Carbohydrate Metabolism

Glucose is central to all of metabolism. It is the universal fuel for human cells and the source of carbon for the synthesis of most other compounds. Every human cell type uses glucose to obtain energy. The release of insulin and glucagon by the pancreas aids in the body's use and storage of glucose. Other dietary sugars (mainly fructose and galactose) are converted to glucose or to intermediates of glucose metabolism.

Glucose is the precursor for the synthesis of an array of other sugars required for the production of specialized compounds, such as lactose, cell surface antigens, nucleotides, or glycosaminoglycans. Glucose is also the fundamental precursor of noncarbohydrate compounds; it can be converted to lipids (including fatty acids, cholesterol, and steroid hormones), amino acids, and nucleic acids. Only those compounds that are synthesized from vitamins, essential amino acids, and essential fatty acids cannot be synthesized from glucose in humans.

More than 40% of the calories in the typical diet in the United States are obtained from starch, sucrose, and lactose. These dietary carbohydrates are converted to glucose, galactose, and fructose in the digestive tract (Fig. 1). Monosaccharides are absorbed from the intestine, enter the blood, and travel to the tissues where they are metabolized.

After glucose is transported into cells, it is phosphorylated by a hexokinase to form glucose 6-phosphate. Glucose 6-phosphate can then enter a number of metabolic pathways. The three that are common to all cell types are glycolysis, the pentose phosphate pathway, and glycogen synthesis (Fig. 2). In tissues, fructose and galactose are converted to intermediates of glucose metabolism. Thus, the fate of these sugars parallels that of glucose (Fig. 3).

The major fate of glucose 6-phosphate is oxidation via the pathway of glycolysis (see Chapter 22), which provides a source of ATP for all cell types. Cells that lack mitochondria cannot oxidize other fuels. They produce ATP from anaerobic glycolysis (the conversion of glucose to lactic acid). Cells that contain mitochondria

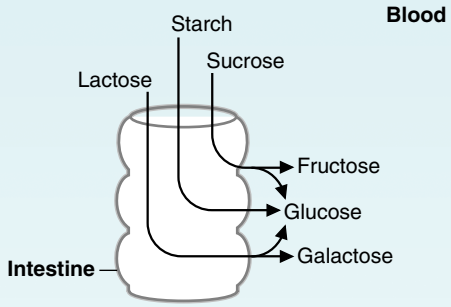


Fig 1. Overview of carbohydrate digestion. The major carbohydrates of the diet (starch, lactose, and sucrose) are digested to produce monosaccharides (glucose, fructose, and galactose), which enter the blood.

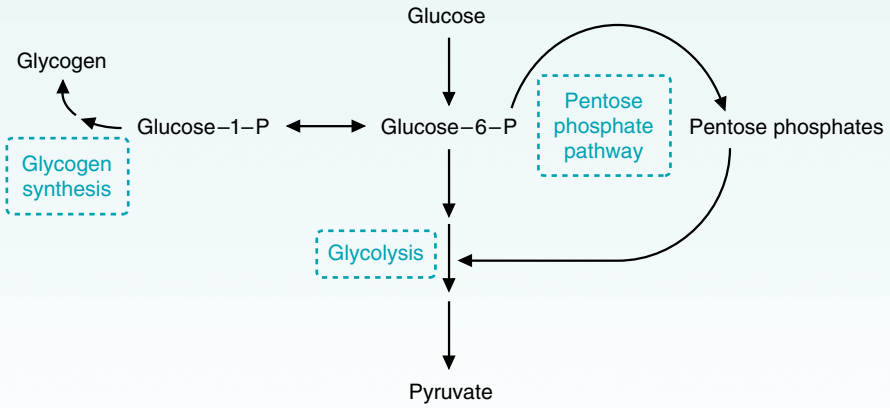


Fig 2. Major pathways of glucose metabolism.

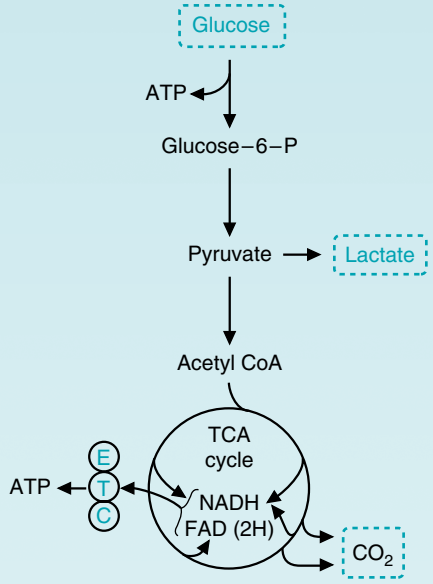


Fig 4. Conversion of glucose to lactate or to CO_2. ETC = electron transport chain.

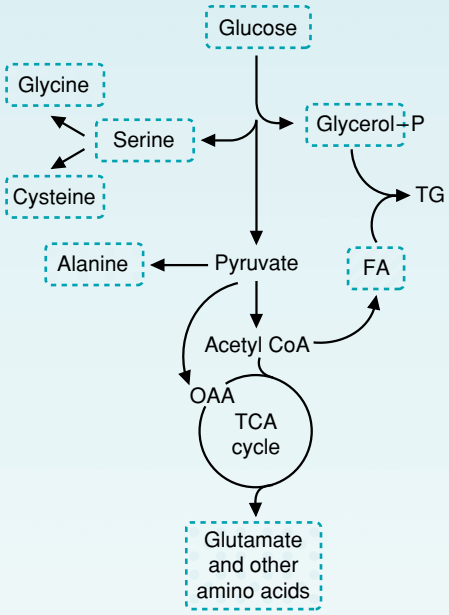


Fig 5. Conversion of glucose to amino acids and to the glycerol and fatty acid (FA) moieties of triacylglycerols (TG). OAA = oxaloacetate.

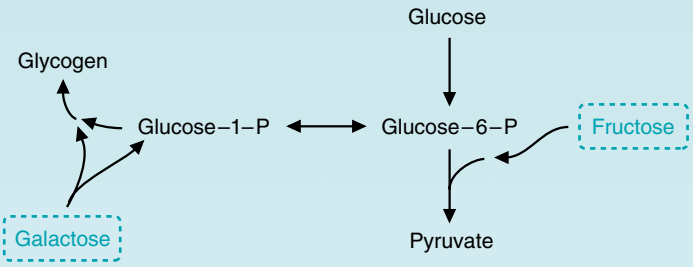


Fig 3. Overview of fructose and galactose metabolism. Fructose and galactose are converted to intermediates of glucose metabolism.

oxidize glucose to CO_2 and H_2O via glycolysis and the TCA cycle (Fig. 4). Some tissues, such as the brain, depend on the oxidation of glucose to CO_2 and H_2O for energy because they have a limited capacity to use other fuels.

Glucose produces the intermediates of glycolysis and the TCA cycle that are used for the synthesis of amino acids and both the glycerol and fatty acid moieties of triacylglycerols (Fig. 5).

Another important fate of glucose 6-phosphate is oxidation via the pentose phosphate pathway, which generates NADPH. The reducing equivalents of NADPH are used for biosynthetic reactions and for the prevention of oxidative damage to cells (see Chapter 24). In this pathway, glucose is oxidatively decarboxylated to 5-carbon sugars (pentoses), which may reenter the glycolytic pathway. They also may be used for nucleotide synthesis (Fig. 6). There are also non-oxidative reactions, which can convert six- and five-carbon sugars.

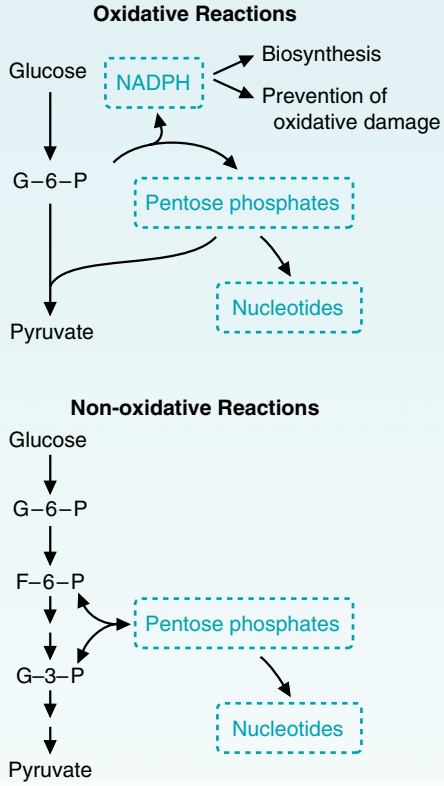


Fig 6. Overview of the pentose phosphate pathway. The oxidative reactions generate both NADPH and pentose phosphates. The non-oxidative reactions only generate pentose phosphates.

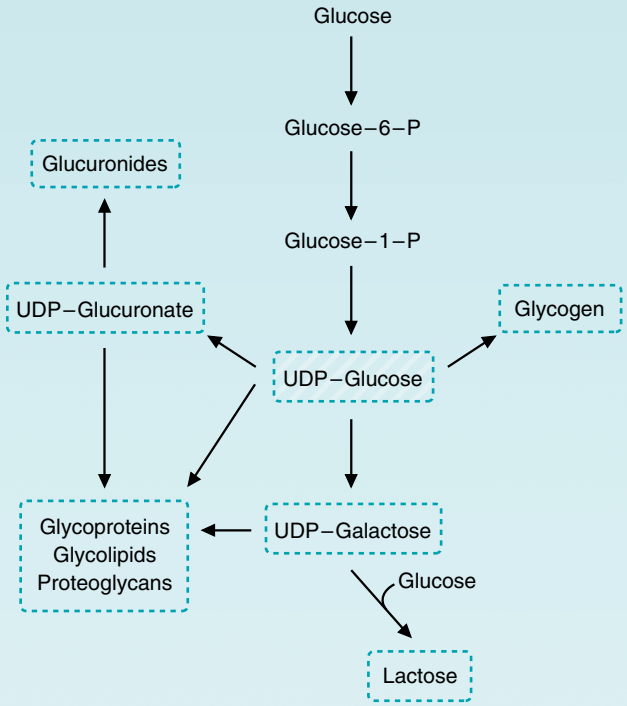


Fig 7. Products derived from UDP-glucose.

Glucose 6-phosphate is also converted to UDP-glucose, which has many functions in the cell (Fig. 7). The major fate of UDP-glucose is the synthesis of glycogen, the storage polymer of glucose. Although most cells have glycogen to provide emergency supplies of glucose, the largest stores are in muscle and liver. Muscle glycogen is used to generate ATP during muscle contraction. Liver glycogen is used to maintain blood glucose during fasting and during exercise or periods of enhanced need. UDP-Glucose is also used for the formation of other sugars, and galactose and glucose are interconverted while attached to UDP. UDP-Galactose is used for lactose synthesis in the mammary gland. In the liver, UDP-glucose is oxidized to UDP-glucuronate, which is used to convert bilirubin and other toxic compounds to glucuronides for excretion (see Fig. 7).

Nucleotide sugars are also used for the synthesis of proteoglycans, glycoproteins, and glycolipids (see Fig. 7). Proteoglycans are major carbohydrate components of the extracellular matrix, cartilage, and extracellular fluids (such as the synovial fluid of joints), and they are discussed in more detail in Chapter 49. Most extracellular proteins are glycoproteins, i.e., they contain covalently attached carbohydrates. For both cell membrane glycoproteins and glycolipids, the carbohydrate portion extends into the extracellular space.

All cells are continuously supplied with glucose under normal circumstances; the body maintains a relatively narrow range of glucose concentration in the blood (approximately 80-100 mg/dL) in spite of the changes in dietary supply and tissue demand as we sleep and exercise. This process is called glucose homeostasis. Low blood glucose levels (hypoglycemia) are prevented by a release of glucose from the large glycogen stores in the liver (glycogenolysis); by synthesis of glucose from lactate, glycerol, and amino acids in liver (gluconeogenesis) (Fig. 8); and to a limited extent by a release of fatty acids from adipose tissue stores (lipolysis) to provide an alternate fuel when glucose is in short supply. High blood glucose levels (hyperglycemia) are prevented both by the conversion of glucose to glycogen and by its conversion to triacylglycerols in liver and adipose tissue. Thus, the pathways for glucose utilization as a fuel cannot be considered as totally separate from pathways involving amino acid and fatty acid metabolism (Fig. 9).

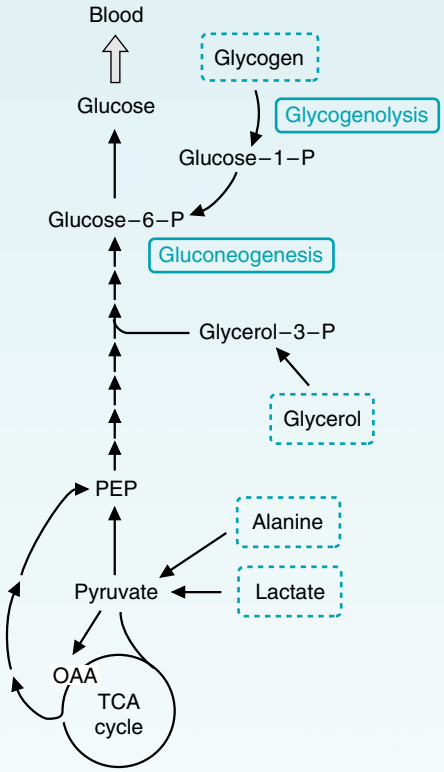


Fig 8. Production of blood glucose from glycogen (by glycogenolysis) and from alanine, lactate, and glycerol (by gluconeogenesis). PEP = phosphoenolpyruvate; OAA = oxaloacetate.

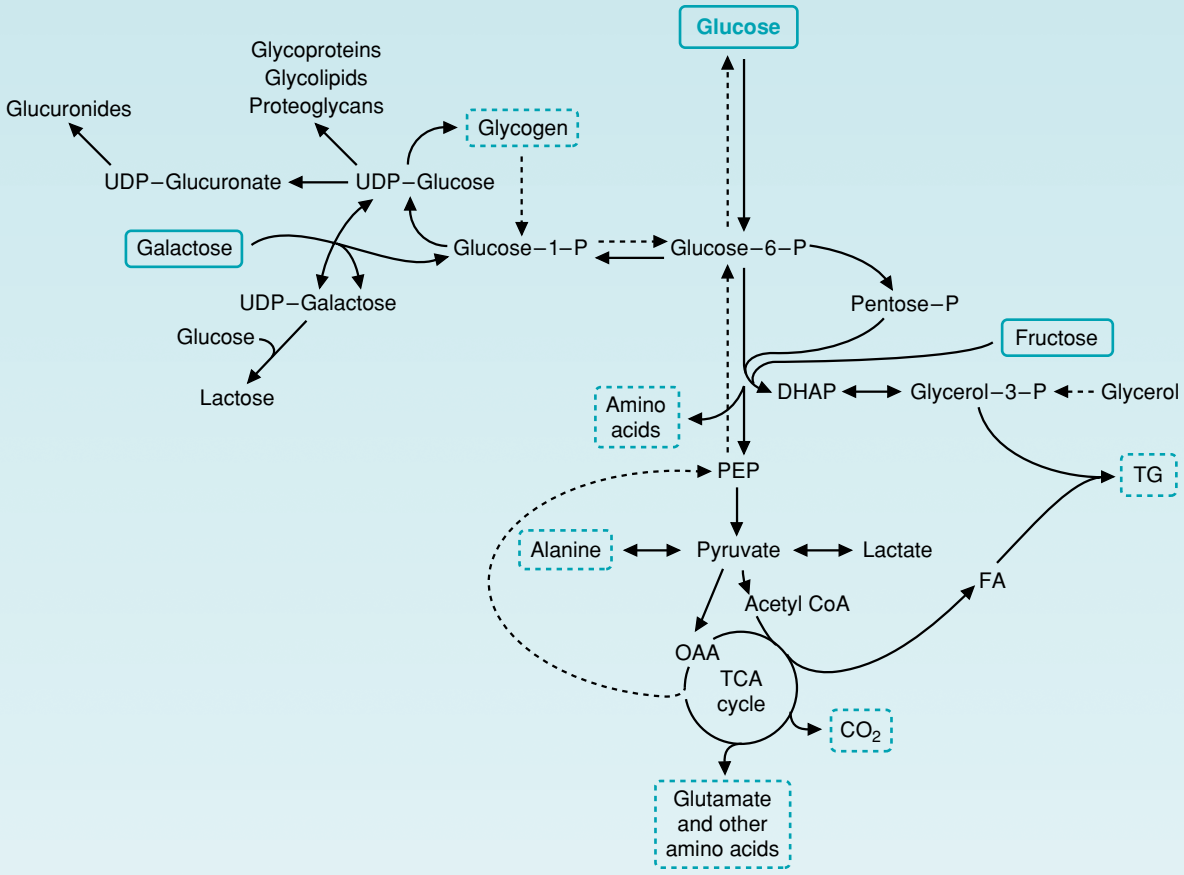


Fig 9. Overview of the major pathways of glucose metabolism. Pathways for production of blood glucose are shown by dashed lines. FA = fatty acids; TG = triacylglycerols; OAA = oxaloacetate; PEP = phosphoenolpyruvate; UDP-G = UDP-glucose; DHAP = dihydroxyacetone phosphate.

Intertissue balance in the utilization and storage of glucose during fasting and feeding is accomplished principally by the actions of the hormones of metabolic homeostasis—insulin and glucagon (Fig. 10). However, cortisol, epinephrine, norepinephrine, and other hormones are also involved in intertissue adjustments of supply and demand in response to changes of physiologic state.

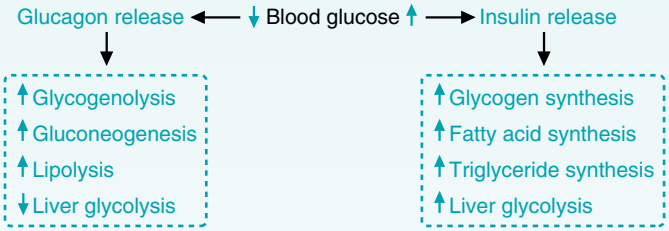


Fig 10. Pathways regulated by the release of glucagon (in response to a lowering of blood glucose levels) and insulin (released in response to an elevation of blood glucose levels). Tissue-specific differences occur in the response to these hormones, as detailed in the subsequent chapters of this section.

26 Basic Concepts in the Regulation of Fuel Metabolism by Insulin, Glucagon, and Other Hormones

All cells continuously use adenosine triphosphate (ATP) and require a constant supply of fuels to provide energy for ATP generation. ***Insulin*** *and* ***glucagon*** *are the two major hormones that regulate fuel mobilization and storage. Their function is to ensure that cells have a constant source of glucose, fatty acids, and amino acids for ATP generation and for cellular maintenance (Fig. 26.1).*

Because most tissues are partially or totally dependent on glucose for ATP generation and for production of precursors of other pathways, insulin and glucagon ***maintain blood glucose*** *levels near 80 to 100 mg/dL (90 mg/dL is the same as 5 mM), despite the fact that carbohydrate intake varies considerably over the course of a day. The maintenance of constant blood glucose levels (****glucose homeostasis****) requires these two hormones to regulate* ***carbohydrate****,* ***lipid****, and* ***amino acid metabolism*** *in accordance with the needs and capacities of individual tissues. Basically, the dietary intake of all fuels in excess of immediate need is stored, and the appropriate fuel is mobilized when a demand occurs. For example, when dietary glucose is not available in sufficient quantities that all tissues can use it, fatty acids are mobilized and made available to skeletal muscle for use as a fuel (see Chapters 2 and 23), and the liver can convert fatty acids to ketone bodies for use by the brain. Fatty acids spare glucose for use by the brain and other glucose-dependent tissues (such as the red blood cell).*

The concentrations of insulin and glucagon in the blood regulate fuel storage and mobilization (Fig. 26.2). Insulin, released in response to carbohydrate ingestion, promotes glucose utilization as a fuel and glucose storage as fat and glycogen. ***Insulin is also the major anabolic hormone of the body****. It increases protein synthesis and cell growth in addition to fuel storage. Blood insulin levels decrease as glucose is taken up by tissues and used. Glucagon, the major* ***counterregulatory hormone*** *of insulin, is decreased in response to a carbohydrate meal and elevated during fasting. Its concentration in the blood signals the absence of dietary glucose, and it promotes glucose production via* ***glycogenolysis*** *(glycogen degradation) and* ***gluconeogenesis*** *(glucose synthesis from amino acids and other noncarbohydrate precursors). Increased levels of glucagon relative to insulin also stimulate the* ***mobilization of fatty acids*** *from adipose tissue.* ***Epinephrine*** *(the fight or flight hormone) and cortisol (a glucocorticoid released from the adrenal cortex in response to fasting and chronic stress) have effects on fuel metabolism that oppose those of insulin. These two hormones are therefore also considered insulin counterregulatory hormones.*

Insulin and glucagon are polypeptide hormones synthesized as ***prohormones*** *in the β and α cells, respectively, in the islets of Langerhans in the pancreas.* ***Proinsulin*** *is cleaved into mature insulin and* ***C-peptide*** *in vesicles and precipitated*

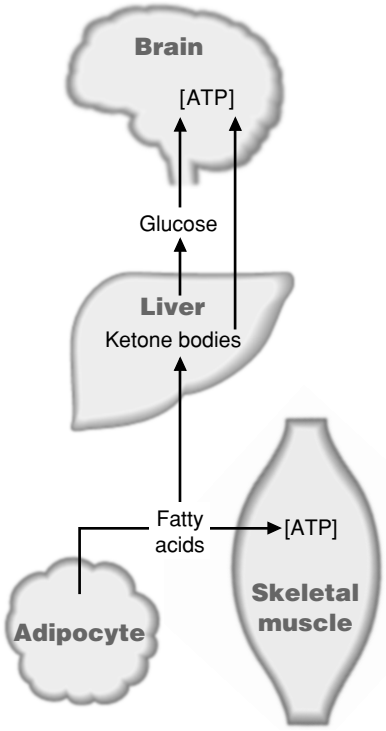


Fig 26.1. Maintenance of fuel supplies to tissues. Glucagon release activates the pathways shown.

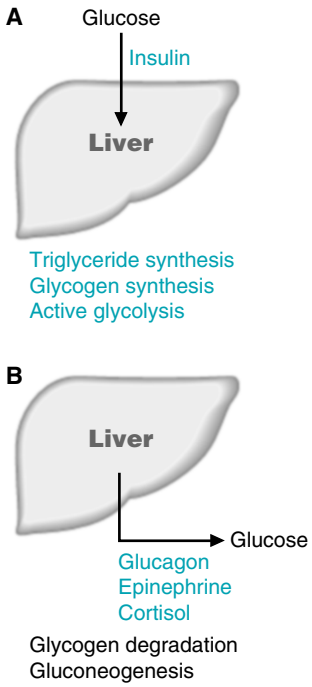


Fig 26.2. Insulin and the insulin counterregulatory hormones. (A) Insulin promotes glucose storage, as triglyceride (TG) or glycogen. (B) Glucagon, epinephrine, and cortisol promote glucose release from the liver, activating glycogenolysis and gluconeogenesis.

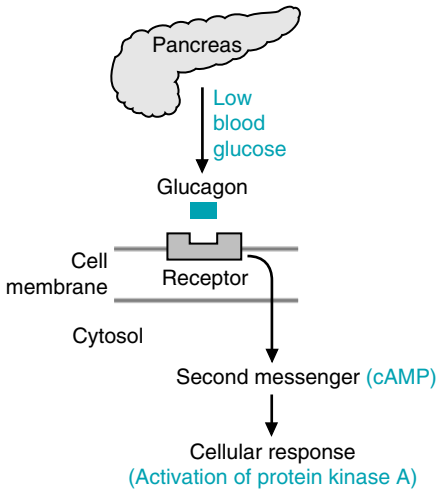


Fig 26.3. Cellular response to glucagon, which is released from the pancreas in response to a decrease in blood glucose levels.

with Zn^{2+}. Insulin secretion is regulated principally by blood glucose levels. Glucagon is also synthesized as a prohormone and cleaved into mature glucagon within storage vesicles. Its release is regulated principally through suppression by glucose and by insulin.

*Glucagon exerts its effects on cells by binding to a receptor on the cell surface, which stimulates the synthesis of the intracellular second messenger, cyclic adenosine monophosphate (**cAMP**) (Fig. 26.3). cAMP activates **protein kinase A**, which phosphorylates key regulatory enzymes, activating some and inhibiting others. Changes of cAMP levels also induce or repress the synthesis of a number of enzymes. Insulin promotes the dephosphorylation of these key enzymes.*

*Insulin binds to a receptor on the cell surface, but the postreceptor events that follow differ from those stimulated by glucagon. Insulin binding activates both autophosphorylation of the receptor and the phosphorylation of other enzymes by the receptor's **tyrosine kinase** domain (see Chapter 11, section III.B.3). The complete routes for **signal transduction** between this point and the final effects of insulin on the regulatory enzymes of fuel metabolism have not yet been fully established.*

THE WAITING ROOM

Ann Sulin returned to her physician for her monthly office visit. She has been seeing her physician for over a year because of obesity and elevated blood glucose levels. She still weighed 198 lb, despite her insistence that she had adhered strictly to her diet. Her blood glucose level at the time of the visit, 2 hours after lunch, was 180 mg/dL (reference range = 80–140).

Bea Selmass is a 46-year-old woman who 6 months earlier began noting episodes of fatigue and confusion as she finished her daily pre-breakfast jog. These episodes were occasionally accompanied by blurred vision and an unusually urgent hunger. The ingestion of food relieved all of her symptoms within 25 to 30 minutes. In the last month, these attacks have occurred more frequently throughout the day, and she has learned to diminish their occurrence by eating between meals. As a result, she has recently gained 8 lb.

A random serum glucose level done at 4:30 PM during her first office visit was subnormal at 46 mg/dL. Her physician, suspecting she had a form of fasting hypoglycemia, ordered a series of fasting serum glucose levels. In addition, he asked Bea to keep a careful daily diary of all of the symptoms that she experienced when her attacks were most severe.

I. METABOLIC HOMEOSTASIS

Living cells require a constant source of fuels from which to derive ATP for the maintenance of normal cell function and growth. Therefore, a balance must be achieved between carbohydrate, fat, and protein intake, their storage when present in excess of immediate need, and their mobilization and synthesis when in demand. The balance between need and availability is referred to as metabolic homeostasis (Fig. 26.4). The intertissue integration required for metabolic homeostasis is achieved in three principal ways:

- The concentration of nutrients or metabolites in the blood affects the rate at which they are used and stored in different tissues;

- Hormones carry messages to individual tissues about the physiologic state of the body and nutrient supply or demand;
- The central nervous system uses neural signals to control tissue metabolism, directly or through the release of hormones.

Insulin and glucagon are the two major hormones that regulate fuel storage and mobilization (see Fig. 26.2). Insulin is the major anabolic hormone of the body. It promotes the storage of fuels and the utilization of fuels for growth. Glucagon is the major hormone of fuel mobilization. Other hormones, such as epinephrine, are released as a response of the central nervous system to hypoglycemia, exercise, or other types of physiologic stress. Epinephrine and other stress hormones also increase the availability of fuels (Fig. 26.5).

The special role of glucose in metabolic homeostasis is dictated by the fact that many tissues (e.g., the brain, red blood cells, the lens of the eye, the kidney medulla, exercising skeletal muscle) are dependent on glycolysis for all or a portion of their energy needs and require uninterrupted access to glucose on a second-to-second basis to meet their rapid rate of ATP utilization. In the adult, a minimum of 190 g glucose is required per day; approximately 150 g for the brain and 40 g for other tissues. Significant decreases of blood glucose below 60 mg/dL limit glucose metabolism in the brain and elicit hypoglycemic symptoms (as experienced by **Bea Selmass**), presumably because the overall process of glucose flux through the blood-brain barrier, into the interstitial fluid, and subsequently into the neuronal cells, is slow at low blood glucose levels because of the K_m values of the glucose transporters required for this to occur (see Chapter 27)

The continuous movement of fuels into and out of storage depots is necessitated by the high amounts of fuel required each day to meet the need for ATP. Disastrous results would occur if even a day's supply of glucose, amino acids, and fatty acids were left circulating in the blood. Glucose and amino acids would be at such high concentrations that the hyperosmolar effect would cause progressively severe neurologic deficits and even coma. The concentration of glucose and amino acids would be above the renal tubular threshold for these substances (the maximal concentration in the blood at which the kidney can completely resorb metabolites), and some of these compounds would be wasted as they spilled over into the urine. Nonenzymatic glycosylation of proteins would increase at higher blood glucose

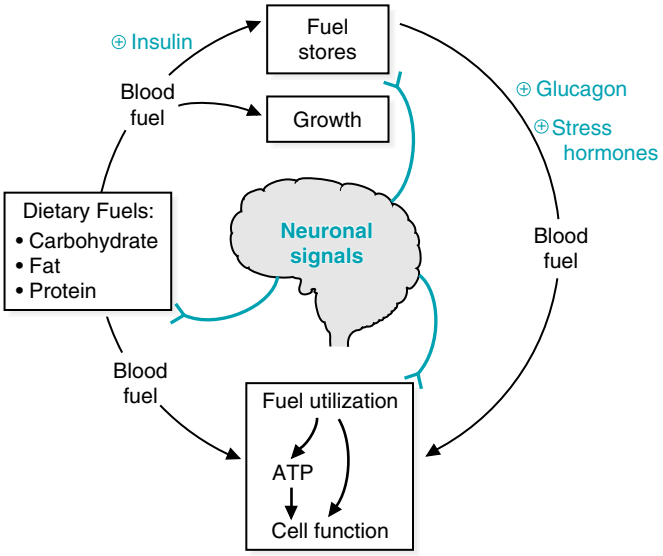


Fig 26.5. Signals that regulate metabolic homeostasis. The major stress hormones are epinephrine and cortisol.

Fatty acids provide an example of the influence that the level of a compound in the blood has on its own rate of metabolism. The concentration of fatty acids in the blood is the major factor determining whether skeletal muscles will use fatty acids or glucose as a fuel (see Chapter 23). In contrast, hormones are (by definition) carriers of messages between tissues. Insulin and glucagon, for example, are two hormonal messengers that participate in the regulation of fuel metabolism by carrying messages that reflect the timing and composition of our dietary intake of fuels. Epinephrine, however, is a flight-or-flight hormone that signals an immediate need for increased fuel availability. Its level is regulated principally through the activation of the sympathetic nervous system.

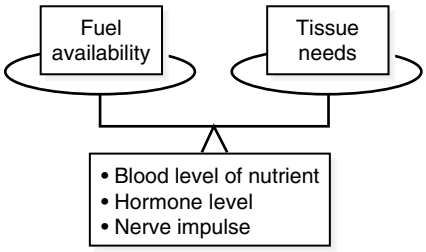


Fig 26.4. Metabolic homeostasis. The balance between fuel availability and the needs of tissues for different fuels is achieved by three types of messages: the level of the fuel or nutrients in the blood, the level of one of the hormones of metabolic homeostasis, or nerve impulses that affect tissue metabolism or the release of hormones.

Hyperglycemia may cause a constellation of symptoms such as polyuria and subsequent polydipsia (increased thirst). The inability to move glucose into cells necessitates the oxidation of lipids as an alternative fuel. As a result adipose stores are used, and the patient with poorly controlled diabetes mellitus loses weight in spite of a good appetite. Extremely high levels of serum glucose can cause nonketotic hyperosmolar coma in patients with type 2 diabetes mellitus. Such patients usually have sufficient insulin responsiveness to block fatty acid release and ketone body formation, but they are unable to significantly stimulate glucose entry into peripheral tissues. The severely elevated levels of glucose in the blood compared with inside the cell leads to an osmotic effect that causes water to leave the cells and enter the blood. Because of the osmotic diuretic effect of hyperglycemia, the kidney produces more urine, leading to dehydration, which in turn may lead to even higher levels of blood glucose. If dehydration becomes severe, further cerebral dysfunction occurs and the patient may become comatose. Chronic hyperglycemia also produces pathologic effects through the nonenzymatic glycosylation of a variety of proteins. Hemoglobin A (HbA), one of the proteins that becomes glycosylated, forms HbA_{1c} (see Chapter 7). **Ann Sulin's** high levels of HbA_{1c} (14% of the total HbA, compared with the reference range of 4.7–6.4%) indicate that her blood glucose has been significantly elevated over the last 12 to 14 weeks, the half-life of hemoglobin in the bloodstream.

All membrane and serum proteins exposed to high levels of glucose in the blood or interstitial fluid are candidates for nonenzymatic glycosylation. This process distorts protein structure and slows protein degradation, which leads to an accumulation of these products in various organs, thereby adversely affecting organ function. These events contribute to the long-term microvascular and macrovascular complications of diabetes mellitus, which include diabetic retinopathy, nephropathy, and neuropathy (microvascular), in addition to coronary artery, cerebral artery, and peripheral artery insufficiency (macrovascular).

levels. Triacylglycerols circulate in cholesterol-containing lipoproteins, and the levels of these lipoproteins would be chronically elevated, increasing the likelihood of atherosclerotic vascular disease. Consequently, glucose and other fuels are continuously moved in and out of storage depots as needed.

II. MAJOR HORMONES OF METABOLIC HOMEOSTASIS

The hormones that contribute to metabolic homeostasis respond to changes in the circulating levels of fuels that, in part, are determined by the timing and composition of our diet. Insulin and glucagon are considered the major hormones of metabolic homeostasis because they continuously fluctuate in response to our daily eating pattern. They provide good examples of the basic concepts of hormonal regulation. Certain features of the release and action of other insulin counterregulatory hormones, such as epinephrine, norepinephrine, and cortisol, will be described and compared with insulin and glucagon.

Insulin is the major anabolic hormone that promotes the storage of nutrients: glucose storage as glycogen in liver and muscle, conversion of glucose to triacylglycerols in liver and their storage in adipose tissue, and amino acid uptake and protein synthesis in skeletal muscle (Fig. 26.6). It also increases the synthesis of albumin and other blood proteins by the liver. Insulin promotes the utilization of glucose as a fuel by stimulating its transport into muscle and adipose tissue. At the same time, insulin acts to inhibit fuel mobilization.

Glucagon acts to maintain fuel availability in the absence of dietary glucose by stimulating the release of glucose from liver glycogen (see Chapter 28), by stimulating gluconeogenesis from lactate, glycerol, and amino acids (see Chapter 31), and, in conjunction with decreased insulin, by mobilizing fatty acids from adipose triacylglycerols to provide an alternate source of fuel (see Chapter 23 and Fig. 26.7). Its sites of action are principally the liver and adipose tissue; it has no influence on skeletal muscle metabolism because muscle cells lack glucagon receptors.

The release of insulin from the beta cells of the pancreas is dictated primarily by the blood glucose level. The highest levels of insulin occur approximately 30 to 45 minutes after a high-carbohydrate meal (Fig. 26.8). They return to basal levels as the blood glucose concentration falls, approximately 120 minutes after the meal. The release of glucagon from the alpha cells of the pancreas, conversely, is controlled principally through suppression by glucose and insulin. Therefore, the lowest levels of glucagon occur after a high-carbohydrate meal. Because all of the effects of glucagon are opposed by insulin, the simultaneous stimulation of insulin release and suppression of glucagon secretion by a high-carbohydrate meal provides an integrated control of carbohydrate, fat, and protein metabolism.

Bea Selmass's studies confirmed that her fasting serum glucose levels were below normal. She continued to experience the fatigue, confusion, and blurred vision she had described on her first office visit. These symptoms are called neuroglycopenic (neurologic symptoms resulting from an inadequate supply of glucose to the brain for the generation of ATP).

Bea also noted the symptoms that are part of the adrenergic response to hypoglycemic stress. Stimulation of the sympathetic nervous system (because of the low levels of glucose reaching the brain) results in the release of epinephrine, a stress hormone, from the adrenal medulla. Elevated epinephrine levels cause tachycardia, palpitations, anxiety, tremulousness, pallor, and sweating.

In addition to the symptoms described by **Bea Selmass**, individuals may experience confusion, lightheadedness, headache, aberrant behavior, blurred vision, loss of consciousness, or seizures.

Ms. Selmass's doctor explained that the general diagnosis of "fasting" hypoglycemia was now established and that a specific cause for this disorder must be found.

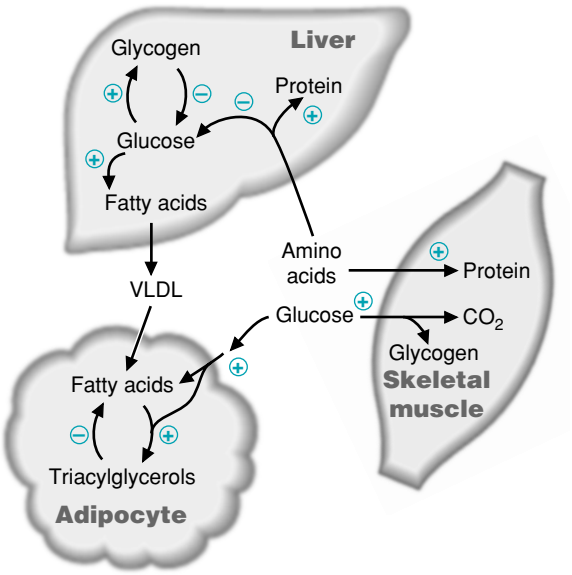


Fig 26.6. Major sites of insulin action on fuel metabolism. + = stimulated by insulin; − = inhibited by insulin.

Insulin and glucagon are not the only regulators of fuel metabolism. The intertissue balance between the utilization and storage of glucose, fat, and protein is also accomplished by the circulating levels of metabolites in the blood, by neuronal signals, and by the other hormones of metabolic homeostasis (epinephrine, norepinephrine, cortisol, and others) (Table 26.1). These hormones oppose the actions of insulin by mobilizing fuels. Like glucagon, they are called insulin counterregulatory hormones (Fig. 26.9). Of all these hormones, only insulin and glucagon are synthe-

The message carried by glucagon is that "glucose is gone"; i.e., the current supply of glucose is inadequate to meet the immediate fuel requirements of the body.

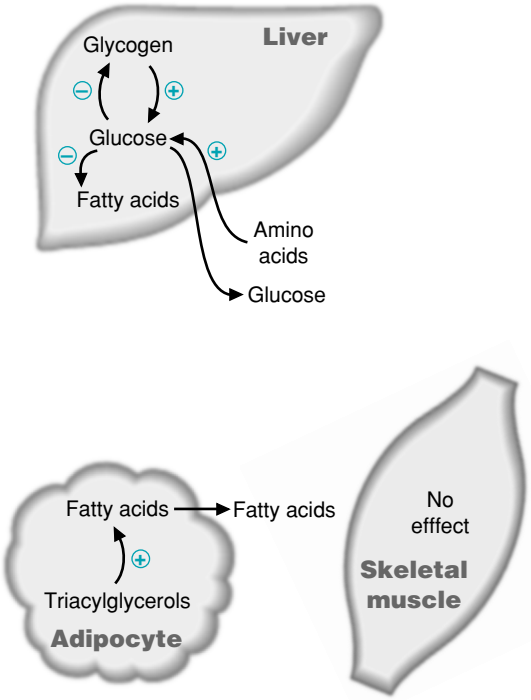


Fig 26.7. Major sites of glucagon action in fuel metabolism. + = pathways stimulated by glucagon; − = pathways inhibited by glucagon.

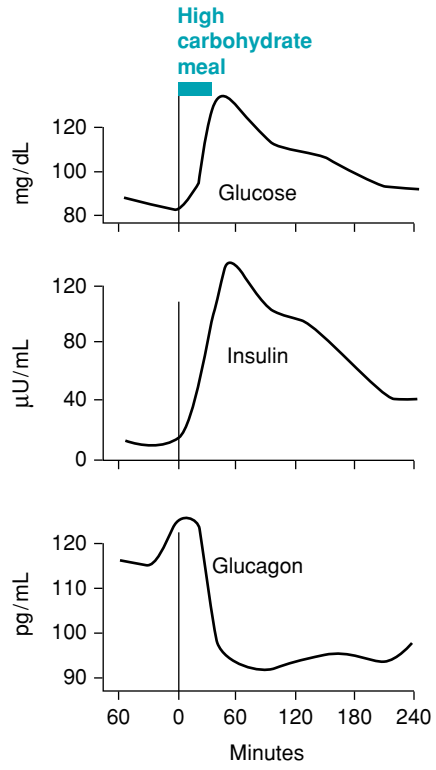


Fig 26.8. Blood glucose, insulin, and glucagon levels after a high-carbohydrate meal.

Table 26.1. Physiologic Actions of Insulin and Insulin Counterregulatory Hormones

Hormone	Function	Major Metabolic Pathways Affected
Insulin	• Promotes fuel storage after a meal • Promotes growth	• Stimulates glucose storage as glycogen (muscle and liver) • Stimulates fatty acid synthesis and storage after a high-carbohydrate meal • Stimulates amino acid uptake and protein synthesis
Glucagon	• Mobilizes fuels • Maintains blood glucose levels during fasting	• Activates gluconeogenesis and glycogenolysis (liver) during fasting • Activates fatty acid release from adipose tissue
Epinephrine	• Mobilizes fuels during acute stress	• Stimulates glucose production from glycogen (muscle and liver) • Stimulates fatty acid release from adipose issue
Cortisol	• Provides for changing requirements over the long-term	• Stimulates amino acid mobilization from muscle protein • Stimulates gluconeogenesis • Stimulates fatty acid release from adipose issue

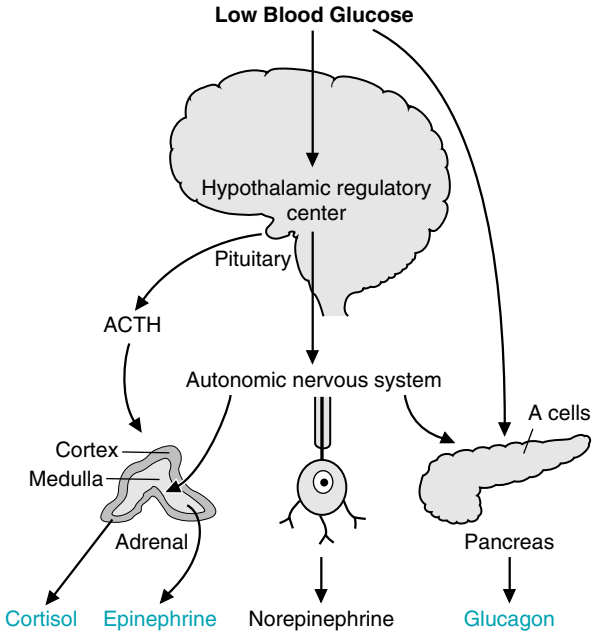


Fig 26.9. Major insulin counterregulatory hormones. The stress of a low blood glucose level mediates the release of the major insulin counterregulatory hormones through neuronal signals. Hypoglycemia is one of the stress signals that stimulates the release of cortisol, epinephrine, and norepinephrine. Adrenocorticotropic hormone (ACTH) is released from the pituitary and stimulates the release of cortisol (a glucocorticoid) from the adrenal cortex. Neuronal signals stimulate the release of epinephrine from the adrenal medulla and norepinephrine from nerve endings. Neuronal signals also play a minor role in the release of glucagon. Although norepinephrine has counterregulatory actions, it is not a major counterregulatory hormone.

sized and released in direct response to changing levels of fuels in the blood. The release of cortisol, epinephrine, and norepinephrine is mediated by neuronal signals. Rising levels of the insulin counterregulatory hormones in the blood, reflect, for the most part, a current increase in the demand for fuel.

III. SYNTHESIS AND RELEASE OF INSULIN AND GLUCAGON

A. Endocrine Pancreas

Insulin and glucagon are synthesized in different cell types of the endocrine pancreas, which consists of microscopic clusters of small glands, the islets of Langerhans, scattered among the cells of the exocrine pancreas. The α cells secrete glucagon, and the β cells secrete insulin into the hepatic portal vein via the pancreatic veins.

B. Synthesis and Secretion of Insulin

Insulin is a polypeptide hormone. The active form of insulin is composed of two polypeptide chains (the A-chain and the B-chain) linked by two interchain disulfide bonds. The A-chain has an additional intrachain disulfide bond (Fig. 26.10).

Insulin, like many other polypeptide hormones, is synthesized as a preprohormone that is converted in the rough endoplasmic reticulum (RER) to proinsulin. The "pre" sequence, a short hydrophobic signal sequence at the N-terminal end, is cleaved as it enters the lumen of the RER. Proinsulin folds into the proper conformation, and disulfide bonds are formed between the cysteine residues. It is then transported in microvesicles to the Golgi complex. It leaves the Golgi complex in storage vesicles, where a protease removes the C-peptide (a fragment with no hormonal activity) and a few small remnants, resulting in the formation of biologically active insulin (see Fig. 26.10). Zinc ions are also transported in these storage vesicles. Cleavage of the C-peptide decreases the solubility of the resulting insulin, which then coprecipitates with zinc. Exocytosis of the insulin storage vesicles from the cytosol of the β cell into the blood is stimulated by rising levels of glucose in the blood bathing the β cells.

Glucose enters the β cell via specific glucose transporter proteins known as GLUT2 (see Chapter 27). Glucose is phosphorylated through the action of glucokinase to form glucose 6-phosphate, which is metabolized through glycolysis, the TCA cycle, and oxidative phosphorylation. These reactions result in an increase in ATP levels within the β cell (circle 1 in Fig. 26.11). As the β cell [ATP]/[ADP] ratio increases, the activity of a membrane-bound, ATP-dependent K^+ channel (K^+_{ATP}) is inhibited (i.e., the channel is closed)(circle 2 in Fig. 26.11). The closing of this channel leads to a membrane depolarization (circle 3, Fig. 26.11), which activates a voltage-gated Ca^{2+} channel that allows Ca^{2+} to enter the β cell such that intracellular Ca^{2+} levels increase significantly (circle 4, Fig. 26.11). The increase in intracellular Ca^{2+} stimulates the fusion of insulin containing exocytotic vesicles with the plasma membrane, resulting in insulin secretion (circle 5, Fig. 26.11). Thus, an increase in glucose levels within the β cells initiates insulin release.

A form of diabetes known as MODY (maturity onset diabetes of the young) results from mutations in either pancreatic glucokinase or specific nuclear transcription factors. MODY type 2 is due to a glucokinase mutation that results in an enzyme with reduced activity, either due to an elevated K_m for glucose or a reduced V_{max} for the reaction. Because insulin release is dependent on normal glucose metabolism within the β cell that yields a critical [ATP]/[ADP] ratio in the β cell, individuals with this glucokinase mutation cannot significantly metabolize glucose unless glucose levels are higher than normal. Thus, although these patients can release insulin, they do so at higher than normal glucose levels, and are therefore almost always in a hyperglycemic state. Interestingly, however, these patients are somewhat resistant to the long-term complications of chronic hyperglycemia.

The message that insulin carries to tissues is that glucose is plentiful and it can be used as an immediate fuel or can be converted to storage forms such as triacylglycerol in adipocytes or glycogen in liver and muscle.

Because insulin stimulates the uptake of glucose into tissues where it may be immediately oxidized or stored for later oxidation, this regulatory hormone lowers blood glucose levels. Therefore, one of the possible causes of **Bea Selmass's** hypoglycemia is an insulinoma, a tumor that produces excessive insulin.

Whenever an endocrine gland continues to release its hormone in spite of the presence of signals that normally would suppress its secretion, this persistent inappropriate release is said to be "autonomous." Secretory neoplasms of endocrine glands generally produce their hormonal product autonomously in a chronic fashion.

Autonomous hypersecretion of insulin from a suspected pancreatic β-cell tumor (an insulinoma) can be demonstrated in several ways. The simplest test is to simultaneously draw blood for the measurement of both glucose and insulin at a time when the patient is spontaneously experiencing the characteristic adrenergic or neuroglycopenic symptoms of hypoglycemia. During such a test, **Bea Selmass's** glucose levels fell to 45 mg/dL (normal = 80–100), and her ratio of insulin to glucose was far higher than normal. The elevated insulin levels markedly increased glucose uptake by the peripheral tissues, resulting in a dramatic lowering of blood glucose levels. In normal individuals, as blood glucose levels drop, insulin levels also drop.

Di Abietes has type 1 diabetes mellitus, formerly known as insulin-dependent diabetes mellitus (IDDM). This metabolic disorder is usually caused by antibody-mediated (autoimmune) destruction of the β cells of the pancreas. Susceptibility to type 1 diabetes mellitus is, in part, conferred by a genetic defect in the human leukocyte antigen (HLA) region of β cells which codes for the major histocompatibility complex II (MHC II). This protein presents an intracellular antigen to the cell surface for "self-recognition" by the cells involved in the immune response. Because of this defective protein, a cell-mediated immune response leads to varying degrees of β cell destruction and eventually to dependence on exogenous insulin administration to control the levels of glucose in the blood.

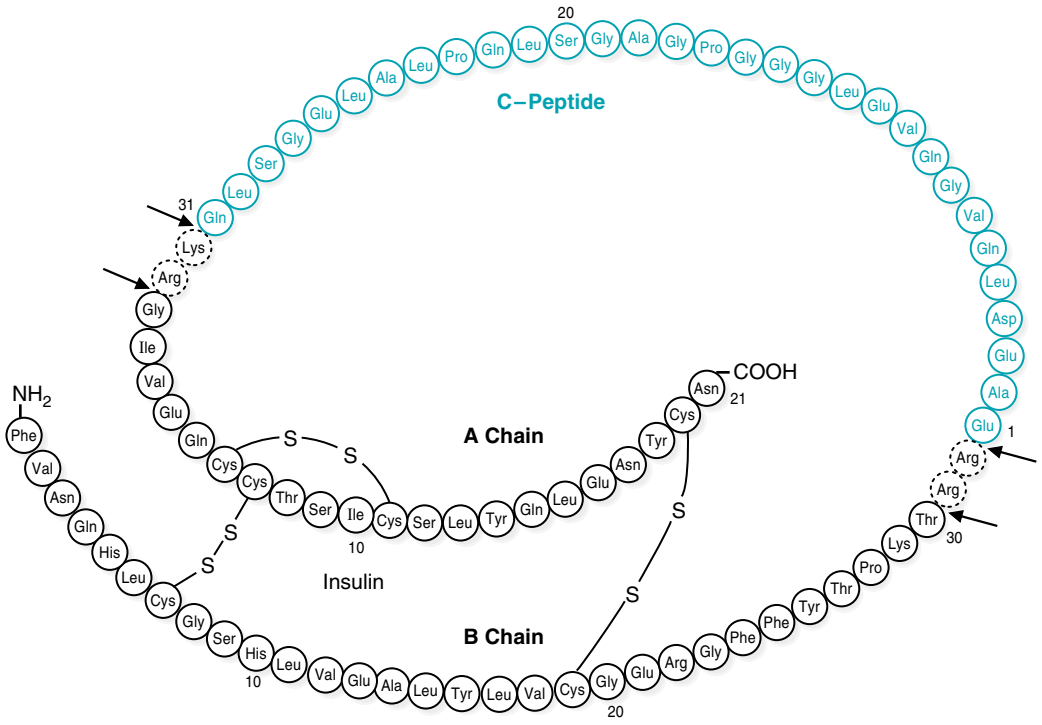


Fig 26.10. Cleavage of proinsulin to insulin. Proinsulin is converted to insulin by proteolytic cleavage, which removes the C-peptide and a few additional amino acid residues. Cleavage occurs at the arrows. From Murray RK, et al. Harper's Biochemistry, 23rd Ed. Stanford, CT: Appleton & Lange, 1993:560.

C. Stimulation and Inhibition of Insulin Release

The release of insulin occurs within minutes after the pancreas is exposed to a high glucose concentration. The threshold for insulin release is approximately 80 mg glucose/dL. Above 80 mg/dL, the rate of insulin release is not an all-or-nothing response but is proportional to the glucose concentration up to approximately 300 mg/dL glucose. As insulin is secreted, the synthesis of new insulin molecules is stimulated, so that secretion is maintained until blood glucose levels fall. Insulin is rapidly removed from the circulation and degraded by the liver (and, to a lesser

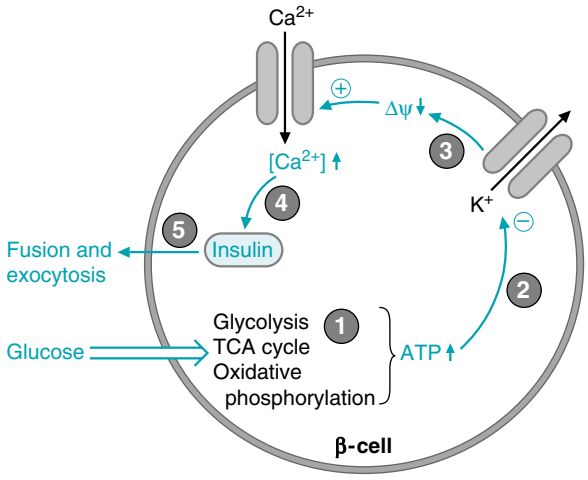


Fig 26.11. Release of insulin by the β-cells. Details are provided in the text.

Table 26.2. Regulators of Insulin Release[a]

Major Regulators	Effect
Glucose	+
Minor regulators	
Amino acids	+
Neural input	+
Gut hormones[b]	+
Epinephrine (adrenergic)	−

[a] + = stimulates
− = inhibits
[b] gut hormones that regulate fuel metabolism are discussed in Chapter 43.

extent, by kidney and skeletal muscle), so that blood insulin levels decrease rapidly once the rate of secretion slows.

A number of factors other than the blood glucose concentration can modulate insulin release (Table 26.2). The pancreatic islets are innervated by the autonomic nervous system, including a branch of the vagus nerve. These neural signals help to coordinate insulin release with the secretory signals initiated by the ingestion of fuels. However, signals from the central nervous system are not required for insulin secretion. Certain amino acids also can stimulate insulin secretion, although the amount of insulin released during a high-protein meal is very much lower than that released by a high-carbohydrate meal. Gastric inhibitory polypeptide (GIP, a gut hormone released after the ingestion of food) also aids in the onset of insulin release. Epinephrine, secreted in response to fasting, stress, trauma, and vigorous exercise, decreases the release of insulin. Epinephrine release signals energy utilization, which indicates that less insulin needs to be secreted, as insulin stimulates energy storage.

D. Synthesis and Secretion of Glucagon

Glucagon, a polypeptide hormone, is synthesized in the α cells of the pancreas by cleavage of the much larger preproglucagon, a 160–amino acid peptide. Like insulin, preproglucagon is produced on the rough endoplasmic reticulum and is converted to proglucagon as it enters the ER lumen. Proteolytic cleavage at various sites produces the mature 29–amino acid glucagon (molecular weight 3,500) and larger glucagon-containing fragments (named glucagon-like peptides 1 and 2). Glucagon is rapidly metabolized, primarily in the liver and kidneys. Its plasma half-life is only about 3 to 5 minutes.

Glucagon secretion is regulated principally by circulating levels of glucose and insulin. Increasing levels of each inhibit glucagon release. Glucose probably has both a direct suppressive effect on secretion of glucagon from the α cell as well as an indirect effect, the latter being mediated by its ability to stimulate the release of insulin. The direction of blood flow in the islets of the pancreas carries insulin from the β cells in the center of the islets to the peripheral α cells, where it suppresses glucagon secretion.

Patients with type 1 diabetes mellitus, such as **Di Abietes,** have almost undetectable levels of insulin in their blood. Patients with type 2 diabetes mellitus, such as **Ann Sulin**, conversely, have normal or even elevated levels of insulin in their blood; however, the level of insulin in their blood is inappropriately low relative to their elevated blood glucose concentration. In type 2 diabetes mellitus, skeletal muscle, liver, and other tissues exhibit a resistance to the actions of insulin. As a result, insulin has a smaller than normal effect on glucose and fat metabolism in such patients. Levels of insulin in the blood must be higher than normal to maintain normal blood glucose levels. In the early stages of type 2 diabetes mellitus, these compensatory adjustments in insulin release may keep the blood glucose levels near the normal range. Over time, as the β cells capacity to secrete high levels of insulin declines, blood glucose levels increase, and exogenous insulin becomes necessary.

Ann Sulin is taking a sulfonylurea compound known as glipizide to treat her diabetes. The sulfonylureas act on the K^+_{ATP} channels on the surface of the pancreatic β cells. The binding of the drug to these channels closes K^+ channels (as do elevated ATP levels), which, in turn, increases Ca^{2+} movement into the interior of the β cell. This influx of calcium modulates the interaction of the insulin storage vesicles with the plasma membrane of the β cell, resulting in the release of insulin into the circulation.

Measurements of proinsulin and the connecting peptide between the α and β chains of insulin (C-peptide) in **Bea Selmass's** blood during her hospital fast provided confirmation that she had an insulinoma. Insulin and C-peptide are secreted in approximately equal proportions from the β cell, but C-peptide is not cleared from the blood as rapidly as insulin. Therefore, it provides a reasonably accurate estimate of the rate of insulin secretion. Plasma C-peptide measurements are also potentially useful in treating patients with diabetes mellitus because they provide a way to estimate the degree of endogenous insulin secretion in patients who are receiving exogenous insulin, which lacks the C-peptide.

Table 26.3 Regulators of Glucagon Release[a]

Major Regulators	Effect
Glucose	−
Insulin	−
Amino acids	+
Minor regulators	
Cortisol	+
Neural (stress)	+
Epinephrine	+
Gut hormones	+

[a] + = stimulates
− = inhibits

Amino acids induce both insulin and glucagon secretion. Although this may seem paradoxical, it actually makes good sense. Insulin release stimulates amino acid uptake by tissues and enhances protein synthesis. However, because glucagon levels also increase in response to a protein meal, gluconeogenesis is enhanced (at the expense of protein synthesis), and the amino acids that are taken up by the tissues serve as a substrate for gluconeogenesis. The synthesis of glycogen and triglycerides is also reduced when glucagon levels rise in the blood.

In fasting subjects, the average level of immunoreactive glucagon in the blood is 75 pg/mL and does not vary as much as insulin during the daily fasting–feeding cycle. However, only 30 to 40% of the measured immunoreactive glucagon is mature pancreatic glucagon. The rest is composed of larger immunoreactive fragments also produced in the pancreas or in the intestinal L cells.

The physiologic importance of insulin's usual action of mediating the suppressive effect of glucose on glucagon secretion is apparent in patients with types 1 and 2 diabetes mellitus. Despite the presence of hyperglycemia, glucagon levels in such patients initially remain elevated (near fasting levels) either because of the absence of insulin's suppressive effect or because of the resistance of the α cells to insulin's suppressive effect even in the face of adequate insulin levels in type 2 patients. Thus, these patients have inappropriately high glucagon levels, leading to the suggestion that diabetes mellitus is actually a "bi-hormonal" disorder.

Certain hormones stimulate glucagon secretion. Among these are the catecholamines (including epinephrine), cortisol, and certain gastrointestinal (gut) hormones (Table 26.3).

Many amino acids also stimulate glucagon release (Fig. 26.12). Thus, the high levels of glucagon that would be expected in the fasting state do not decrease after a high-protein meal. In fact, glucagon levels may increase, stimulating gluconeogenesis in the absence of dietary glucose. The relative amounts of insulin and glucagon in the blood after a mixed meal are dependent on the composition of the meal, because glucose stimulates insulin release, and amino acids stimulate glucagon release.

IV. MECHANISMS OF HORMONE ACTION

For a hormone to affect the flux of substrates through a metabolic pathway, it must be able to change the rate at which that pathway proceeds by increasing or decreasing the rate of the slowest step(s). Either directly or indirectly, hormones affect the

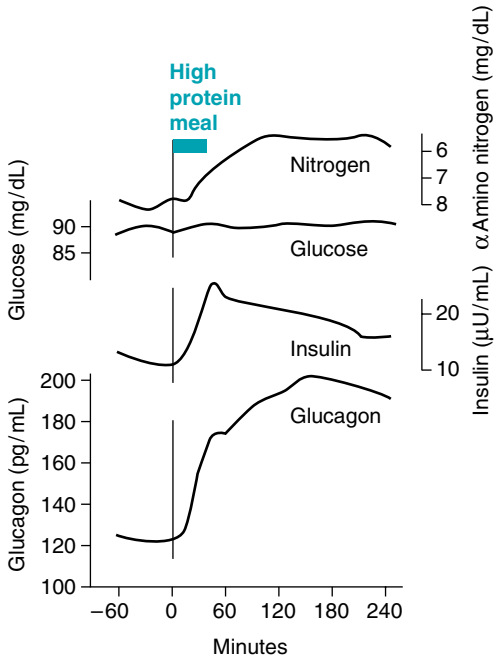


Fig 26.12. Release of insulin and glucagon in response to a high-protein meal. This figure shows the increase in the release of insulin and glucagon into the blood after an overnight fast followed by the ingestion of 100 g protein (equivalent to a slice of roast beef). Insulin levels do not increase nearly as much as they do after a high-carbohydrate meal (see Fig. 26.8). The levels of glucagon, however, significantly increase above those present in the fasting state.

activity of specific enzymes or transport proteins that regulate the flux through a pathway. Thus, ultimately, the hormone must either cause the amount of the substrate for the enzyme to increase (if substrate supply is a rate-limiting factor), change the conformation at the active site by phosphorylating the enzyme, change the concentration of an allosteric effector of the enzyme, or change the amount of the protein by inducing or repressing its synthesis or by changing its turnover rate or location. Insulin, glucagon, and other hormones use all of these regulatory mechanisms to regulate the rate of flux in metabolic pathways. The effects mediated by phosphorylation or changes in the kinetic properties of an enzyme occur rapidly, within minutes. In contrast, it may take hours for induction or repression of enzyme synthesis to change the amount of an enzyme in the cell.

The details of hormone action were previously described in Chapter 11 and are only summarized here.

During the "stress" of hypoglycemia, the autonomic nervous system stimulates the pancreas to secrete glucagon, which tends to restore the serum glucose level to normal. The increased activity of the adrenergic nervous system (through epinephrine) also alerts a patient, such as **Bea Selmass,** to the presence of increasingly severe hypoglycemia. Hopefully, this will induce the patient to ingest simple sugars or other carbohydrates, which, in turn, will also increase glucose levels in the blood. **Bea Selmass** gained 8 lb before resection of her pancreatic insulin-secreting adenoma through this mechanism.

A. Signal Transduction by Hormones That Bind to Plasma Membrane Receptors

Hormones initiate their actions on target cells by binding to specific receptors or binding proteins. In the case of polypeptide hormones (such as insulin and glucagon), and catecholamines (epinephrine and norepinephrine), the action of the hormone is mediated through binding to a specific receptor on the plasma membrane (see Chapter 11, section III). The first message of the hormone is transmitted to intracellular enzymes by the activated receptor and an intracellular second messenger; the hormone does not need to enter the cell to exert its effects. (In contrast, steroid hormones such as cortisol and the thyroid hormone triiodothyronine [T_3] enter the cytosol and eventually move into the cell nucleus to exert their effects.)

The mechanism by which the message carried by the hormone ultimately affects the rate of the regulatory enzyme in the target cell is called signal transduction. The three basic types of signal transduction for hormones binding to receptors on the plasma membrane are (*a*) receptor coupling to adenylate cyclase which produces cAMP, (*b*) receptor kinase activity, and (*c*) receptor coupling to hydrolysis of phosphatidylinositol bisphosphate (PIP_2). The hormones of metabolic homeostasis each use one of these mechanisms to carry out their physiologic effect. In addition, some hormones and neurotransmitters act through receptor coupling to gated ion channels (previously described in Chapter 11).

1. SIGNAL TRANSDUCTION BY INSULIN

Insulin initiates its action by binding to a receptor on the plasma membrane of insulin's many target cells (see Fig. 11.13). The insulin receptor has two types of subunits, the α-subunits to which insulin binds, and the β-subunits, which span the membrane and protrude into the cytosol. The cytosolic portion of the β-subunit has tyrosine kinase activity. On binding of insulin, the tyrosine kinase phosphorylates tyrosine residues on the β-subunit (autophosphorylation) as well as on several other enzymes within the cytosol. A principal substrate for phosphorylation by the receptor, insulin receptor substrate (IRS-1), then recognizes and binds to various signal transduction proteins in regions referred to as SH_2 domains. IRS-1 is involved in many of the physiologic responses to insulin through complex mechanisms that are the subject of intensive investigation. The basic tissue-specific cellular responses to insulin, however, can be grouped into five major categories: (*a*) insulin reverses glucagon-stimulated phosphorylation, (*b*) insulin works through a phosphorylation cascade that stimulates the phosphorylation of several enzymes, (*c*) insulin induces and represses the synthesis of specific enzymes, (*d*) insulin acts as a growth factor and has a general stimulatory effect on protein synthesis, and (*e*) insulin stimulates glucose and amino acid transport into cells (see Fig. 10 of section introduction, p. 484).

A number of mechanisms have been proposed for the action of insulin in reversing glucagon-stimulated phosphorylation of the enzymes of carbohydrate metabolism. From the student's point of view, the ability of insulin to reverse glucagon-stimulated phosphorylation occurs as if it were lowering cAMP and stimulating phosphatases that could remove those phosphates added by protein kinase A. In reality, the mechanism is more complex and still not fully understood.

2. SIGNAL TRANSDUCTION BY GLUCAGON

The pathway for signal transduction by glucagon is one common to a number of hormones; the glucagon receptor is coupled to adenylate cyclase and cAMP production (see Fig. 11.11). Glucagon, through G proteins, activates the membrane-bound adenylate cyclase, increasing the synthesis of the intracellular second messenger 3′,5′-cyclic AMP (cAMP) (see Fig. 9.10). cAMP activates protein kinase A (cAMP-dependent protein kinase), which changes the activity of enzymes by phosphorylating them at specific serine residues. Phosphorylation activates some enzymes and inhibits others.

The G proteins, which couple the glucagon receptor to adenylate cyclase, are proteins in the plasma membrane that bind guanosine triphosphate (GTP) and have dissociable subunits that interact with both the receptor and adenylate cyclase. In the absence of glucagon, the stimulatory G_s protein complex binds guanosine diphosphate (GDP) but cannot bind to the unoccupied receptor or adenylate cyclase (see Fig. 11.17). Once glucagon binds to the receptor, the receptor also binds the G_s complex, which then releases GDP and binds GTP. The α-subunit then dissociates from the βγ-subunits and binds to adenylate cyclase, thereby activating it. As the GTP on the α-subunit is hydrolyzed to GDP, the subunit dissociates and recomplexes with the β- and γ-subunits. Only continued occupancy of the glucagon receptor can keep adenylate cyclase active.

Although glucagon works by activating adenylate cyclase, a few hormones inhibit adenylate cyclase. In this case, the inhibitory G protein complex is called a G_i complex.

cAMP is very rapidly degraded to AMP by a membrane-bound phosphodiesterase. The concentration of cAMP is thus very low in the cell so that changes in its concentration can occur rapidly in response to changes in the rate of synthesis. The amount of cAMP present at any time is a direct reflection of hormone binding and the activity of adenylate cyclase. It is not affected by ATP, ADP, or AMP levels in the cell.

cAMP transmits the hormone signal to the cell by activating protein kinase A (cAMP-dependent protein kinase). As cAMP binds to the regulatory subunits of protein kinase A, these subunits dissociate from the catalytic subunits, which are thereby activated (see Figs. 9.9 and 9.11). Activated protein kinase A phosphorylates serine residues of key regulatory enzymes in the pathways of carbohydrate and fat metabolism. Some enzymes are activated and others are inhibited by this change in phosphorylation state. The message of the hormone is terminated by the action of semispecific protein phosphatases that remove phosphate groups from the enzymes. The activity of the protein phosphatases is also controlled through hormonal regulation.

Changes in the phosphorylation state of proteins that bind to cAMP response elements (CREs) in the promoter region of genes contribute to the regulation of gene transcription by a number of cAMP-coupled hormones (see Chapter 16). For instance, cAMP response element binding protein (CREB) is directly phosphorylated by protein kinase A, a step essential for the initiation of transcription. Phosphorylation at other sites on CREB, by a variety of kinases, also may play a role in regulating transcription.

cAMP is the intracellular second messenger for a number of hormones that regulate fuel metabolism. The specificity of the physiologic response to each hormone results from the presence of specific receptors for that hormone in target tissues. For example, glucagon activates glucose production from glycogen in liver, but not in skeletal muscle because glucagon receptors are present in liver but absent in skeletal muscle. However, skeletal muscle has adenylate cyclase, cAMP, and protein kinase A, which can be activated by epinephrine binding to the β_2 receptors in the membrane of muscle cells. Liver cells also have epinephrine receptors.

Phosphodiesterase is inhibited by methylxanthines, a class of compounds that includes caffeine. Would the effect of a methylxanthine on fuel metabolism be similar to fasting or to a high-carbohydrate meal?

The mechanism for signal transduction by glucagon illustrates some of the important principles of hormonal signaling mechanisms. The first principle is that specificity of action in tissues is conferred by the receptor on a target cell for glucagon. In general, the major actions of glucagon occur in liver, adipose tissue, and certain cells of the kidney that contain glucagon receptors. The second principle is that signal transduction involves amplification of the first message. Glucagon and other hormones are present in the blood in very low concentrations. However, these minute concentrations of hormone are adequate to initiate a cellular response because the binding of one molecule of glucagon to one receptor ultimately activates many protein kinase A molecules, each of which phosphorylates hundreds of downstream enzymes. The third principle involves integration of metabolic responses. For instance, the glucagon-stimulated phosphorylation of enzymes simultaneously activates glycogen degradation, inhibits glycogen synthesis, and inhibits glycolysis in the liver (see Fig. 10 in section introduction, p. 484.). The fourth principle involves augmentation and antagonism of signals. An example of augmentation involves the actions of glucagon and epinephrine (which is released during exercise). Although these hormones bind to different receptors, each can increase cAMP and stimulate glycogen degradation. A fifth principle is that of rapid signal termination. In the case of glucagon, both the termination of the G_s protein activation and the rapid degradation of cAMP contribute to signal termination.

B. Signal Transduction by Cortisol and Other Hormones That Interact with Intracellular Receptors

Signal transduction by the glucocorticoid cortisol and other steroids and by thyroid hormone involves hormone binding to intracellular (cytosolic) receptors or binding proteins, after which this hormone–binding protein complex moves into the nucleus, where it interacts with chromatin. This interaction changes the rate of gene transcription in the target cells (see Chapter 16). The cellular responses to these hormones will continue as long as the target cell is exposed to the specific hormones. Thus, disorders that cause a chronic excess in their secretion will result in an equally persistent influence on fuel metabolism. For example, chronic stress such as that seen in prolonged sepsis may lead to varying degrees of glucose intolerance if high levels of epinephrine and cortisol persist.

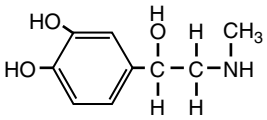
The effects of cortisol on gene transcription are usually synergistic to those of certain other hormones. For instance, the rates of gene transcription for some of the enzymes in the pathway for glucose synthesis from amino acids (gluconeogenesis) are induced by glucagon as well as by cortisol.

C. Signal Transduction by Epinephrine and Norepinephrine

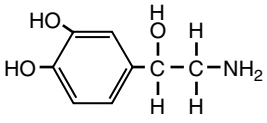
Epinephrine and norepinephrine are catecholamines (Fig. 26.13). They can act as neurotransmitters or as hormones. A neurotransmitter allows a neural signal to be transmitted across the juncture or synapse between the nerve terminal of a proximal nerve axon and the cell body of a distal neuron. A hormone, conversely, is released into the blood and travels in the circulation to interact with specific receptors on the plasma membrane or cytosol of the target organ. The general effect of these catecholamines is to prepare us for fight or flight. Under these acutely stressful circumstances, these "stress" hormones increase fuel mobilization, cardiac output, blood flow, etc., which enable us to meet these stresses. The catecholamines bind to adrenergic receptors (the term *adrenergic* refers to nerve cells or fibers that are part of the involuntary or autonomic nervous system, a system that employs norepinephrine as a neurotransmitter).

Inhibition of phosphodiesterase by methylxanthine would increase cAMP and have the same effects on fuel metabolism as would an increase of glucagon and epinephrine, in the fasted state. Increased fuel mobilization would occur through glycogenolysis (the release of glucose from glycogen), and through lipolysis (the release of fatty acids from triacylglycerols).

Protein kinases are a class of enzymes that change the activity of other enzymes by phosphorylating them at serine or tyrosine residues and are referred to as serine or tyrosine kinases, respectively. Serine kinases also phosphorylate some enzymes at threonine residues. Protein kinase A (a serine kinase) phosphorylates many of the enzymes in the pathways of fuel metabolism.



Epinephrine



Norepinephrine

Fig 26.13. Structure of epinephrine and norepinephrine. Epinephrine and norepinephrine are synthesized from tyrosine and act as both hormones and neurotransmitters. They are catecholamines, the term *catechol* referring to a ring structure containing two hydroxyl groups.

There are nine different types of adrenergic receptors: α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, and β_3. Only the three β and α_1 receptors are discussed here. The three β receptors work through the adenylate cyclase–cAMP system, activating a G_s protein, which activates adenylate cyclase, and eventually protein kinase A. The β_1 receptor is the major adrenergic receptor in the human heart and is primarily stimulated by norepinephrine. On activation, the β_1 receptor increases the rate of muscle contraction, in part because of PKA-mediated phosphorylation of phospholamban (see Chapter 47). The β_2 receptor is present in liver, skeletal muscle, and other tissues and is involved in the mobilization of fuels (such as the release of glucose through glycogenolysis). It also mediates vascular, bronchial, and uterine smooth muscle contraction. Epinephrine is a much more potent agonist for this receptor than norepinephrine, whose major action is neurotransmission. The β_3 receptor is found predominantly in adipose tissue and to a lesser extent in skeletal muscle. Activation of this receptor stimulates fatty acid oxidation and thermogenesis, and agonists for this receptor may prove to be beneficial weight loss agents. The α_1 receptors, which are postsynaptic receptors, mediate vascular and smooth muscle contraction. They work through the phosphatidylinositol bisphosphate system (see Chapter 11, section III.B.2) through activation of a G_q protein, and phospholipase C-β. This receptor also mediates glycogenolysis in liver.

Ann O'Rexia, to stay thin, frequently fasts for prolonged periods, but jogs every morning (see Chapter 2). The release of epinephrine and norepinephrine and the increase of glucagon and fall of insulin during her exercise provide coordinated and augmented signals that stimulate the release of fuels above the fasting levels. Fuel mobilization will occur, of course, only as long as she has fuel stored as triacylglycerols.

Ann Sulin, a patient with type 2 diabetes mellitus, is experiencing insulin resistance. Her levels of circulating insulin are normal to high, although inappropriately low for her elevated level of blood glucose. However, her insulin target cells, such as muscle and fat, do not respond as those of a nondiabetic subject would to this level of insulin. For most type 2 patients, the site of insulin resistance is subsequent to binding of insulin to its receptor; i.e., the number of receptors and their affinity for insulin is near normal. However, the binding of insulin at these receptors does not elicit most of the normal intracellular effects of insulin discussed earlier. Consequently, there is little stimulation of glucose metabolism and storage after a high-carbohydrate meal and little inhibition of hepatic gluconeogenesis.

CLINICAL COMMENTS

Di Abietes has type 1 diabetes mellitus (formally designated insulin-dependent diabetes mellitus, IDDM) whereas **Ann Sulin** has type 2 diabetes mellitus (formally called non–insulin-dependent diabetes mellitus). Although the pathogenesis differs for these major forms of diabetes mellitus, both cause varying degrees of hyperglycemia. In type 1, the pancreatic β cells are gradually destroyed by antibodies directed at a variety of proteins within the β cells. As insulin secretory capacity by the β cells gradually diminishes below a critical level, the symptoms of chronic hyperglycemia develop rapidly. In type 2 diabetes mellitus, these symptoms develop more subtly and gradually over the course of months or years. Eighty-five percent or more of type 2 patients are obese and, like **Ivan Applebod,** have a high waist–hip ratio with regard to adipose tissue disposition. This abnormal distribution of fat in the visceral (peri-intestinal) adipocytes is associated with reduced sensitivity of fat cells, muscle cells, and liver cells to the actions of insulin outlined above. This insulin resistance can be diminished through weight loss, specifically in the visceral depots.

Bea Selmass underwent a high-resolution ultrasonographic (ultrasound) study of her upper abdomen, which showed a 2.6-cm mass in the midportion of her pancreas. With this finding, her physicians decided that further noninvasive studies would not be necessary before surgical exploration of her upper abdomen was performed. At the time of surgery, a yellow-white 2.8-cm mass consisting primarily of insulin-rich β cells was resected from her pancreas. No cytologic changes of malignancy were seen on cytologic examination of the surgical specimen, and no gross evidence of malignant behavior by the tumor (such as local metastases) was found. Bea had an uneventful postoperative recovery and no longer experienced the signs and symptoms of insulin-induced hypoglycemia.

BIOCHEMICAL COMMENTS

One of the important cellular responses to insulin is the reversal of glucagon-stimulated phosphorylation of enzymes. Mechanisms proposed for this action include the inhibition of adenylate cyclase, a reduction of

cAMP levels, the stimulation of phosphodiesterase, the production of a specific protein (insulin factor), the release of a second messenger from a bound glycosylated phosphatidylinositol, and the phosphorylation of enzymes at a site that antagonizes protein kinase A phosphorylation. Not all of these physiologic actions of insulin occur in each of the insulin-sensitive organs of the body.

Insulin is also able to antagonize the actions of glucagon at the level of specific induction or repression of key regulatory enzymes of carbohydrate metabolism. For instance, the rate of synthesis of mRNA for phosphoenolpyruvate carboxykinase, a key enzyme of the gluconeogenic pathway, is increased severalfold by glucagon (via cAMP) and decreased by insulin. Thus, all of the effects of glucagon, even the induction of certain enzymes, can be reversed by insulin. This antagonism is exerted through an insulin-sensitive hormone response element (IRE) in the promoter region of the genes. Insulin causes repression of the synthesis of enzymes that are induced by glucagon.

The general stimulation of protein synthesis by insulin (its mitogenic or growth-promoting effect) appears to occur through both a general increase in rates of mRNA translation for a broad spectrum of structural proteins. These actions result from a phosphorylation cascade initiated by autophosphorylation of the insulin receptor and ending in the phosphorylation of subunits of proteins that bind to and inhibit eukaryotic protein synthesis initiation factors (eIFs). When phosphorylated, the inhibitory proteins are released from the eIFs, allowing translation of mRNA to be stimulated. In this respect, the actions of insulin are similar to those of hormones that act as growth factors and also have receptors with tyrosine kinase activity.

In addition to signal transduction, activation of the insulin receptor mediates the internalization of receptor-bound insulin molecules increasing their subsequent degradation. Although unoccupied receptors can be internalized and eventually recycled to the plasma membrane, the receptor can be irreversibly degraded after prolonged occupation by insulin. The result of this process, referred to as receptor downregulation, is an attenuation of the insulin signal. The physiologic importance of receptor internalization on insulin sensitivity is poorly understood but could eventually lead to chronic hyperglycemia.

Suggested References

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REVIEW QUESTIONS—CHAPTER 26

1. A patient with type I diabetes mellitus takes an insulin injection before eating dinner but then gets distracted and does not eat. Approximately 3 hours later, the patient becomes shaky, sweaty, and confused. These symptoms have occurred because of which of the following?

   (A) Increased glucagon release from the pancreas
   (B) Decreased glucagon release from the pancreas
   (C) High blood glucose levels
   (D) Low blood glucose levels
   (E) Elevated ketone body levels

2. Caffeine is a potent inhibitor of the enzyme cAMP phosphodiesterase. Which of the following consequences would you expect to occur in the liver after drinking two cups of strong expresso coffee?

   (A) A prolonged response to insulin
   (B) A prolonged response to glucagon
   (C) An inhibition of protein kinase A
   (D) An enhancement of glycolytic activity
   (E) A reduced rate of glucose export to the circulation

3. Assume that an increase in blood glucose concentration from 5 to 10 mM would result in insulin release by the pancreas. A mutation in pancreatic glucokinase can lead to MODY because of which of the following within the pancreatic β-cell?

   (A) An inability to raise cAMP levels
   (B) An inability to raise ATP levels
   (C) An inability to stimulate gene transcription
   (D) An inability to activate glycogen degradation
   (E) An inability to raise intracellular lactate levels

4. Which one of the following organs has the highest demand for glucose as a fuel?

   (A) Brain
   (B) Muscle (skeletal)
   (C) Heart
   (D) Liver
   (E) Pancreas

5. Glucagon release does not alter muscle metabolism because of which of the following?

   (A) Muscle cells lack adenylate cyclase.
   (B) Muscle cells lack protein kinase A.
   (C) Muscle cells lack G proteins.
   (D) Muscle cells lack GTP.
   (E) Muscle cells lack the glucagon receptor.