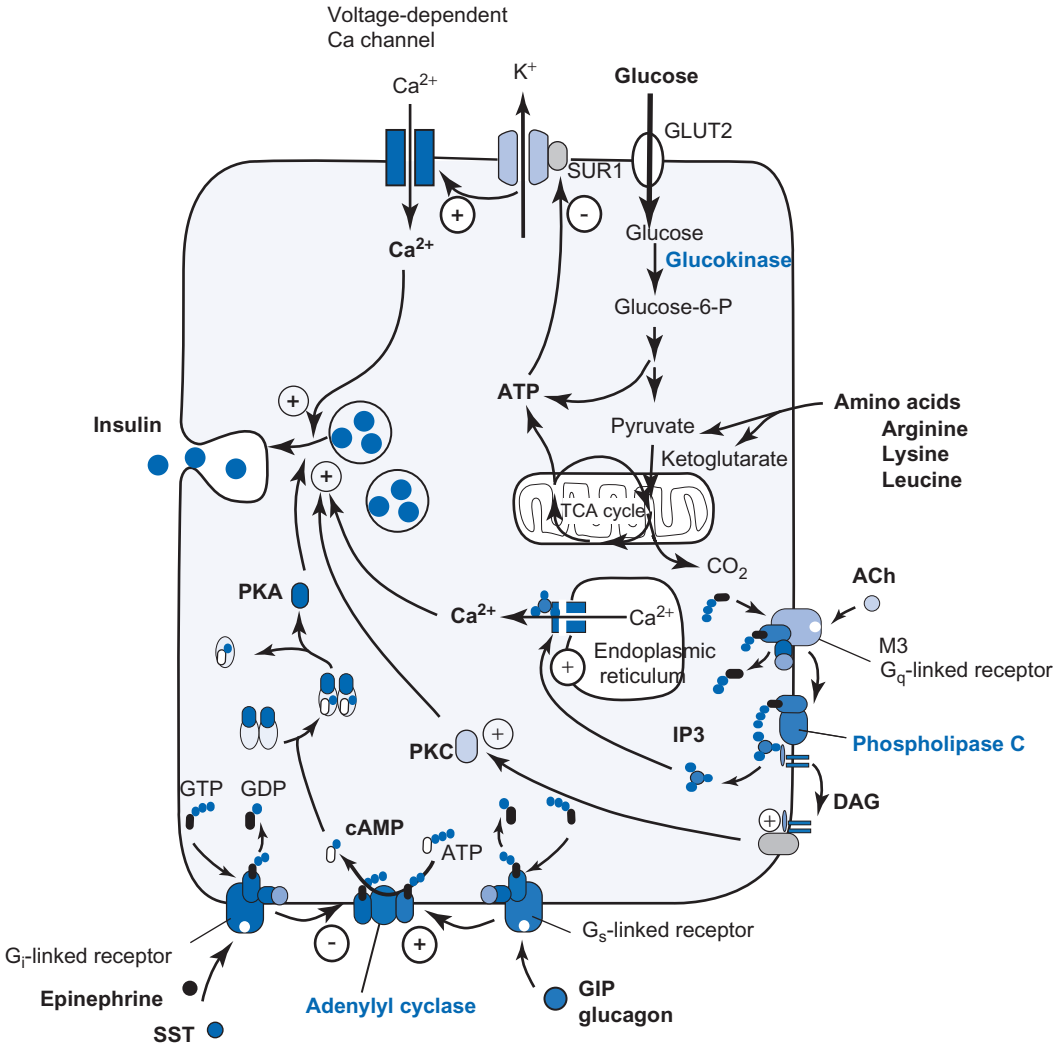

FIGURE 9.4.3 Mechanisms of regulation of insulin secretion. Exocytosis of insulin-containing granules is dependent on increases in cytoplasmic [Ca^{2+}]. This is achieved by depolarization of the cell that opens a voltage-dependent Ca^{2+} channel. Depolarization of the cell is generally achieved by closing an ATP-dependent K^+ channel (K_{ATP}). However, acetylcholine may increase a Na^+ conductance pathway to effect depolarization. Secretion of insulin is modulated by a variety of hormones and neurotransmitters. Epinephrine and norepinephrine inhibit insulin secretion through inhibition of adenylyl cyclase. Glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) both stimulate insulin secretion by activating adenylyl cyclase, increasing cAMP and stimulating protein kinase A (PKA). Acetylcholine increases insulin secretion through an M3 receptor that activates PLC through a G_q mechanism. PLC releases diacylglycerol (DAG) that activates PKC, and inositol trisphosphate (IP3) that releases Ca^{2+} from intracellular stores in the endoplasmic reticulum. The released Ca^{2+} contributes to increased cytoplasmic [Ca^{2+}] that causes exocytosis of insulin-containing granules. Acetylcholine also depolarizes the cell, probably by activating a Na^+ channel.

Voltage-dependent Ca^{2+} channels in the membrane open in response to the depolarization, causing an influx of Ca^{2+} and an increase in cytoplasmic [Ca^{2+}]. The increased cytoplasmic [Ca^{2+}] induces vesicle fusion and insulin secretion (see Figures 9.4.3 and 9.4.4).

GLP-1 AND *GIP* STIMULATE INSULIN SECRETION; *SOMATOSTATIN* INHIBITS IT

Endocrine cells in the small intestine release **glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)**. In general, these hormones are not secretagogues in themselves, but they increase the sensitivity of the islet β cells for glucose. GLP-1 and GIP both increase cAMP through G_s-coupled receptors. Activation of G_q-coupled receptors also potentiates insulin release. Somatostatin, SST, inhibits insulin release, probably by a paracrine mechanism. These effects explain the fact that insulin secretion is greater with an oral dose of glucose than with an infusion—the **incretin** effect.

PARASYMPATHETIC STIMULATION INCREASES INSULIN SECRETION; SYMPATHETIC STIMULATION INHIBITS IT

Parasympathetic stimulation increases insulin secretion through M3, muscarinic receptor type 3, which is

a G_q-coupled receptor. Sympathetic inhibition appears to be mediated by α_2 receptors that are linked to G_i proteins that inhibit adenylyl cyclase. Acetylcholine also appears to depolarize β cells by activating a Na^+ conductance on the surface of the cells. This depolarization would open voltage-dependent Ca^{2+} channels and stimulate insulin secretion. Despite these effects, innervation cannot be considered essential to islet function because the islets continue to secrete insulin and maintain blood sugar levels when they are transplanted to another location in the body where reinnervation is impossible.

AMINO ACIDS STIMULATE INSULIN SECRETION

Amino acids such as arginine, lysine, and leucine stimulate insulin secretion. The mechanism by which this occurs is not established. The working hypothesis is that these amino acids increase ATP supply by their oxidation as fuels, thereby stimulating insulin release. The enzyme glutamine dehydrogenase (GDH) converts glutamic acid to α-ketoglutaric acid, which feeds into the TCA cycle (see Chapter 2.11). Leucine stimulates this enzyme, and the stimulation disappears with high ATP/ADP ratio. Thus, leucine can raise the ATP/ADP ratio at low glucose concentrations, thereby stimulating insulin release, but it cannot stimulate insulin release at high glucose levels. This hypothesis is strengthened by the occurrence of hyperinsulinism in persons with mutations in the regulatory site of GDH.

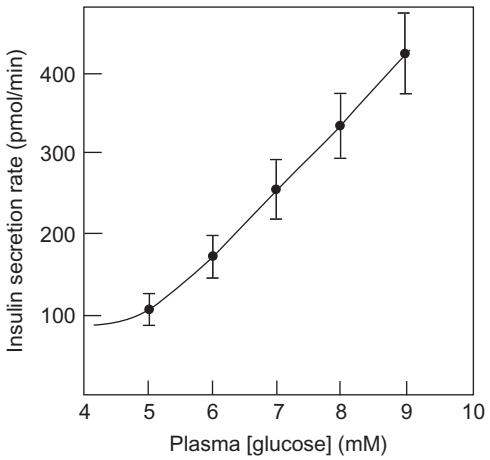

FIGURE 9.4.4 Rate of insulin secretion as a function of plasma glucose concentration. Over a considerable range, insulin secretion is quasi-linear with plasma glucose concentration. *(Source: From C.N. Jones, D. Pei, and P. Staris, Alterations in the glucose-stimulated insulin secretory response curve and insulin clearance in nondiabetic insulin-resistant individuals,* J. Clin. Endocrinol. Metab. ***82****:1834–1838, 1997.)*

SULFONYLUREAS CLOSE THE K_{ATP} CHANNEL AND THEREBY INCREASE INSULIN SECRETION

The K_{ATP} channel consists of a **sulfonylurea receptor (SUR1)** and a K^+ channel, either KIR6.1 or KIR6.2 (referring to inwardly rectifying K^+ channel). In the pancreatic β cell, SUR1 and KIR6.2 form a pair, and four pairs form an octameric K_{ATP} channel. The SUR is sensitive to a class of drugs called **sulfonylureas** that includes oral hypoglycemic agents such as **tolbutamide** and **glyburide**. Other insulin secretagogues also bind to the SUR1 but at distinct sites from the sulfonylureas. Closing the K_{ATP} channel depolarizes the cell, and opens the voltage-sensitive Ca^{2+} channels, leading to exocytosis of granules containing insulin and C peptide.

INSULIN RELEASE IS PULSATILE

About 50% of the total amount of insulin secreted each day is due to basal stimulation. The remaining 50% is secreted in response to meals. The average insulin secretion rate over a 24-h period for normal persons is shown in Figure 9.4.5A. The average secretion rates tend to blunt random spikes in the individual records because these are not synchronized. Individual records show that insulin is secreted in multiple bursts (Figure 9.4.5B).

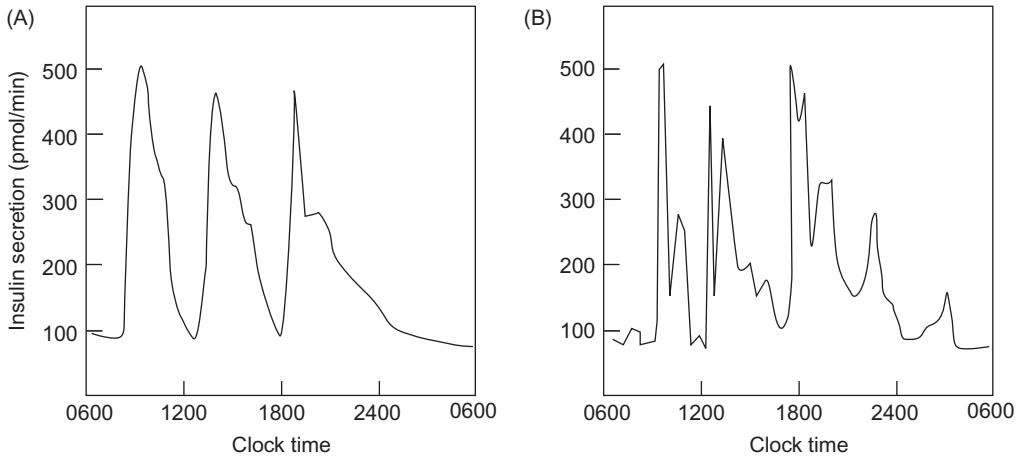

FIGURE 9.4.5 Pulsatile pattern of insulin secretion. Basal secretion amounts to about 100 pmol min^{-1}. This is augmented tremendously by feeding, as shown in the three large peaks from averaged data shown at left **(A)**. In the averaged data, pulsatile patterns of release are averaged out. Individual records of insulin secretion (right, **B**) show multiple peaks of insulin secretion after each meal. *(Source: Redrawn from K.S. Polonsky, B.D. Given, and E. van Cauter, Twenty four hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects,* J. Clin. Invest. ***81****:442–448, 1988.)*

This pattern of pulsatile release is also seen in isolated islets of Langerhans from experimental animals. Stepwise increases in the glucose concentration cause a brief, pulse-like insulin release, followed by a longer, more sustained period of lesser release (see Figure 9.4.6). Analysis of repetitive stimulations suggests that the β cells contain about 10,000 vesicles full of insulin, but only a small fraction, some 0.5%, is in a **readily releasable pool** (RRP) that is adjacent to the voltage-dependent Ca^{2+} channel. Another 1000 or so vesicles are morphologically docked with the membrane but are not readily releasable. They constitute the **immediately releasable pool** (IRP). These undergo "priming" to convert the vesicles into readily releasable vesicles.

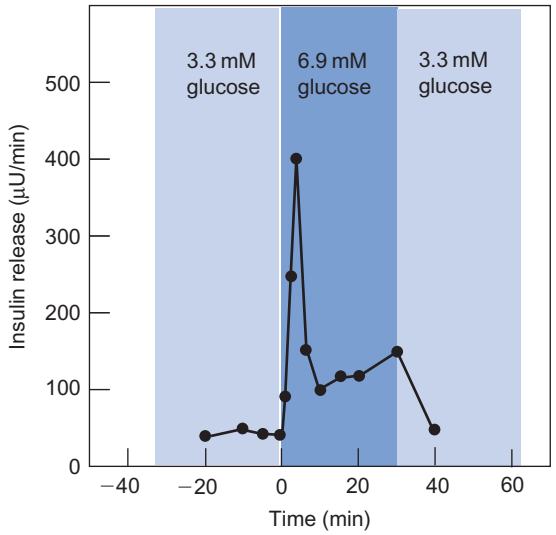

FIGURE 9.4.6 Biphasic course of insulin release from isolated rat pancreatic islets in response to a step change in glucose concentration. Insulin release shows a prompt phase lasting less than 10 min, followed by a slower and more sustained phase. *(Source: From R. Nesher and E. Cerasi, Modeling phasic insulin release. Immediate and time-dependent effects of glucose,* Diabetes ***51****: S53—S59, 2002.)*

INSULIN PHOSPHORYLATES INSULIN RECEPTOR SUBSTRATES VIA A TYROSINE KINASE

Insulin binds to the extracellular surface of its receptor, which is a $\alpha_2\beta_2$ dimer, even in the absence of insulin. Insulin can bind to both halves of this dimer, activating its intrinsic tyrosine kinase activity. The activated tyrosine kinase phosphorylates the intracellular parts of the β chain of the receptor and a set of proteins called **i**nsulin **r**eceptor **s**ubstrates, or **IRS**, consisting of IRS-1, IRS-2, IRS-3, and IRS-4.

Phosphorylation of these IRS proteins exposes a docking surface for other proteins, including **phosphatidyl inositol-3-kinase**, which makes phosphatidyl inositol-3,4,5-trisphosphate, or PIP3. The PIP3 activates **phosphoinositide-dependent protein kinase**, **PDK1** and **PDK2**. This activates **protein kinase B** and isoforms of **protein kinase C** (PKC) that go on to phosphorylate target proteins. Some of these targets are involved with apoptosis, or programmed cell death. Phosphorylation of these by PKB inactivates the "death" proteins and activates death-inhibitory proteins. Insulin activates another pathway through **Grb-2** leading to a cascade resulting in the activation of **MAP kinase**, **m**itogen **a**ctivated **p**rotein **kinase**. MAP kinase phosphorylates components of a gene regulatory complex that alters gene expression. Thus, insulin promotes survival and growth of cells (see Figure 9.4.7). The overall physiological actions of insulin are summarized in Table 9.4.1.

LOW GLUCOSE STIMULATES GLUCAGON RELEASE FROM α CELLS IN THE ISLETS OF LANGERHANS

The α cells make up 25% of the islets of Langerhans and secrete glucagon, a 29-amino-acid peptide, in response to hypoglycemia. The α cells synthesize proglucagon which is then cleaved by a proprotein convertase to

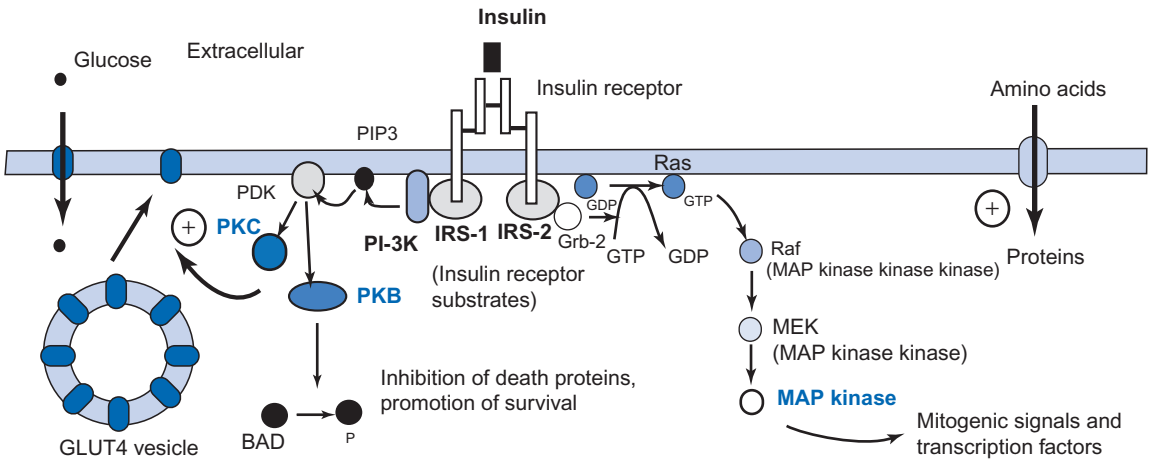

FIGURE 9.4.7 Mechanism of action of insulin on target cells. Insulin binds to both halves of a homodimer with intrinsic tyrosine kinase activity, activating phosphorylation of insulin receptor substrates. These activate PI-3K and Grb-2. PI-3K forms PIP3 in the membranes, which activates PDK1 and PDK2, which in turn activate PKC and PKB. PKB phosphorylates another protein, BAD, that inhibits BAD's ill effects. A second signaling pathway occurs through Grb-2, growth factor receptor binding protein. Grb-2 catalyzes the exchange of GTP for GDP on Ras, which then initiates a phosphorylation cascade through Raf and MEK, finally activating MAP kinase. MAP kinase signals the nucleus to promote growth and survival.

TABLE 9.4.1 Overview of the Physiological Actions of Insulin

1 **Effects on Carbohydrate Metabolism**
- 1.1 Insulin recruits the GLUT4 transporter to the surface membrane
- 1.2 Insulin increases glucose uptake by adipose and muscle tissue
- 1.3 By increasing peripheral uptake, insulin reduces plasma [glucose]
- 1.4 Insulin increases glucokinase activity in the liver, so [glucose-6-P] increases
- 1.5 Insulin stimulates glycogen synthase so that glycogenesis in liver and muscle increases
- 1.6 Insulin decreases glycogenolysis in liver and muscle
- 1.7 Insulin decreases gluconeogenesis in liver

2 **Effects on protein metabolism**
- 2.1 Insulin increases amino acid transport into liver, muscle, and adipose cells
- 2.2 Insulin increases protein synthesis and decreases protein breakdown

3 **Effects on fat metabolism**
- 3.1 Insulin increases uptake of free fatty acids (FFAs) by adipose tissue by stimulating lipoprotein lipase
- 3.2 Insulin increases lipogenesis
- 3.3 Insulin decreases lipolysis by inhibiting hormone-sensitive adipose lipase
- 3.4 Insulin decreases β oxidation of FFA in the liver
- 3.5 Insulin decreases plasma [FFA]

4 **Effects on ions**
- 4.1 Insulin increases cellular uptake of K^+, PO_4^{-3}, and Mg^{2+}
- 4.2 Insulin stimulates Na^+–K^+-ATPase

5 **Overall effects**
- 5.1 Insulin stimulates anabolic reactions of carbohydrates, lipids, and proteins
- 5.2 All tissues of the body are affected either directly or indirectly

form glucagon. Glucagon restores blood glucose levels by mobilizing glucose primarily from the liver. Glucagon also affects adipose tissue.

In addition to low glucose, ingestion of proteins stimulates glucagon secretion and insulin inhibits it. Free fatty acids (FFAs) inhibit glucagon release, and both parasympathetic and sympathetic stimulation increase it. These effects are relatively unimportant compared to the profound stimulation of glucagon release caused by low blood glucose.

GLUCAGON STIMULATES LIVER GLYCOGENOLYSIS THROUGH A G_s AND G_q MECHANISM

Glucagon binds to G-protein-coupled receptors on the surface of hepatocytes. The G_s-coupled receptor activates **adenylyl cyclase**. The G_q-coupled receptor activates **phospholipase C (PLC)**. Both of these actions result in the activation of protein kinases. Increasing cytoplasmic [cAMP] activates **protein kinase A**, and increasing cytoplasmic [Ca^{2+}] through IP3-induced release of Ca^{2+} from the endoplasmic reticulum activates calmodulin-dependent protein kinase (**CAM kinase**). Activation of protein kinase A begins a cascade of events that results in the activation of **phosphorylase**, the enzyme that breaks down glycogen and inhibits glycogen synthase. At the same time, specific enzymes are activated that decrease glycolysis and enhance gluconeogenesis, the formation of glucose from amino acids. The final result is as follows:

- Decreased glycolysis
- Decreased glycogen synthesis
- Increased glycogenolysis
- Increased gluconeogenesis.

The combined effects of glucagon on liver cells are shown diagrammatically in Figure 9.4.8.

BLOOD GLUCOSE IS MAINTAINED BETWEEN 70 AND 110 mg% IN THE FACE OF CONSTANT DEPLETION

The fasting blood glucose level is typically between 70 and 110 mg% (4.0 to 6.0 mM) with an average of about 90 mg% (5 mM). This level is maintained by a balance between influx of glucose into the circulation and efflux out of it. The brain needs a continuous supply of glucose because it requires glucose and cannot make glucose or store more than a few minutes' worth as glycogen. The rate of glucose uptake by the brain depends entirely on the plasma glucose concentration. At rest, the brain accounts for about 60% of the basal glucose utilization. During exercise, muscle glucose consumption increases many fold, and the fraction of glucose used by the brain is greatly reduced. Increased glucose consumption during exercise must be met with increased glucose supply, or blood glucose levels would fall precipitously and cause **hypoglycemia**.

PLASMA GLUCOSE CONCENTRATIONS ARE MAINTAINED BY *ABSORPTION*, *GLYCOGENOLYSIS*, AND *GLUCONEOGENESIS*

Plasma glucose is derived from three sources:

1. **Absorption** of glucose from the gastrointestinal tract following ingestion of carbohydrates.
2. **Glycogenolysis**, the breakdown of the polymerized storage form of glucose.
3. **Gluoneogenesis**, the formation of glucose from other precursors including lactate, pyruvate, amino acids, and glycerol.

After a meal, carbohydrates in the food are digested to monosaccharides and absorbed into the blood (see Chapter 8.5). The rate of glucose absorption into the circulation can be more than twice the rate of fasting endogenous glucose production. If glucose utilization is not increased, glucose absorption causes blood glucose to rise. The postprandial hyperglycemia increases insulin secretion, which blunts the hyperglycemia due to insulin

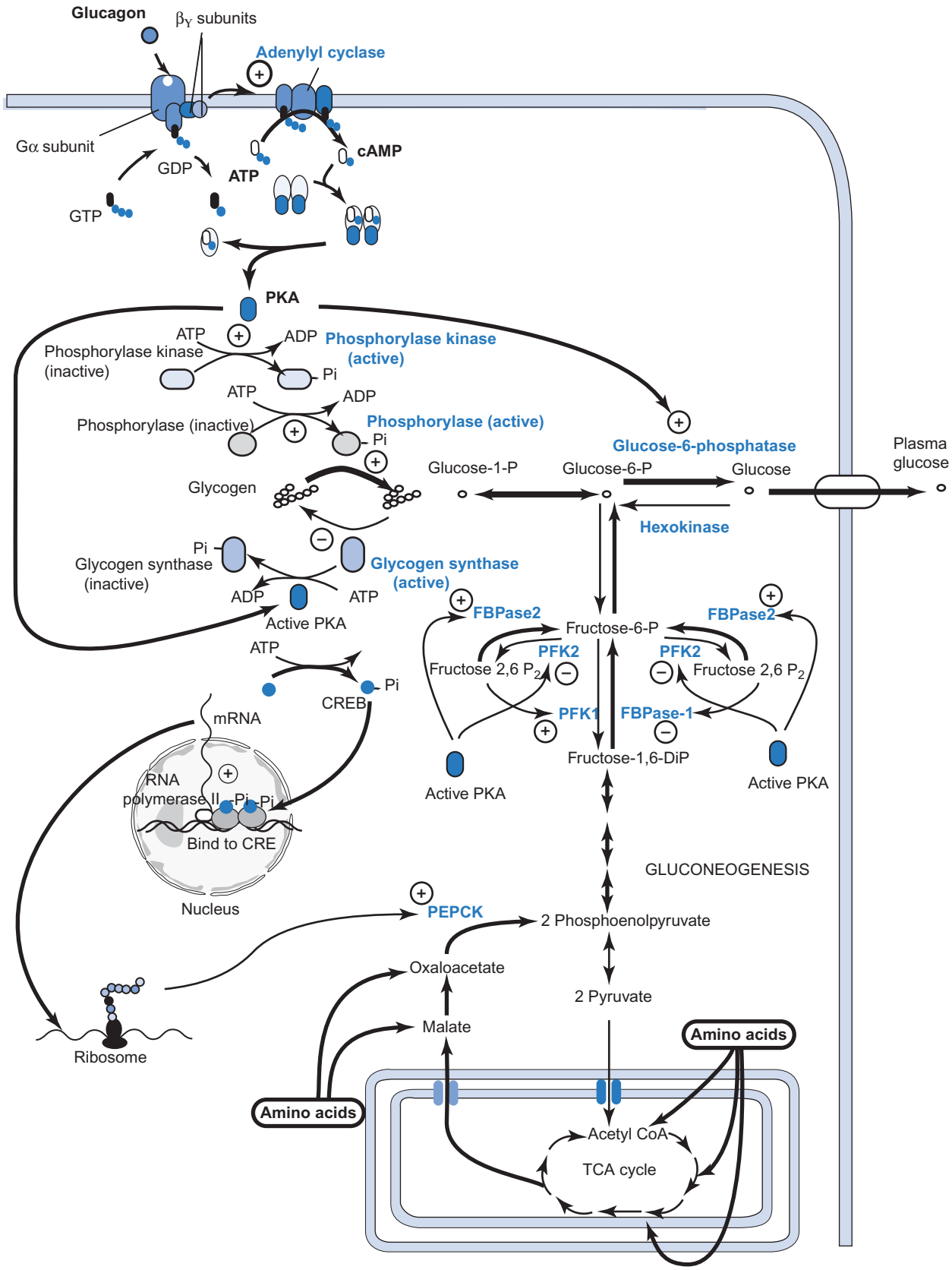

FIGURE 9.4.8 Mechanism of action of glucagon on liver cells to put glucose into the blood. Binding of glucagon to receptors on the surface of the liver cell is coupled through a heterotrimeric G_s protein to the activation of **adenylyl cyclase**, which increases the production of 3′,5′ cyclic AMP. Increased cytosolic [cAMP] activates **PKA**, which phosphorylates **phosphorylase kinase**, thereby activating it. The activated phosphorylase kinase then phosphorylates **phosphorylase**, converting it from its inactive to active form. The activated phosphorylase then phosphorylates **glycogen**, which then can be broken down to release **glucose-1-phosphate**. Phosphoglucomutase converts glucose-1-phosphate to **glucose-6-phosphate**.

stimulation of peripheral glucose uptake by liver, muscle, and fat. In persons with a deficit in insulin secretion, the postprandial glucose peak is larger and longer lasting. This is the basis of the **oral glucose tolerance test** for prediabetic persons, in which 1.75 g of glucose per kilogram of body weight is given orally (or 75 g for an adult) and blood glucose is measured with time.

Most tissues can make glycogen and break it down. The **breakdown of glycogen produces glucose-1-phosphate**, which is isomerized to glucose-6-phosphate by phosphoglucomutase. Thus, glycogenolysis never produces free glucose. Glycolysis of cytoplasmic glucose also begins by forming glucose-6-phosphate from glucose and ATP. **Gluconeogenesis is a reversal of glycolysis to form glucose-6-phosphate**. Thus, glycogenolysis, gluconeogenesis, and glycolysis all funnel through glucose-6-phosphate (see Figure 9.4.8). Tissues that lack glucose-6-phosphatase cannot form free glucose from either glycogen or amino acid precursors. Only the liver, kidney, and intestine possess **glucose-6-phosphatase**, so only these tissues can produce cytoplasmic glucose. Glucose-6-phosphate cannot exit the cell, so only these tissues can contribute glucose to the blood, either from glycogenolysis or from gluconeogenesis.

MULTIPLE HORMONES AND NERVES CONTROL GLUCOSE FLUX

Systemic glucose levels are controlled by two competing systems that regulate the influx of glucose into the circulation and the efflux of glucose out of the circulation. Insulin primarily lowers plasma glucose by controlling efflux of glucose from the blood—it controls the GLUT4 receptors on skeletal muscle and fat to increase their uptake of glucose. Glucagon and epinephrine raise plasma glucose by increasing glycogenolysis and gluconeogenesis. Because glucagon is released into the portal circulation, it is believed to affect only the liver under physiological conditions. Epinephrine, on the other hand, affects multiple organ systems. These two control systems prevent excessive hyperglycemia following feeding and hypoglycemia during fasting. Other hormones are also involved in the regulation of metabolism, including growth hormone and cortisol. Both of these defend against hypoglycemia. The response of insulin and glucagon and their effects on liver, muscle, and adipose tissue is shown schematically in Figure 9.4.9.

EXERCISE HAS AN INSULIN-LIKE EFFECT

Glucose carriers can be inserted into the muscle cell membrane independently of insulin when the muscle is repetitively activated. Thus, exercise has an insulin-like effect and muscle activity promotes peripheral glucose uptake at lower levels of insulin. For this reason, diabetic persons must titrate their injected insulin according to their daily carbohydrate intake and taking into account their projected level of exercise. Strenuous or long-lasting exercise requires less insulin.

In the fasting state, glucose influx into the circulation from the intestines stops because there is no more food in the intestines. Constant drains on blood glucose by the brain and other metabolizing tissues tend to reduce blood glucose concentration. This shuts off insulin secretion and turns on glucagon secretion to reduce plasma glucose efflux from the circulation and to increase glucose influx. Muscles use their glycogen stores and plasma fatty acids instead of plasma glucose, and adipose tissue reduces glucose uptake. Neither of these tissues can provide glucose for the other tissues of the body because they lack glucose-6-phosphatase activity. Glucagon stimulates the liver to form new glucose from amino acids, glycerol, and lactic acid produced by active muscle. Complete regulation of carbohydrate, amino acid, and fat metabolism is considerably more complicated, involving additional actions by epinephrine, growth hormone, and cortisol and involving more metabolic pathways than described here.

SUMMARY

β Cells in the islets of Langerhans in the pancreas secrete insulin in response to hyperglycemia. Insulin is synthesized as a single polypeptide chain that is cleaved repeatedly to form the final insulin and a C peptide. All derive from the single proinsulin. The secreted insulin consists of two chains, A and B, linked by two disulfide bonds. Because the C peptide is degraded more slowly than insulin itself, its level can be used as an indicator of insulin secretion.

Insulin exerts its effects by binding to a homodimer insulin receptor with intrinsic tyrosine kinase activity. The receptor phosphorylates a set of proteins called insulin receptor substrates. Among other actions, these activate a phosphatidyl inositol-3-kinase which makes phosphatidyl inositol-

FIGURE 9.4.8 (*Continued*) Glucose-6-phosphatase removes the phosphate from glucose-6-phosphate to produce glucose. This glucose can be released into the bloodstream. Simultaneous with this activation of **glycogenolysis**, the increased PKA also phosphorylates glycogen synthase, inactivating it. This decreases glycogen synthesis. PKA also phosphorylates **CREB**, the **cyclic AMP responsive element binding protein**. This activates its binding to the CRE, cAMP responsive element. Activation of CRE increases the transcription of another transcriptional activator that then turns on the synthesis of **PEPCK (phosphoenolpyruvate carboxy kinase**). This enzyme converts **oxaloacetate** to **phosphoenolpyruvate**. The oxaloacetate is a common carbohydrate intermediate formed from the glucogenic amino acids. PKA also indirectly regulates a key controlling enzyme in glycolysis: **phosphofructokinase 1/fructose biphosphatase 1 (PFK1/FBPase1)**. PFK1 converts fructose-6-phosphate to fructose-1,6-biphosphate; FBPase1 converts fructose-1,6-biphosphate to fructose-6-phosphate. The FBPase1 activity and PFK1 activities are regulated by cytosolic levels of **fructose-2,6-biphosphate (FBP)**. Fructose-2,6-biphosphate stimulates PFK activity and inhibits FBPase activity. Fructose-2,6-biphosphate levels are determined by the activity of **phosphofructo kinase 2** and **fructose-2,6-biphosphatase (FBPase2)** that convert fructose-6-phosphate to fructose-2,6-biphosphate. The activities of PFK2/FBPase2 reside on a single polypeptide chain. PKA phosphorylates PFK2/FBPase2, stimulating the FBPase2 activity and inhibiting the PFK2 activity. This reduces the level of fructose-2,6-biphosphate, which subsequently removes activation of PFK1 and removes inhibition of FBPase1. The net result is an inhibition of PFK1, which thereby slows glycolysis, and activation of FBPase1, which increases gluconeogenesis.

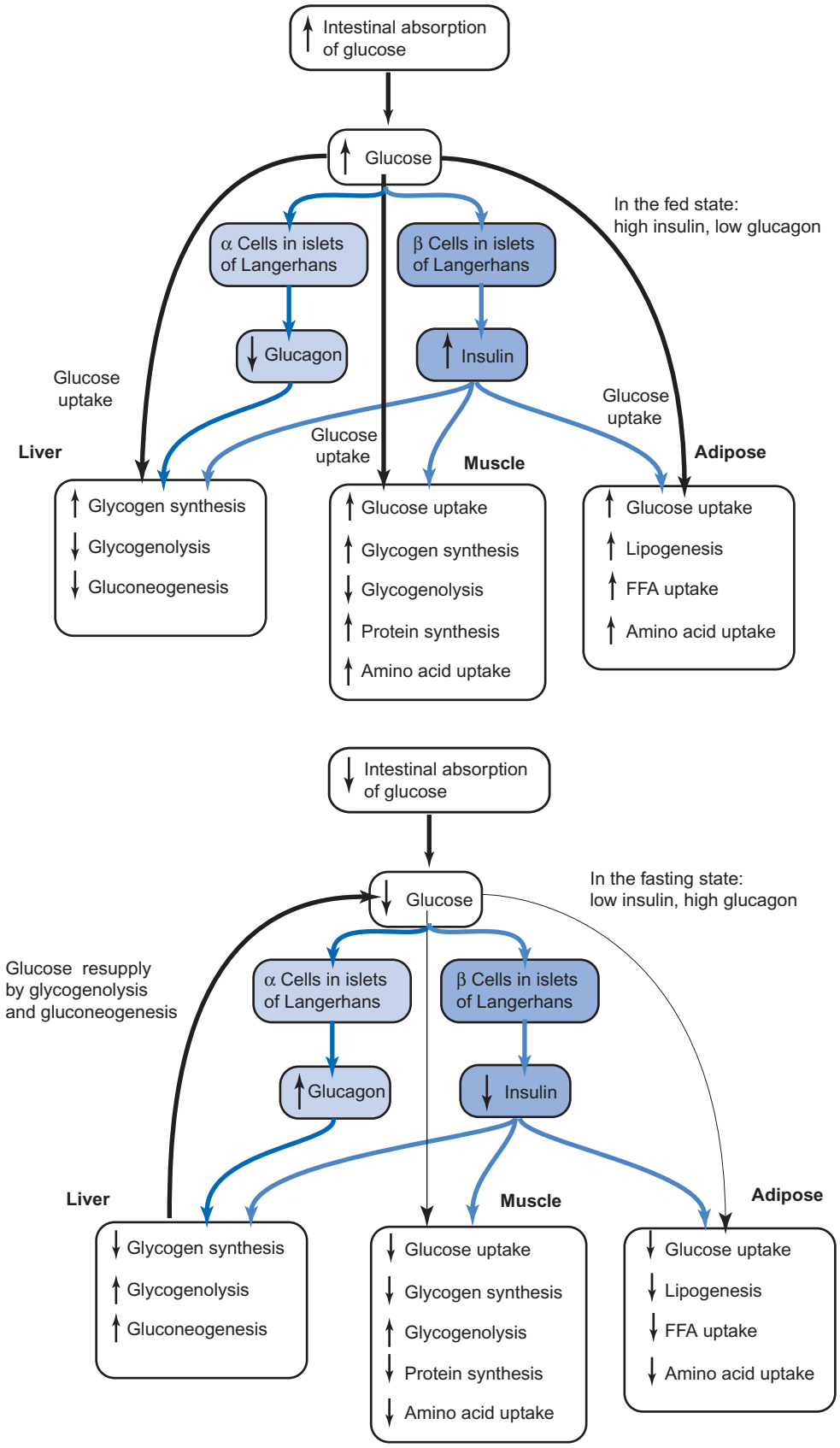

FIGURE 9.4.9 Regulation of plasma glucose concentration during the fed state (top) and the fasting state (bottom). During the fed state, absorption of glucose from the intestine and metabolism of amino acids to glucose produce a prolonged elevation of plasma glucose concentration. This suppresses glucagon secretion and stimulates insulin secretion. Glucagon mainly affects the liver. The withdrawal of glucagon and stimulation by insulin increases liver glycogen synthesis and protein synthesis and reduces glycogenolysis and gluconeogenesis. Insulin increases glucose uptake in both muscle and adipose tissue and the glucose taken up is stored either as glycogen in muscle or triglycerides in adipose tissue.

Clinical Applications: Diabetes Mellitus

The descriptive term "diabetes mellitus" derives from the Greek meaning "to siphon" ("diabetes") and "sweet" ("mellitus"). These terms describe the large volume of urine produce by persons with diabetes mellitus and the sweet taste of the urine. The hallmark of the disease is high plasma glucose concentrations that exceed the plasma threshold of the kidney. The filtered load of glucose is too great for the kidney to reabsorb it all, and the glucose that exceeds the transport maximum is carried through to the final urine. The glucose in the distal nephron exerts an osmotic pressure that draws water in from the surrounding kidney interstitium, thereby causing a large volume of urine with high concentrations of glucose. All of this wasted glucose represents a metabolic drain, and even well-hydrated persons gradually waste away.

There are two major types of diabetes mellitus. Both are characterized by high plasma glucose concentrations. The elevated plasma glucose results from a relative or absolute deficiency in insulin action. This is due to either (1) deficient secretion of insulin by the β cells of the islets of Langerhans or (2) a deficient response of the target cells to adequate insulin levels. Deficient secretion of insulin is called **insulin-dependent diabetes mellitus** (**IDDM**) or **Type 1 diabetes**. Reduced sensitivity to insulin is called **noninsulin-dependent diabetes mellitus** (**NIDDM**) or **Type 2 diabetes**.

Type I diabetes arises from destruction of the β cells in the pancreas, usually from autoimmune processes. The etiology of the disease is not entirely clear. Some individuals appear to have a genetic predisposition to the disease, which is brought about, generally in adolescence, by environmental components such as viral infections. The affected individuals are diagnosed from their polyuria and hyperglycemia. Because they lack insulin, persons with Type I diabetes cannot take up adequate glucose into muscle and adipose tissue, and so these tissues experience starvation in the midst of plenty. As a result, these tissues rely on fat metabolism and produce large quantities of **ketone bodies: acetoacetic acid, β-hydroxybutyric acid,** and **acetone**. These ketone bodies are acids, and the resulting condition is called **ketoacidosis**. These ketone bodies can exceed their renal threshold and spill over into the urine. Because they are acids, they draw with them cations such as Na^+ and K^+. If left untreated, the resulting acidosis and electrolyte imbalance eventually causes coma and death.

As little as 80 years ago Type I diabetes was uniformly fatal. Now afflicted persons can be kept healthy by injecting insulin. However, this form of diabetes makes up just 5% of the total cases in the United States. Some 95% of diabetics have Type II diabetes. In this disease, the afflicted person has normal or higher than normal concentrations of insulin, but the target tissues do not respond normally. This condition is called **insulin resistance**. The condition is related to obesity; losing excess body fat often reduces the severity of the disease and can return the person to normal.

Most diabetics are managed through a program of modified diet, insulin injections for IDDM or oral hypoglycemic agents for NIDDM, and exercise. Exercise increases peripheral uptake of glucose, an insulin-like effect. Thus, diabetics taking insulin injections adjust their dose depending on the amount of exercise they have taken.

The degree of control of a diabetic is measured by the long-term average glucose concentrations. Persons with poor control have widely varying levels of plasma glucose that generally average higher than normal. Glucose forms a glycosylated hemoglobin, HbA_{1C}, whose value reflects the long-term average glucose concentration. Its upper limit of normal is 6%. Long-term control of blood glucose levels is important because diabetes is associated with a number of long-term changes in the basement membranes of capillaries. Microvasculature lesions can lead to **diabetic retinopathy** and **diabetic nephropathy**, in which the microvasculature nourishing the retina degrades, causing blindness, or the microvasculature in the kidney fails to nourish the kidney. Long-standing diabetics also develop circulatory problems in the extremities that can result in amputation.

3,4,5-triphosphate, or PIP3, which subsequently activates a phosphoinositide-dependent protein kinase, PDK. This activates PKB and PKC. One of the consequences of the phosphorylation of their targets is the insertion into the plasma membrane of more copies of the glucose transport protein GLUT4. This increases glucose uptake by tissues that have insulin receptors, which applies to most peripheral tissues. Insulin also has profound effects on lipid metabolism by activating lipoprotein lipase and inhibiting the hormone-sensitive adipose lipase. The result is decreased lipolysis and increased lipogenesis.

α Cells in the islets of Langerhans secrete glucagon in response to hypoglycemia. Glucagon is a single polypeptide chain of 29 amino acids. It raises blood glucose by increasing glycogenolysis and gluconeogenesis. In hepatocytes, glucagon acts through a G_s and G_q mechanism. PKA phosphorylates a crucial enzyme, phosphofructokinase 2/fructose-2,6-biphosphatase. Both of these activities reside on a single polypeptide chain. Phosphorylation inhibits the PFK activity and activates the FBPase2 activity. The consequence is a reduction in fructose-2,6-biphosphate. Fructose-2,6-biphosphate stimulates PFK activity and inhibits FBPase activity, so its reduction lowers the PFK activity (necessary for glycolysis) and increases FBPase (necessary for gluconeogenesis). In this way, glucagon enhances gluconeogenesis.

In the fed state, glucose and other nutrients enter the bloodstream and increase plasma glucose concentration. Consequently, postprandial levels of glucagon are low and insulin levels are high. Peripheral tissues take up glucose, and make glycogen, proteins, and lipids. In the fasting state, plasma glucose levels fall and glucagon rises while insulin falls. This situation is marked by glycogenolysis, gluconeogenesis, and lipolysis.

REVIEW QUESTIONS

1. What is insulin? Where is it produced? What cells secrete it? What stimulates its release?
2. How is insulin secretion stimulated? How do oral hypoglycemic agents work?
3. What effects does insulin have on muscle? On liver? Adipose tissue? Can you consider insulin to be mainly a hormone of carbohydrate metabolism?
4. What is insulin's mechanism of action?
5. What is glucagon? Where is it produced? What cells secrete it? What stimulates its release?
6. What effects does glucagon have on liver? Does it affect muscle or adipose tissue?
7. What is glucagon's mechanism of action?