

Tissue Metabolism

Although many of the pathways described previously are present in all tissues of the body, many tissues also carry out specialized functions and contain unique biochemical pathways. This section describes a number of such tissues and, in some cases, how the tissues interact with the rest of the body to coordinate their functions.

The previous chapters of this text have focused primarily on insulin and glucagon as the major mediators for regulating metabolic pathways; however, a large number of other hormones also regulate the storage and utilization of metabolic fuels (see Chapter 43). These hormones primarily counteract the effects of insulin and are called counter-regulatory hormones. They include growth hormone; thyroid hormone; glucocorticoids, such as cortisol; small peptides, such as the somatostatins; and small molecules, such as the catecholamines. Growth hormone works, in part, by inducing the synthesis of the insulin-like growth factors. These hormones can exert their effects rapidly (through covalent modification of selected enzymes) or long-term (through alterations in the rate of synthesis of selected enzymes). The interplay of these hormones with insulin and glucagon is discussed, as are the synthesis, secretion, and conditions leading to secretion of each hormone.

The proteins and cells in the blood form their own tissue system (see Chapter 44). All blood cells are derived from a common precursor, the stem cell, in the bone marrow. Different cytokine signals trigger differentiation of a particular blood cell lineage. For example, when there is a decreased supply of oxygen to the tissues, the kidney responds by releasing erythropoietin. This hormone specifically stimulates the production of red blood cells.

The red blood cell has limited metabolic functions, owing to its lack of internal organelles. Its main function is to deliver oxygen to the tissues through the binding of oxygen to hemoglobin. When the number of red blood cells is reduced, an anemia is said to have developed. This can be attributable to many causes, including nutritional deficiencies or mutations (hereditary anemias). The morphology of the red blood cell can sometimes aid in distinguishing between the various types of anemia.

Red blood cell metabolism is geared toward preserving the ability of these cells to transport oxygen, as well as to regulate oxygen binding to hemoglobin. Glycolysis provides energy and NADH to protect the oxidation state of the heme-bound iron. The hexose monophosphate shunt pathway generates NADPH to protect red blood cell membranes from oxidation. Heme synthesis, which uses succinyl CoA and glycine for all of the carbon and nitrogen atoms in the structure, occurs in the precursors of red blood cells. Inherited defects in heme synthesis lead to a class of diseases known as the porphyrias. Because the red blood cell normally passes through the very narrow capillaries, its membrane must be easily deformable. This deformability is, in part, attributable to the complex cytoskeletal structure that surrounds the erythrocyte. Mutations in these structural proteins can lead to less deformable cells. This, in turn, can result in a hemolytic anemia.

Among other functions, the hematologic system is responsible for hemostasis as well as for maintaining a constant blood volume (see Chapter 45). A tear in the wall

of a vessel can lead to blood loss, which, when extensive, can be fatal. Repairing vessel damage, whether internal or external, is accomplished by a complicated series of zymogen activations of circulating blood proteins resulting in the formation of a fibrin clot (the coagulation cascade). Platelets play a critical role in hemostasis not only through their release of procoagulants but through their ability to form aggregates within the thrombus (clot) as well. Clots function as a plug, allowing vessel walls to repair and preventing further blood loss. Conversely, inappropriate clot formation in vessels that supply blood to vital organs or tissues can have devastating consequences, such as an acute cerebral or myocardial infarction. Because clotting must be tightly controlled, intricate mechanisms exist that regulate this important hematologic function.

The liver is an altruistic organ that provides multiple services for other tissues (see Chapter 46). It supplies glucose and ketone bodies to the rest of the body when fuel stores are limiting. It disposes of ammonia as urea when amino acid degradation occurs. It is the site of detoxification of xenobiotics, and it synthesizes many of the proteins found in the blood. The liver synthesizes fatty acids and cholesterol and distributes them to other tissues in the form of very-low-density lipoprotein (VLDL). The liver also synthesizes bile acids for fat digestion in the intestine. The liver recycles cholesterol and triglyceride through its uptake of intermediate density lipoprotein (IDL), chylomicron and VLDL remnants, and low-density lipoprotein (LDL) particles. Because of its protective nature and its strategic location between the gut and the systemic circulation, the liver has “first crack” at all compounds that enter the blood through the enterohepatic circulation. Thus, xenobiotic compounds can be detoxified as they enter the liver before they have a chance to reach other tissues.

Muscle cells contain unique pathways that allow them to store energy as creatine phosphate and to closely regulate their use of fatty acids as an energy source (see Chapter 47). The adenosine monophosphate (AMP)-activated protein kinase is an important regulator of muscle energy metabolism. Muscle is comprised of different types of contractile fibers that derive their energy from different sources. For example, the slow-twitch type I fibers use oxidative energy pathways, whereas the type II fast-twitch fibers use the glycolytic pathway for their energy requirements.

The nervous system consists of various cell types that are functionally interconnected so as to allow efficient signal transmission throughout the system (see Chapter 48). The cells of the central nervous system are protected from potentially toxic compounds by the blood-brain barrier, which restricts entry of compounds into the nervous system (ammonia, however, is a notable exception). The brain cells communicate with each other and with other organs, through the synthesis of neurotransmitters and neuropeptides. Many of the neurotransmitters are derived from amino acids, most of which are synthesized within the nerve cell. Because the pathways of amino acid and neurotransmitter biosynthesis require cofactors (such as pyridoxal phosphate, thiamine pyrophosphate, and vitamin B12), deficiencies of these cofactors can lead to neuropathies (dysfunction of specific neurons within the nervous system).

Because of the restrictions imposed by the blood-brain barrier, the brain also must synthesize its own lipids. An adequate supply of lipids is vital to the central nervous system because they are constituents of the myelin sheath that surrounds the neurons and allows them to conduct impulses normally. The neurodegenerative disorders, such as multiple sclerosis, are a consequence of varying degrees of demyelination of the neurons.

Connective tissue, which consists primarily of fibroblasts, produces extracellular matrix materials that surround cells and tissues, determining their appropriate position within the organ (see Chapter 49). These materials include structural proteins (collagen and elastin), adhesive proteins (fibronectin), and glycosaminoglycans (heparan sulfate, chondroitin sulfate). The unique structures of the proteins and carbohydrates found within the extracellular matrix allow tissues and organs to carry out their many functions. A loss of these supportive and barrier functions of connective tissue sometimes leads to significant clinical consequences, such as those that result from the microvascular alterations that lead to blindness or renal failure, or peripheral neuropathies in patients with diabetes mellitus.

43 Actions of Hormones That Regulate Fuel Metabolism

Many hormones affect fuel metabolism, including those that regulate appetite as well as those that influence absorption, transport, and oxidation of foodstuffs. The major hormones that influence nutrient metabolism and their actions on muscle, liver, and adipose tissue are listed in Table 43.1.

Insulin is the major **anabolic hormone**. It promotes the **storage** of **nutrients** as **glycogen** in liver and muscle, and as **triacylglycerols** in adipose tissue. It also stimulates the **synthesis** of **proteins** in tissues such as muscle. At the same time, insulin acts to inhibit fuel mobilization.

Glucagon is the major **counterregulatory** hormone. The term counterregulatory means that its actions are generally opposed to those of insulin (contrainsular). The major action of glucagon is to **mobilize fuel reserves** by stimulating **glycogenolysis** and **gluconeogenesis**. These actions ensure that glucose will be available to glucose-dependent tissues between meals.

Epinephrine, **norepinephrine**, **cortisol**, **somatostatin**, and **growth hormone** also have **contrainsular** activity. **Thyroid hormone** also must be classified as an insulin counterregulatory hormone because it **increases** the rate of **fuel consumption** and also increases the sensitivity of the target cells to other insulin counterregulatory hormones.

Insulin and the counterregulatory hormones exert two types of metabolic regulation (see Chapter 26). The first type of control occurs within minutes to hours of the hormone–receptor interaction and usually results from changes in the catalytic activity or kinetics of key preexisting enzymes, caused by phosphorylation or dephosphorylation of these enzymes. The second type of control involves regulation of the **synthesis of key enzymes** by mechanisms that stimulate or inhibit transcription and translation of mRNA. These processes are slow and require hours to days.



THE WAITING ROOM



Otto Shape, now a third-year medical student, was assigned to do a history and physical examination on a newly admitted 47-year-old patient named **Corti Solemia**. Mr. Solemia had consulted his physician for increasing weakness and fatigue and was found to have a severely elevated serum glucose level. While examining the patient, Otto noted marked redness of the patient's facial skin as well as reddish-purple stripes (striae) in the skin of the patient's lower abdomen and thighs. The patient's body fat was unusually distributed in that it appeared to be excessively

Table 43.1. Major Hormones that Regulate Fuel Metabolism

Hormones	Muscle			Liver						Adipose Tissue	
	Glucose Uptake	Glucose Utilization	Protein Synthesis	Glucose Output	Ketogenesis	Gluconeogenesis	Glycogenolysis	Glycogenesis	Protein Synthesis	Fat Synthesis	Lipolysis
Anabolic hormone Insulin	↑↑	↑↑	↑↑	↓↓	↓↓	↓↓	↓↓	↑	↑	↑↑	↓↓
Counterregulatory hormones ^a Glucagon	-	-	-	↑↑	↑	↑	↑↑	↓	-	-	↑ (at large doses) ↑↑
Epinephrine and norepinephrine	-	↑	-	↑↑	-	↑	↑↑ (initial)	↑↓	-	-	↑↑
Glucocorticoid	↓	↓	↓	↑	↑	↑ (mainly permissive)	-	↑	↑	-	↑ (permissive)
Growth hormone	↓ (weakly)	↓ (weakly)	↑	↑	↑	↑	-	-	↑	-	↑ (mainly permissive)
Thyroid hormone	-	↑	↑	↑	↑	↑	-	-	-	-	↑ (permissive)
Somatostatin ^b	-	-	-	-	-	-	-	-	-	-	-

^a Hormones with actions that are generally opposed to those of insulin.

^b Somatostatin's effects on metabolism are indirect via suppression of secretion of insulin, glucagon, growth hormone, and thyroid hormone and by effects on gastric acid secretion, gastric emptying time, and pancreatic exocrine secretion (see text).

deposited centrally in his face, neck, upper back, chest and abdomen, while the distal portions of his arms and legs appeared to be almost devoid of fat. The patient's skin appeared thinned, and large bruises were present over many areas of his body, for which Mr. Solemia had no explanation. The neurologic examination showed severe muscle weakness, especially in the proximal arms and legs, where the muscles seemed atrophied.



Sam Atotrope, a 42-year-old jeweler, noted increasingly severe headaches behind his eyes sometimes associated with a “flash of light” in his visual fields. At times his vision seemed blurred, making it difficult to perform some of the intricate work required of a jeweler. He consulted his ophthalmologist, who was impressed with the striking change in Sam's facial features that had occurred since he last saw the patient 5 years earlier. The normal skin creases in Sam's face had grown much deeper, his skin appeared to be thickened, his nose and lips appeared more bulbous, and his jaw seemed more prominent. The doctor also noted that Sam's hands appeared bulky, and his voice had deepened. An eye examination showed that Sam's optic nerves appeared slightly atrophied, and there was a loss of the upper outer quadrants of his visual fields.

I. PHYSIOLOGIC EFFECTS OF INSULIN

The effects of insulin on fuel metabolism and substrate flux were considered in many of the earlier chapters of this book, particularly in Chapter 26. Insulin stimulates the storage of glycogen in liver and muscle and the synthesis of fatty acids and triacylglycerols and their storage in adipose tissue. In addition, insulin stimulates the synthesis in various tissues of more than 50 proteins, some of which contribute to the growth of the organism. In fact, it is difficult to separate the effects of insulin on cell growth from those of a family of proteins known as the somatomedins or the insulin-like growth factors I and II (IGF-I and IGF-II) (see Section III.B.6. of this chapter).

Finally, insulin has paracrine actions within the pancreatic islet cells. When insulin is released from the β cells, it suppresses glucagon release from the α cells.

II. PHYSIOLOGIC EFFECTS OF GLUCAGON

Glucagon is one of several counterregulatory (contra-insular) hormones. It is synthesized as part of a large precursor protein, proglucagon. Proglucagon is produced in the α cells of the islets of Langerhans in the pancreas and in the L cells of the intestine. It contains a number of peptides linked in tandem: glicentin-related peptide, glucagon, glucagon-related peptide 1 (GLP-1), and glucagon-related peptide 2 (GLP-2). Proteolytic cleavage of proglucagon releases various combinations of its constituent peptides. Glucagon is cleaved from proglucagon in the pancreas and constitutes 30 to 40% of the immunoreactive glucagon in the blood. The remaining immunoreactivity is caused by other cleavage products of proglucagon released from the pancreas and the intestine. Pancreatic glucagon has a plasma half-life of 3 to 6 minutes and is removed mainly by the liver and kidney.

Glucagon promotes glycogenolysis, gluconeogenesis, and ketogenesis by stimulating the generation of cyclic adenosine monophosphate (cAMP) in target cells. The liver is the major target organ for glucagon, in part because the concentrations of this hormone bathing the liver cells in the portal blood are higher than in the peripheral circulation. Portal vein levels of glucagon may reach concentrations as high as 500 pg/mL.

Finally, glucagon stimulates insulin release from the β cells of the pancreas. Whether this is a paracrine effect or an endocrine effect has not been established. The pattern of blood flow in the pancreatic islet cells is believed to bathe the β cells

first and then the α -cells. Therefore, the β cells may influence α -cell function by an endocrine mechanism, whereas the influence of β -cell hormone on α -cell function is more likely to be paracrine.

III. PHYSIOLOGIC EFFECTS OF OTHER COUNTERREGULATORY HORMONES

A. Somatostatin

1. BIOCHEMISTRY

Preprosomatostatin, a 116–amino acid peptide, is encoded on the long arm of chromosome 3. Somatostatin (SS-14), a cyclic peptide with a molecular weight of 1,600, is produced from the 14 amino acids at the C-terminus of this precursor molecule. SS-14 was first isolated from the hypothalamus and named for its ability to inhibit the release of growth hormone (GH, somatotropin) from the anterior pituitary. It also inhibits the release of insulin. In addition to the hypothalamus, somatostatin is also secreted from the D cells (δ cells) of the pancreatic islets, many areas of the central nervous system outside of the hypothalamus, and in gastric and duodenal mucosal cells. SS-14 predominates in the central nervous system (CNS) and is the sole form secreted by the δ cells of the pancreas. In the gut, however, prosomatostatin (SS-28), which has 14 additional amino acids extending from the C-terminal portion of the precursor, makes up 70 to 75% of the immunoreactivity (the amount of hormone that reacts with antibodies to SS-14). The prohormone SS-28 is 7 to 10 times more potent in inhibiting the release of GH and insulin than is SS-14.

2. SECRETION OF SOMATOSTATIN

The secretagogues for somatostatin are similar to those that cause secretion of insulin. The metabolites that increase somatostatin release include glucose, arginine, and leucine. The hormones that stimulate somatostatin secretion include glucagon, vasoactive intestinal polypeptide (VIP), and cholecystokinin (CCK). Insulin, however, does not directly influence somatostatin secretion.

3. PHYSIOLOGIC EFFECTS OF SOMATOSTATIN

Five somatostatin receptors have been identified and characterized, all of which are members of the G protein–coupled receptor superfamily. Four of the five receptors do not distinguish between SS-14 and SS-28. Somatostatin binds to its plasma membrane receptors on target cells. These “activated” receptors interact with inhibitory G proteins of adenylate cyclase. As a result, the production of cAMP is inhibited, and protein kinase A is not activated. This inhibitory effect suppresses secretion of GH and thyroid-stimulating hormone (TSH) from the anterior pituitary gland as well as the secretion of insulin and glucagon from the pancreatic islets. If one were to summarize the action of somatostatin in one phrase, it would be “somatostatin inhibits the secretion of many other hormones.” As such, it acts to regulate the effects of those other hormones. In addition to these effects on hormones that regulate fuel metabolism, somatostatin also reduces nutrient absorption from the gut by prolonging gastric emptying time (through a decrease in the secretion of gastrin, which reduces gastric acid secretion), by diminishing pancreatic exocrine secretions (i.e., digestive enzymes, bicarbonate, and water), and by decreasing visceral blood flow. Thus, somatostatin exerts a broad, albeit indirect, influence on nutrient absorption and, therefore, the utilization of fuels.

Somatostatin and its synthetic analogs are used clinically to treat a variety of secretory neoplasms such as GH-secreting tumors of the pituitary. Such tumors can cause gigantism if growth hormone is secreted in excess before the closure of the



Tolbutamide, a sulfonylurea drug that increases insulin secretion, also increases the secretion of pancreatic somatostatin.



In addition to its effects on normal GH secretion, somatostatin also suppresses the pathologic increase in GH that occurs in acromegaly (caused by a GH-secreting pituitary tumor), diabetes mellitus, and carcinoid tumors (tumors that secrete serotonin). Somatostatin also suppresses the basal secretion of TSH, TRH, insulin, and glucagon. The hormone also has a suppressive effect on a wide variety of nonendocrine secretions.

The major limitation in the clinical use of native somatostatin is its short half-life of less than 3 minutes in the circulation. Analogs of native somatostatin, however, have been developed that are resistant to degradation and, therefore, have a longer half-life. One such analog is octreotide, an octapeptide variant of somatostatin with a half-life of approximately 110 minutes.

growth centers of the ends of long bones or acromegaly if excess growth hormone is chronically secreted after the closure of these centers (as in **Sam Atrope**).

B. Growth Hormone

1. BIOCHEMISTRY

Growth hormone is a polypeptide that, as its name implies, stimulates growth. Many of its effects are mediated by insulin-like growth factors (IGFs, also known as somatomedins) that are produced by cells in response to the binding of GH to its cell membrane receptors (see Section 6 below). However, GH also has direct effects on fuel metabolism.

Human growth hormone is a water-soluble 22-kDa polypeptide with a plasma half-life of 20 to 50 minutes. It is composed of a single chain of 191 amino acids having two intramolecular disulfide bonds (Fig. 43.1). The gene for GH is located on chromosome 17. It is secreted by the somatotroph cells (the cells that synthesize and release GH) present in the lateral areas of the anterior pituitary. GH is structurally related to human prolactin and to human chorionic somatomammotropin (hCS) from the placenta, a polypeptide that stimulates growth of the developing fetus. Yet the hCS peptide has only 0.1% of the growth-inducing potency of GH. Growth hormone is the most abundant trophic hormone in the anterior pituitary, being present in concentrations of 5 to 15 mg per gram of tissue. The other anterior pituitary hormones are present in microgram-per-gram of tissue quantities.

The actions of GH can be classified as those that occur as a consequence of the hormone's direct effect on target cells and those that occur indirectly through the ability of GH to generate other factors, particularly IGF-I.

The IGF-I-independent actions of GH are exerted primarily in hepatocytes. GH administration is followed by an early increase in the synthesis of 8 to 10 proteins, among which are IGF-I, α_2 -macroglobulin, and the serine protease inhibitors Spi 2.1 and Spi 2.3. Expression of the gene for ornithine decarboxylase, an enzyme active in polyamine synthesis (and, therefore, in the regulation of cell proliferation), is also significantly increased by GH.

Muscle and adipocyte cell membranes contain GH receptors that mediate direct, rapid metabolic effects on glucose and amino acid transport as well as on lipolysis. These receptors use associated cytoplasmic tyrosine kinases for signal transduction (such as the janus kinases; see Chapter 11, section III.C.). For example, in adipose tissue, GH has acute insulinlike effects followed by increased lipolysis, inhibition of lipoprotein lipase, stimulation of hormone-sensitive lipase, decreased glucose transport, and decreased lipogenesis. In muscle, GH causes increased amino acid transport, increased nitrogen retention, increased fat-free (lean) tissue, and increased energy expenditure. GH also has growth-promoting effects. GH receptors

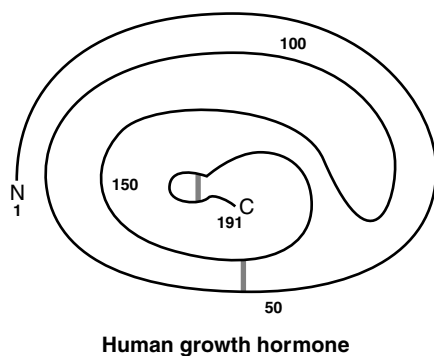


Fig. 43.1. Structure of human growth hormone. From Murray, RK, et al, Harper's Biochemistry, 23rd Ed. Stamford, CT: Appleton & Lange, 1993:502.



An MRI scan of **Sam Atotrope's** brain showed a macroadenoma (a tumor greater than 10 mm in diameter) in the pituitary gland, with superior extension that compressed the optic nerve as it crossed above the sella turcica, causing his visual problems. The skeletal and visceral changes noted by the ophthalmologist are characteristic of acromegalic patients with chronically elevated serum levels of GH and IGF-I.

Therapeutic alternatives for acromegaly caused by a GH-secreting tumor of the anterior pituitary gland include lifelong medical therapy with the somatostatin analog octreotide or the GH receptor antagonist pegvisomant. Other therapeutic options include stereotactic radiation therapy or surgical resection of the neoplasm. If the excessive secretion of GH is controlled successfully, some of the visceral or soft tissue changes of acromegaly may slowly subside to varying degrees. The skeletal changes, however, cannot be reversed.



The ophthalmologist ordered a morning fasting serum GH level on **Sam Atotrope**, which was elevated at 56 ng/mL (normal = 0–5 ng/mL)



Sam Atotrope was given an oral dose of 100 g glucose syrup. This dose would suppress serum GH levels to less than 2 ng/mL in normal subjects, but not in patients with acromegaly who have an autonomously secreting pituitary tumor making GH. Because Sam's serum GH level was 43 ng/mL after the oral glucose load, a diagnosis of acromegaly was made. The patient was referred to an endocrinologist for further evaluation.



GH not only stimulates IGF-I gene expression in the liver but in a number of extrahepatic tissues as well. In acromegalics, rising levels of IGF-I cause a gradual generalized increase in skeletal, muscular, and visceral growth. As a consequence, a diffuse increase occurs in the bulk of all tissues (enlargement = “megaly”) especially in the “acral” (most peripheral) tissues of the body, such as the face, the hands, and the feet, hence the term “acromegaly.”

Sam Atotrope’s coarse facial features and bulky hands are typical of patients with acromegaly.

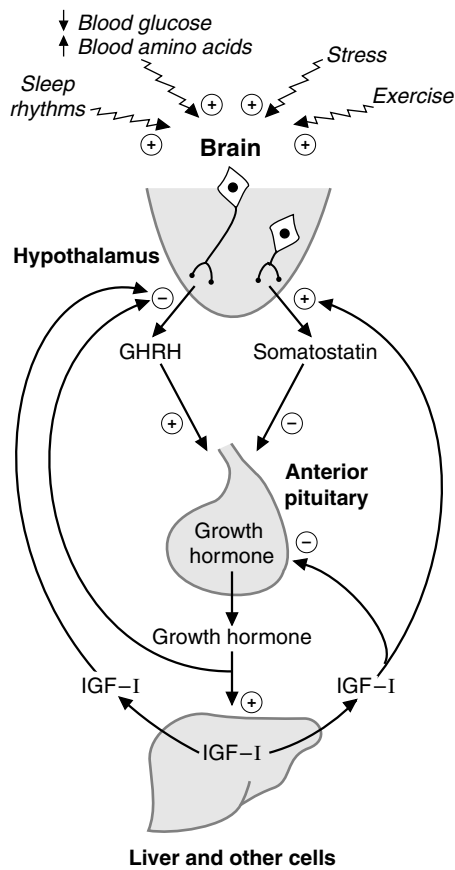


Fig. 43.2. Control of growth hormone secretion. Various factors stimulate the release of GHRH from the hypothalamus. The hypothalamus also releases somatostatin in response to other stimuli. GHRH stimulates and somatostatin inhibits the release of growth hormone from the anterior pituitary. Growth hormone causes the release of IGF-I from liver and other tissues. IGF-I inhibits GHRH release and stimulates somatostatin release.

are present on a variety of tissues in which GH increases IGF-I gene expression. The subsequent rise in IGF-I levels contributes to cell multiplication and differentiation by autocrine or paracrine mechanisms. These, in turn, lead to skeletal, muscular, and visceral growth. These actions are accompanied by a direct anabolic influence of GH on protein metabolism with a diversion of amino acids from oxidation to protein synthesis and a shift to a positive nitrogen balance.

2. CONTROL OF SECRETION OF GROWTH HORMONE

Although the regulation of GH secretion is complex, the major influence is hormonal (Fig. 43.2). The pulsatile pattern of GH secretion reflects the interplay of two hypothalamic regulation peptides. Release is stimulated by growth hormone–releasing hormone (GHRH, also called somatotrin). The structure of GHRH was identified in 1982 (Fig. 43.3). It exists as both a 40– and a 44–amino acid peptide encoded on chromosome 20 and produced exclusively in cells of the arcuate nucleus. Its C-terminal leucine residue is amidated. Full biologic activity of this releasing hormone resides in the first 29 amino acids of the N-terminal portion of the molecule. GHRH interacts with specific receptors on the plasma membranes of the somatotrophs. The intracellular signaling mechanisms that result in GH synthesis and release appear to be multiple, as cAMP and calcium-calmodulin both stimulate GH release.

Conversely, GH secretion is suppressed by growth hormone release-inhibiting hormone (GHRH, also called somatostatin, which has already been discussed). In addition, IGF-I, produced primarily in the liver in response to the action of GH on hepatocytes, feeds back negatively on the somatotrophs to limit GH secretion. Other physiologic factors (e.g., exercise and sleep) and many pathologic factors control its release (Table 43.2).

In addition, GH release is modulated by plasma levels of all of the metabolic fuels, including proteins, fats, and carbohydrates. A rising level of glucose in the blood normally suppresses GH release, whereas hypoglycemia increases GH

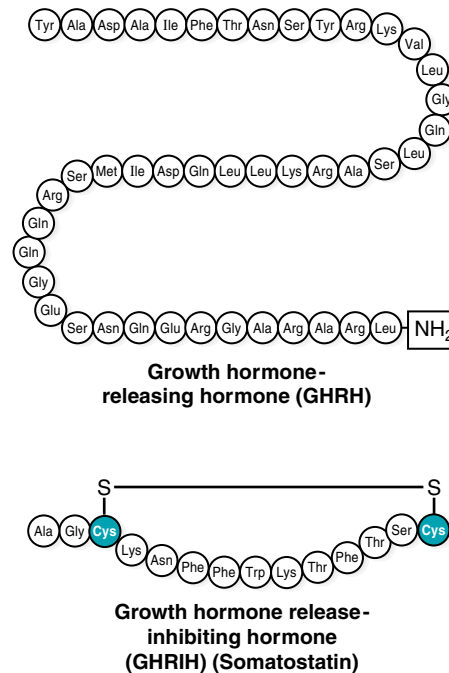


Fig. 43.3. Structures of growth hormone–releasing hormone (GHRH) and growth hormone release-inhibiting hormone (GHRH, also called somatostatin). GHRH has an amide at the C-terminal.

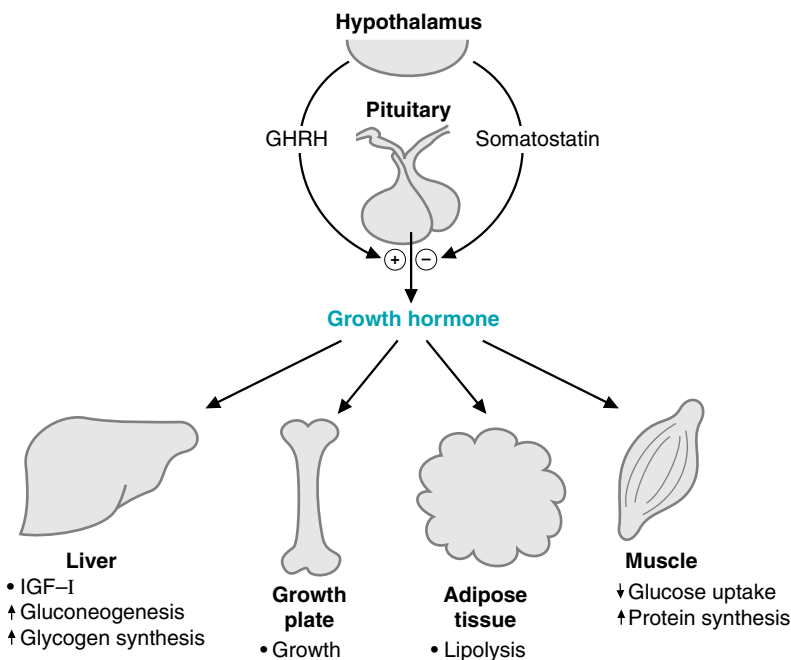
Table 43.2. Some Factors Affecting Growth Hormone Secretion

	Stimulate	Suppress
Physiologic	Low blood glucose after meals High blood amino acids after meals Exercise Sleep Stress	High blood glucose after meals High blood fatty acids
Pharmacologic	GHRH Estrogens α -Adrenergic agonists β -Adrenergic antagonists Dopamine agonists Serotonin precursors K^+ infusion	Somatostatin Progesterone α -Adrenergic antagonists β -Adrenergic agonists Dopamine antagonists
Pathologic	Starvation Anorexia nervosa Ectopic GHRH production Acromegaly Chronic renal failure Hypoglycemia	Growth hormone and IGF-I Obesity Hypothyroidism Hyperthyroidism

secretion in normal subjects. Amino acids, such as arginine, stimulate release of GH when their concentrations rise in the blood. Rising levels of fatty acids may blunt the GH response to arginine or a rapidly dropping blood glucose level. However, prolonged fasting, in which fatty acids are mobilized in an effort to spare protein, is associated with a rise in GH secretion. Some of the physiologic, pharmacologic, and pathologic influences on GH secretion are given in Table 43.2.

3. EFFECTS OF GROWTH HORMONE ON ENERGY METABOLISM

GH affects the uptake and oxidation of fuels in adipose tissue, muscle, and liver and indirectly influences energy metabolism through its actions on the islet cells of the pancreas. In summary, GH increases the availability of fatty acids, which are oxidized for energy. This and other effects of GH spare glucose and protein; that is, GH indirectly decreases the oxidation of glucose and amino acids (Fig. 43.4).

**Fig. 43.4.** Anabolic effects of growth hormone on various tissues.

These modulators of GH secretion provide the basis for clinical suppression and stimulation tests in patients suspected of having excessive or deficient GH secretion.



While **Sam Atotrope** was trying to decide which of the major alternatives for the treatment of his growth hormone (GH)-secreting pituitary tumor to choose, he noted progressive fatigue and the onset of increasing urinary frequency associated with a marked increase in thirst. In addition, he had lost 4 lb over the course of the last 6 weeks in spite of a good appetite. His physician suspected that Mr. Atotrope had developed diabetes mellitus, perhaps related to the chronic hypersecretion of GH. This suspicion was confirmed when Sam's serum glucose level, drawn before breakfast, was reported to be 236 mg/dL.



As a result of the metabolic effects of GH, the clinical course of acromegaly may be complicated by impaired glucose tolerance or even overt diabetes mellitus, as occurred with **Sam Atotrope**.

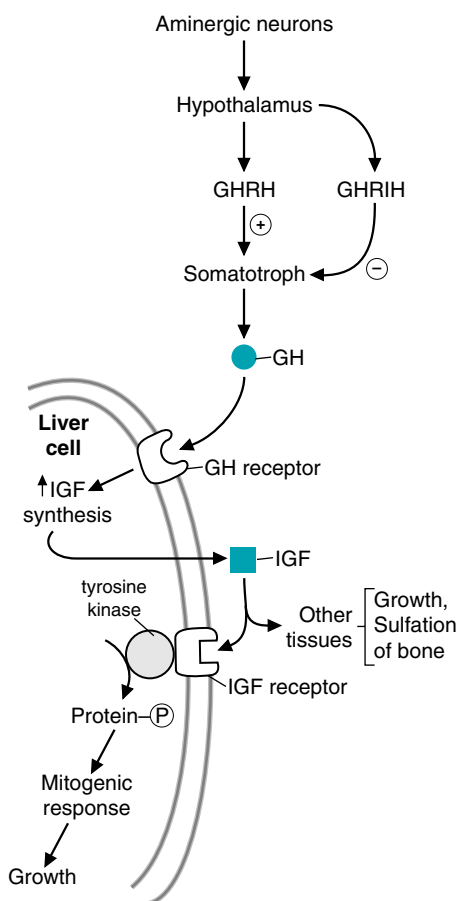


Fig 43.5. Production and action of IGFs. The hypothalamus produces growth hormone-releasing hormone (GHRH), which stimulates somatotrophs in the anterior pituitary to release growth hormone (GH). Growth hormone release-inhibiting hormone (GHRH) inhibits GH release. GH binds to cell surface receptors and stimulates IGF production and release by liver and other tissues. IGF binds to cell surface receptors and stimulates the phosphorylation of proteins that cause mitosis and growth.



High levels of circulating IGF-1 has been linked to the development of breast, prostate, colon, and lung cancer. Additionally, experimental modulation of IGF-1 receptor activity can alter the growth of different types of tumor cells. Current research is aimed at targeting the interaction of IGF-1 and its receptor to reduce tumor cell proliferation.

4. EFFECTS OF GROWTH HORMONE ON ADIPOSE TISSUE

Growth hormone increases the sensitivity of the adipocyte to the lipolytic action of the catecholamines and decreases its sensitivity to the lipogenic action of insulin. These actions lead to the release of free fatty acids and glycerol into the blood to be metabolized by the liver. GH also decreases esterification of fatty acids, thereby reducing triacylglycerol synthesis within the fat cell. Recent evidence suggests that GH may impair glucose uptake by both fat and muscle cells by a postreceptor inhibition of insulin action.

5. EFFECTS OF GROWTH HORMONE ON MUSCLE

The lipolytic effects of GH increase free fatty acid levels in the blood bathing muscle. These fatty acids are preferentially used as fuel, indirectly suppressing glucose uptake by muscle cells. Through the effects on glucose uptake, the rate of glycolysis is proportionately reduced.

GH increases the transport of amino acids into muscle cells, providing substrate for protein synthesis. Through a separate mechanism, GH increases the synthesis of DNA and RNA. The positive effect on nitrogen balance is reinforced by the protein-sparing effect of GH-induced lipolysis that makes fatty acids available to muscle as an alternative fuel source.

6. EFFECTS OF GROWTH HORMONE ON THE LIVER

When plasma insulin levels are low, as in the fasting state, GH enhances fatty acid oxidation to acetyl CoA. This effect in concert with the increased flow of fatty acids from adipose tissue enhances ketogenesis. The increased amount of glycerol reaching the liver as a consequence of enhanced lipolysis acts as a substrate for gluconeogenesis.

Hepatic glycogen synthesis is also stimulated by GH in part because of the increased gluconeogenesis in the liver. Finally, glucose metabolism is suppressed by GH at several steps in the glycolytic pathway.

A major effect of GH on liver is to stimulate production and release of IGFs. The IGFs are also known as somatomedins. The two somatomedins in humans share structural homologies with proinsulin, and both have substantial insulin-like growth activity; hence the designations, insulin-like growth factor I (human IGF-I, or somatomedin-C) and insulin-like growth factor II (human IGF-II, or somatomedin A). IGF-I is a single-chain basic peptide having 70 amino acids, and IGF-II is slightly acidic with 67 amino acids. These two peptides are identical to insulin in half of their residues. In addition, they contain a structural domain that is homologous to the C-peptide of proinsulin.

A broad spectrum of normal cells respond to high doses of insulin by increasing thymidine uptake and initiating cell propagation. In most instances, IGF-I causes the same response as insulin in these cells but at significantly smaller, more physiologic concentrations. Thus, the IGFs are more potent than insulin in their growth-promoting actions.

Evidence suggests that the IGFs exert their effects through either an endocrine or a paracrine/autocrine mechanism. IGF-I appears to stimulate cell propagation and growth by binding to specific IGF-I receptors on the plasma membrane of target cells, rather than binding to GH receptors (Fig. 43.5).

Like insulin, the intracellular portion of the plasma membrane receptor for IGF-I (but not IGF-II) has intrinsic tyrosine kinase activity. The fact that the receptors for insulin and a number of other growth factors have intrinsic tyrosine kinase activity indicates that tyrosine phosphorylation initiates the process of cellular replication and growth. Subsequently, a chain of kinases is activated, which include a number of proto-oncogene products (see Chapters 11 and 18).

Most cells of the body have mRNA for IGF, but the liver has the greatest concentration of these messengers, followed by kidney and heart. The synthesis of IGF-I is regulated, for the most part, by GH, whereas hepatic production of IGF-II is independent of GH levels in the blood.

C. Catecholamines (Epinephrine, Norepinephrine, Dopamine)

The catecholamines belong to a family of bioamines and are secretory products of the sympathoadrenal system, which are required for the body to adapt to a great variety of acute and chronic stresses. Epinephrine (80–85% of stored catecholamines) is synthesized primarily in the cells of the adrenal medulla, whereas norepinephrine (15–20% of stored catecholamines) is synthesized and stored not only in the adrenal medulla but also in various areas of the central nervous system (CNS) and in the nerve endings of the adrenergic nervous system. Dopamine, another catecholamine, acts primarily as a neurotransmitter and has little effect on fuel metabolism.

The first total chemical synthesis of epinephrine was accomplished by F. Stolz et al in 1904. In 1950, Earl Sutherland was the first to demonstrate that epinephrine (and glucagon) induces glycogenolysis. This marked the beginning of our understanding of the molecular mechanisms through which hormones act.

1. SYNTHESIS OF THE CATECHOLAMINES

Tyrosine is the precursor of the catecholamines. The pathway for the biosynthesis of these molecules is described in Chapter 48.

2. SECRETION OF THE CATECHOLAMINES

Secretion of epinephrine and norepinephrine from the adrenal medulla is stimulated by a variety of stresses, including pain, hemorrhage, exercise, hypoglycemia, and hypoxia. Release is mediated by stress-induced transmission of nerve impulses emanating from adrenergic nuclei in the hypothalamus. These impulses stimulate the release of the neurotransmitter acetylcholine from preganglionic neurons that innervate the adrenomedullary cells. Acetylcholine depolarizes the plasma membranes of these cells, allowing the rapid entry of extracellular calcium (Ca^{2+}) into the cytosol. Ca^{2+} stimulates the synthesis and release of epinephrine and norepinephrine from the chromaffin granules into the extracellular space by exocytosis.

3. PHYSIOLOGIC EFFECTS OF EPINEPHRINE AND NOREPINEPHRINE

The catecholamines act through two major types of receptors on the plasma membrane of target cells, the α -adrenergic and the β -adrenergic receptors (see Chapter 26, section IV.C).

The actions of epinephrine and norepinephrine in the liver, the adipocyte, the skeletal muscle cell, and the α and β cells of the pancreas directly influence fuel metabolism (Fig. 43.6). These catecholamines are counterregulatory hormones that have metabolic effects directed toward mobilization of fuels from their storage sites for oxidation by cells to meet the increased energy requirements of acute and chronic stress. They simultaneously suppress insulin secretion, which ensures that fuel fluxes will continue in the direction of fuel utilization rather than storage as long as the stressful stimulus persists.

In addition, norepinephrine works as a neurotransmitter and affects the sympathetic nervous system in the heart, lungs, blood vessels, bladder, gut, and other



In patients suspected of having a neoplasm of the adrenal medulla that is secreting excessive quantities of epinephrine or norepinephrine (a pheochromocytoma), either the catecholamines themselves (epinephrine, norepinephrine, and dopamine) or their metabolites (the metanephrines and vanillylmandelic acid, VMA) may be measured in a 24-hour urine collection, or the level of catecholamines in the blood may be measured. A patient who has consistently elevated levels in the blood or urine should be considered to have a pheochromocytoma, particularly if the patient has signs and symptoms of catecholamine excess, such as excessive sweating, palpitations, tremulousness, and hypertension.

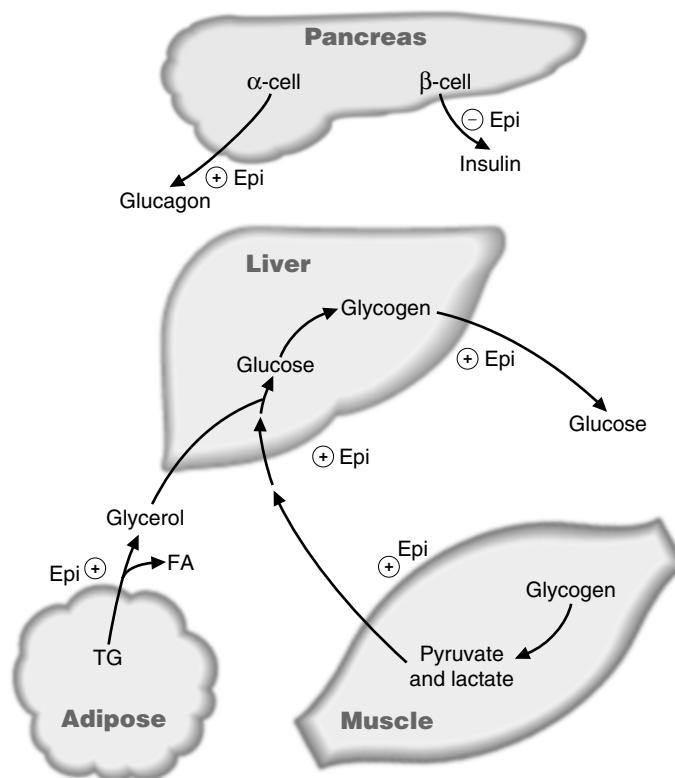


Fig. 43.6. Effects of epinephrine on fuel metabolism and pancreatic endocrine function. Epinephrine (Epi) stimulates glycogen breakdown in muscle and liver, gluconeogenesis in liver, and lipolysis in adipose tissue. Epinephrine further reinforces these effects because it increases the secretion of glucagon, a hormone that shares many of the same effects as epinephrine. Epi also inhibits insulin release but stimulates glucagon release from the pancreas.

Q: A relatively rare form of secondary hypertension (high blood pressure) is caused by a catecholamine-secreting neoplasm of the adrenal medulla, known as a pheochromocytoma. Patients with the tumor periodically secrete large amounts of epinephrine and norepinephrine into the bloodstream. Symptoms related to this secretion include a sudden and often severe increase in blood pressure, heart palpitations, a throbbing headache, and inappropriate and diffuse sweating. In addition, chronic hypersecretion of these catecholamines may lead to impaired glucose tolerance or even overt diabetes mellitus. Describe the actions of these hormones that lead to the significant rise in glucose levels.

Q: Glucocorticoids, such as cortisol, were named for their ability to raise blood glucose levels. These steroids are among the “counterregulatory” hormones that protect the body from insulin-induced hypoglycemia.

organs. These effects of catecholamines on the heart and blood vessels serve to increase cardiac output and systemic blood pressure, hemodynamic changes that facilitate the delivery of blood borne fuels to metabolically active tissues.

Epinephrine has a short half-life in the blood and to be effective pharmacologically must be administered parenterally. It may be used clinically to support the beating of the heart, to dilate inflamed bronchial muscles, and even to decrease bleeding from organs during surgery.

4. METABOLISM AND INACTIVATION OF CATECHOLAMINES

Catecholamines have a relatively low affinity for both α - and β -receptors. After binding, the catecholamine disassociates from its receptor quickly, causing the duration of the biologic response to be brief. The free hormone is degraded in several ways, as outlined in Chapter 48.

D. Glucocorticoids

1. BIOCHEMISTRY

Cortisol (hydrocortisone) is the major physiologic glucocorticoid (GC) in humans, although corticosterone also has some glucocorticoid activity. The biosynthesis of steroid hormones and their basic mechanism of action has been described in Chapters 34 and 17.

2. SECRETION OF GLUCOCORTICOIDS

The synthesis and secretion of cortisol is controlled by a cascade of neural and endocrine signals linked in tandem in the cerebrocortical-hypothalamic-pituitary-adrenocortical axis. Cerebrocortical signals to the midbrain are initiated in the cerebral cortex by “stressful” signals such as pain, hypoglycemia, hemorrhage, and exercise (Fig. 43.7). These nonspecific “stresses” elicit the production of monoamines in the cell bodies of neurons of the midbrain. Those that stimulate the synthesis and release of corticotropin-releasing hormone (CRH) are acetylcholine and serotonin. These neurotransmitters then induce the production of CRH by neurons originating in the paraventricular nucleus. These neurons discharge CRH into the hypothalamo-hypophyseal portal blood. CRH is delivered through these portal vessels to specific receptors on the cell membrane of the adrenocorticotropic hormone (ACTH)-secreting cells of the anterior pituitary gland (corticotrophs). This hormone–receptor interaction causes ACTH to be released into the general circulation to eventually interact with specific receptors for ACTH on the plasma membranes of cells in the zona fasciculata and zona reticulosa of the adrenal cortex. The major trophic influence of ACTH on cortisol synthesis is at the level of the conversion of cholesterol to pregnenolone, from which the adrenal steroid hormones are derived (see Chapter 34 for the biosynthesis of the steroid hormones).

Cortisol is secreted from the adrenal cortex in response to ACTH. The concentration of free (unbound) cortisol that bathes the CRH-producing cells of the hypothalamus and the ACTH-producing cells of the anterior pituitary acts as a negative feedback signal that has a regulatory influence on the release of CRH and ACTH (see Fig. 43.7). High cortisol levels in the blood suppress CRH and ACTH secretion, and low cortisol levels stimulate secretion. In severe stress, however, the negative feedback signal on ACTH secretion exerted by high cortisol levels in the blood is overridden by the stress-induced activity of the higher portions of the axis (see Fig. 43.7).

The effects of glucocorticoids on fuel metabolism in liver, skeletal muscle, and adipose tissue are outlined in Table 43.1 and in Figure 43.8. Their effects on other tissues are diverse and, in many instances, essential for life. Some of the nonmetabolic actions of GCs are listed in Table 43.3.

3. EFFECTS OF GLUCOCORTICOIDS

Glucocorticoids have diverse actions that affect most tissues of the body. At first glance, some of these effects may appear to be contradictory (such as inhibition of



When Otto was writing his list of differential diagnoses to explain the clinical presentation of **Corti Solemia**, he suddenly thought of a relatively rare endocrine disorder that could explain all of the presenting signs and symptoms. He made a provisional diagnosis of excessive secretion of cortisol secondary to an excess secretion of ACTH (Cushing’s “disease”) or by a primary increase of cortisol production by an adrenocortical tumor (Cushing’s syndrome).

Otto suggested that resting, fasting plasma cortisol and ACTH levels be measured at 8:00 the next morning. These studies showed that Mr. Solemia’s morning plasma ACTH and cortisol levels were both significantly above the reference range. Therefore, Otto concluded that Mr. Solemia probably had a tumor that was producing ACTH autonomously (i.e., not subject to normal feedback inhibition by cortisol). The high plasma levels of ACTH were stimulating the adrenal cortex to produce excessive amounts of cortisol. Additional laboratory and imaging studies indicated that the hypercortisolemia was caused by a benign ACTH-secreting adenoma of the anterior pituitary gland (Cushing’s “disease”).

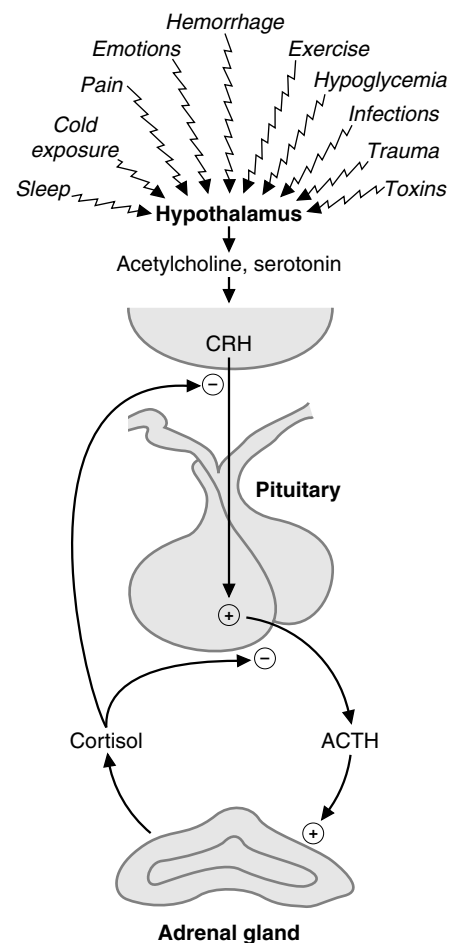


Fig. 43.7. Regulation of cortisol secretion. Various factors act on the hypothalamus to stimulate the release of corticotrophin-releasing hormone (CRH). CRH stimulates the release of ACTH from the anterior pituitary, which stimulates the release of cortisol from the adrenal cortex. Cortisol inhibits the release of CRH and ACTH.



The catecholamines are counterregulatory hormones that mobilize fuels from their storage sites for oxidation in target cells to meet the increased energy requirements that occur during acute or chronic stress, or, in this case, the release of catecholamines by a tumor in the adrenal medulla. These actions provide the liver, for example, with increased levels of substrate needed for gluconeogenesis. Although in normal individuals most of the glucose generated through this mechanism is oxidized, blood glucose levels rise in the process. In addition, the catecholamines suppress insulin secretion to ensure that fuels will continue to flow in the direction of utilization rather than storage under these circumstances. Hence, blood glucose levels may rise in patients who have a pheochromocytoma.

Table 43.3. Some Nonmetabolic Physiologic Actions of Glucocorticoids

On electrolyte and water balance:
 Increase sodium and water retention (1/3,000 the potency of aldosterone)
 Increase renal glomerular filtration rate to maintain water excretion rate
 Suppress arginine vasopressin (ADH) release from posterior pituitary (?)

On cardiovascular system:
 Indirect effect of glucocorticoid actions on sodium and water metabolism (above)
 Maintain volume of microcirculation to tissues (cardiac output)
 Maintain normal vasomotor response to vasoconstricting agents

On skeletal muscle:
 Maintain muscle function by providing normal microcirculation to muscle
 Influence muscle mass by enhancing protein catabolism and suppressing protein synthesis

On central nervous system:
 Indirect
 Maintain normal cerebral microcirculation
 Direct
 Influence mood, behavior
 Influence sensitivity of special senses to stimuli
 Suppress CRH, ACTH, and ADH secretion

On formed elements in blood:
 Increase red blood cell mass and granulocyte proliferation
 Decrease lymphocyte, monocyte, and basophil proliferation

Anti-inflammatory actions:
 Inhibit early inflammatory process (i.e., edema, fibrin deposition, capillary dilation, leukocyte migration, and phagocytic action)
 Inhibit late inflammatory process (proliferation of capillaries and fibroblasts, deposition of collagen, and, later, scar formation)

Immune suppressant actions (of questionable significance at physiologic levels):
 Prevent manifestations of humoral and cellular immunity
 Interfere with production of cytokines needed for immune competence via cell-to-cell communication

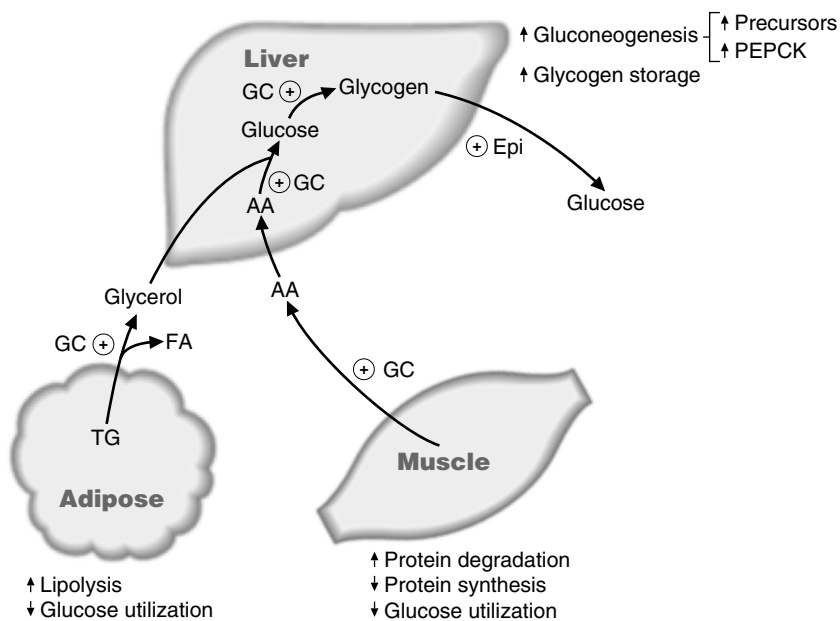


Fig. 43.8. Effects of glucocorticoids (GC) on fuel metabolism. Glucocorticoids stimulate lipolysis in adipose tissue and the release of amino acids from muscle protein. In liver, glucocorticoids stimulate gluconeogenesis and the synthesis of glycogen. The breakdown of liver glycogen is stimulated by epinephrine.

glucose uptake by certain tissues), but taken together they promote survival in times of stress.

In many tissues, GCs inhibit DNA, RNA, and protein synthesis and stimulate the degradation of these macromolecules. In response to chronic stress, GCs act to make fuels available, so that when the acute alarm sounds and epinephrine is released, the organism can fight or flee. When GCs are elevated, glucose uptake by the cells of many tissues is inhibited, lipolysis occurs in peripheral adipose tissue, and proteolysis occurs in skin, lymphoid cells, and muscle. The fatty acids that are released are oxidized by the liver for energy, and the glycerol and amino acids serve in the liver as substrates for the production of glucose, which is converted to glycogen and stored. The alarm signal of epinephrine stimulates liver glycogen breakdown, making glucose available as fuel to combat the acute stress.

The mechanism by which GCs exert these effects involves binding of the steroid to intracellular receptors, interaction of the steroid-receptor complex with GC response elements on DNA, transcription of genes, and synthesis of specific proteins (see Chapter 16, section III.C.2.). In some cases, the specific proteins responsible for the GC effect are known (e.g., the induction of phosphoenolpyruvate carboxykinase that stimulates gluconeogenesis). In other cases, the proteins responsible for the GC effect have not yet been identified.

E. Thyroid Hormone

1. BIOCHEMISTRY

The secretory products of the thyroid acinar cells are tetraiodothyronine (thyroxine, T_4) and triiodothyronine (T_3). Their structures are shown in Figure 43.9. The basic steps in the synthesis of T_3 and T_4 in these cells involve the transport or trapping of iodide from the blood into the thyroid acinar cell against an electrochemical gradient; the oxidation of iodide to form an iodinating species; the iodination of tyrosyl residues on the protein, thyroglobulin, to form iodotyrosines; and the coupling of residues of monoiodo- and diiodotyrosine in thyroglobulin to form residues of T_3 and T_4 (Fig. 43.10). Proteolytic cleavage of thyroglobulin releases free T_3 and T_4 . The steps in thyroid hormone synthesis are stimulated by thyroid-stimulating hormone (TSH), a glycoprotein produced by the anterior pituitary.

Iodide transport from the blood into the thyroid acinar cell is accomplished through an energy-requiring, iodide-trapping mechanism that is poorly defined but may involve the Na^+, K^+ -ATPase coupled to a cotransporter for Na^+ and iodide in the plasma membrane of the acinar cell.



The “central” deposition of fat in patients, such as **Corti Solemia**, with Cushing’s “disease” or syndrome is not readily explained because GCs actually cause lipolysis in adipose tissue. The increased appetite caused by an excess of GC and the lipogenic effects of the hyperinsulinemia that accompanies the GC-induced chronic increase in blood glucose levels have been suggested as possible causes. Why the fat is deposited centrally under these circumstances, however, is not understood. This central deposition leads to the development of a large fat pad at the center of the upper back (“buffalo hump”), to accumulation of fat in the cheeks and jowls (“moon facies”) and neck area, as well as a marked increase in abdominal fat. Simultaneously, there is a loss of adipose and muscle tissue below the elbows and knees, exaggerating the appearance of “central obesity” in Cushing’s “disease” or syndrome.



Approximately 35% of T_4 is deiodinated at the 5' position to form T_3 , and 43% is deiodinated at the 3' position to form the inactive “reverse” T_3 . Further deiodination or oxidative deamination leads to formation of compounds that have no biologic activity.



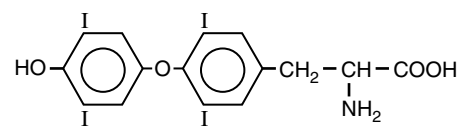
Otto was now able to explain the mechanism for most of **Corti Solemia’s** signs and symptoms. For example, Otto knew the metabolic explanation for the patient’s hyperglycemia. Some of Mr. Solemia’s muscle wasting and weakness were caused by the catabolic effect of hypercortisolemia on protein stores, such as those in skeletal muscle, to provide amino acids as precursors for gluconeogenesis. This catabolic action also resulted in the degradation of elastin, a major supportive protein of the skin, as well as an increased fragility of the walls of the capillaries of the cutaneous tissues. These changes resulted in the easy bruisability and the torn subcutaneous tissues of the lower abdomen, which resulted in red striae or stripes. The plethora (redness) of Mr. Solemia’s facial skin was also caused in part by the thinning of the skin as well as by a cortisol-induced increase in the bone marrow production of red blood cells, which enhanced the “redness” of the subcutaneous tissues.



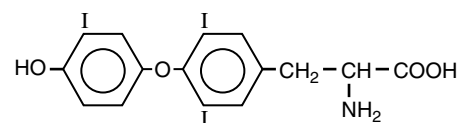
If **Corti Solemia’s** problem had been caused by a neoplasm of the adrenal cortex, what would his levels of blood ACTH and cortisol have been?



Normally, the thyroid gland secretes 80–100 μg T_4 and approximately 5 μg T_3 per day. The additional 22–25 μg T_3 “produced” daily is the result of the deiodination of the 5'-carbon of T_4 in peripheral tissues. T_3 is believed to be the predominant biologically active form of thyroid hormone in the body.



3,5,3',5'-Tetraiodothyronine (T_4)



3,5,3'-Triiodothyronine (T_3)

Fig. 43.9. Thyroid hormones, T_3 and T_4 .

A: If **Corti Solemia's** problem had resulted from primary hypersecretion of cortisol by a neoplasm of the adrenal cortex, his blood cortisol levels would have been elevated. The cortisol would have acted on the CRH-producing cells of the hypothalamus and the ACTH-secreting cells of the anterior pituitary by a negative feedback mechanism to decrease ACTH levels in the blood.

Because his cortisol and ACTH levels were both high, Mr. Solemia's tumor was most likely in the pituitary gland or possibly in neoplastic extrapituitary tissue that was secreting ACTH "ectopically." (Ectopic means that the tumor or neoplasm is producing and secreting a substance that is not ordinarily made or secreted by the tissue from which the tumor developed.) Mr. Solemia's tumor was in the anterior pituitary, not in an extrapituitary ACTH-producing site.

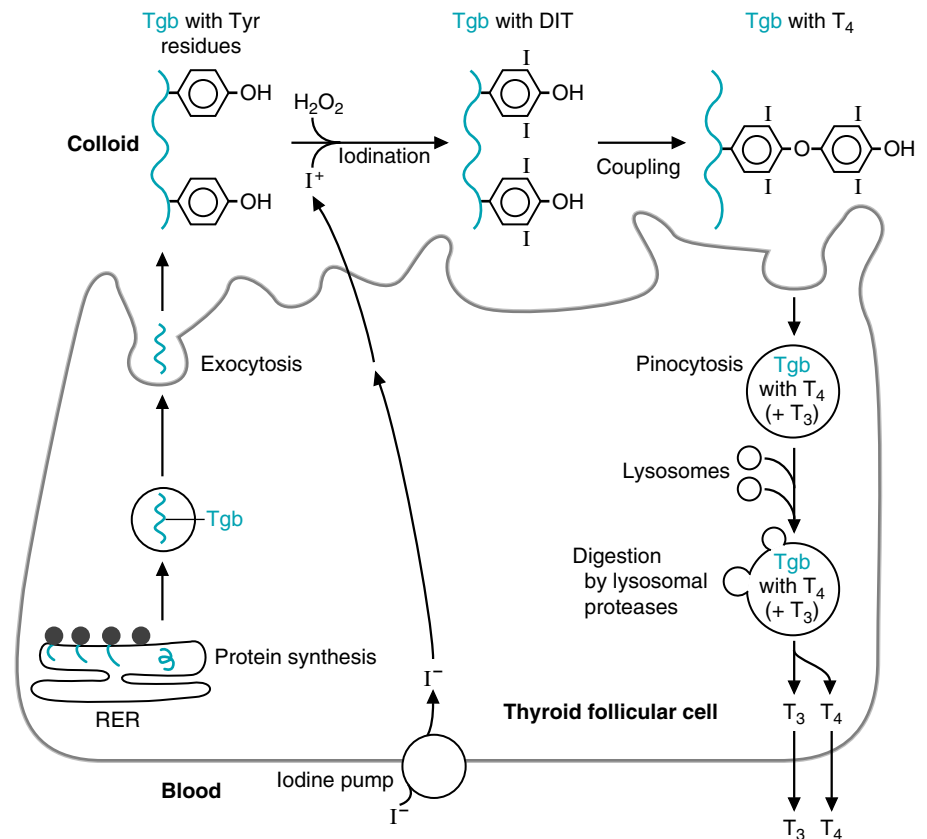


Fig. 43.10. Synthesis of the thyroid hormones (T_3 and T_4). The protein thyroglobulin (Tgb) is synthesized in thyroid follicular cells and secreted into the colloid. Iodination and coupling of tyrosine residues in Tgb produce T_3 and T_4 residues, which are released from Tgb by pinocytosis (endocytosis) and lysosomal action. The coupling of a monoiodotyrosine with a diiodotyrosine (DIT) to form triiodothyronine (T_3) is not depicted here.

The iodide concentrating or trapping process present in the plasma membrane of thyroid acinar cells creates iodide levels within the thyroid cell that are several hundredfold greater than those in the blood, depending on the current size of the total body iodide pool and the present need for new hormone synthesis.

In areas of the world in which the soil is deficient in iodide, hypothyroidism is prevalent. The thyroid gland enlarges (forms a goiter) in an attempt to produce more thyroid hormone. In the United States, table salt (NaCl) enriched with iodide (iodized salt) is used to prevent hypothyroidism caused by iodine deficiency.

The thyroid gland is unique in that it has the capacity to store large amounts of hormone as amino acid residues in thyroglobulin within its colloid space. This storage accounts for the low overall turnover rate of T_3 and T_4 in the body.

The rate of iodide transport is influenced by the absolute concentration of iodide within the thyroid cell. An internal autoregulatory mechanism decreases transport of iodide into the cell when the intracellular iodide concentration exceeds a certain threshold and increases transport when intracellular iodide falls below this threshold level.

The oxidation of intracellular iodide is catalyzed by thyroid peroxidase (located at the apical border of the thyroid acinar cell) in what may be a two-electron oxidation step forming I^+ (iodinium ion). Iodinium ion may react with a tyrosine residue in the protein thyroglobulin to form a tyrosine quinoid and then a 3'-monoiodotyrosine (MIT) residue. It has been suggested that a second iodide is added to the ring by similar mechanisms to form a 3,5-diiodotyrosine (DIT) residue. Because iodide is added to these organic compounds, iodination is also referred to as the "organification of iodide."

The biosynthesis of thyroid hormone proceeds with the coupling of an MIT and a DIT residue to form a triiodothyronine (T_3) residue or of two DIT residues to form a tetraiodothyronine (T_4) residue. T_3 and T_4 are stored in the thyroid follicle as amino acid residues in thyroglobulin. Under most circumstances, the T_4/T_3 ratio in thyroglobulin is approximately 13:1.

The plasma half-life of T_4 is approximately 7 days, and that of T_3 is 1 to 1.5 days. These relatively long plasma half-lives result from binding of T_3 and T_4 to several transport proteins in the blood. Of these transport proteins, thyroid-binding globulin (TBG) has the highest affinity for these hormones and carries approximately 70% of

bound T_3 and T_4 . Only 0.03% of total T_4 and 0.3% of total T_3 in the blood are in the unbound state. This free fraction of hormone has biologic activity because it is the only form that is capable of diffusing across target cell membranes to interact with intracellular receptors. The transport proteins, therefore, serve as a large reservoir of hormone that can release additional free hormone as the metabolic need arises.

The thyroid hormones are degraded in liver, kidney, muscle, and other tissues by deiodination, which produces compounds with no biologic activity.

2. SECRETION OF THYROID HORMONE

The release of T_3 and T_4 from thyroglobulin is controlled by thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH stimulates the endocytosis of thyroglobulin to form endocytic vesicles within the thyroid acinar cells (see Fig. 43.10). Lysosomes fuse with these vesicles, and lysosomal proteases hydrolyze thyroglobulin, releasing free T_4 and T_3 into the blood in a 10:1 ratio. In various tissues, T_4 is deiodinated, forming T_3 , which is the active form of the hormone.

TSH is synthesized in the thyrotropic cells of the anterior pituitary. Its secretion is primarily regulated by a balance between the stimulatory action of hypothalamic thyroid-releasing hormone (TRH) and the inhibitory (negative feedback) influence of thyroid hormone (primarily T_3) at levels above a critical threshold in the blood bathing the pituitary thyrotrophs. TSH secretion occurs in a circadian pattern, a surge beginning late in the afternoon and peaking before the onset of sleep. In addition, TSH is secreted in a pulsatile fashion with intervals of 2 to 6 hours between peaks.

TSH stimulates all phases of thyroid hormone synthesis by the thyroid gland, including iodide trapping from the plasma, organification of iodide, coupling of monoiodotyrosine and diiodotyrosine, endocytosis of thyroglobulin, and proteolysis of thyroglobulin to release triiodothyronine (T_3) and tetraiodothyronine (T_4) (see Fig. 43.10). In addition, the vascularity of the thyroid gland increases as TSH stimulates hypertrophy and hyperplasia of the thyroid acinar cells.

The predominant mechanism of action of TSH is mediated by binding of TSH to its specific receptor on the plasma membrane of the thyroid acinar cell, leading to an increase in the concentration of cytosolic cAMP. Recent evidence indicates, however, that TSH also increases the cellular levels of inositol trisphosphate and diacylglycerol, causing a rise in cytosolic Ca^{2+} within the thyroid cell.

The large protein thyroglobulin, which contains T_3 and T_4 in peptide linkage, is stored extracellularly in the colloid that fills the central space of each thyroid follicle. Each of the biochemical reactions that leads to the release and eventual secretion of T_3 and T_4 , such as those that lead to their formation in thyroglobulins, is TSH-dependent. Rising levels of serum TSH stimulate the endocytosis of stored thyroglobulin into the thyroid acinar cell. Lysosomal enzymes then cleave T_3 and T_4 from thyroglobulin. T_3 and T_4 are secreted into the bloodstream in response to rising levels of TSH.

As the free T_3 level in the blood bathing the thyrotrophs of the anterior pituitary gland rises, the feedback loop is closed. Secretion of TSH is inhibited until the free T_3 levels in the systemic circulation fall just below a critical level, which once again signals the release of TSH. This feedback mechanism ensures an uninterrupted supply of biologically active free T_3 in the blood (Fig. 43.11). High levels of T_3 also inhibit the release of TRH from the hypothalamus.

3. PHYSIOLOGIC EFFECTS OF THYROID HORMONE

Only those physiologic actions of thyroid hormone that influence fuel metabolism are considered here. It is important to stress the term *physiologic*, because the effects of supraphysiologic concentrations of thyroid hormone on fuel metabolism may not be simple extensions of their physiologic effects. In general, the following

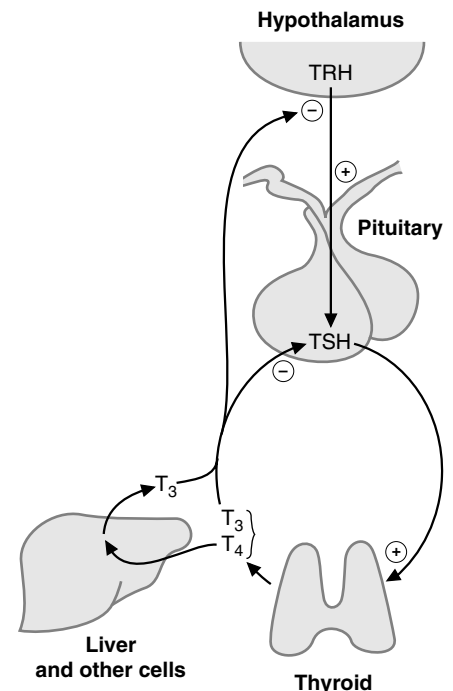


Fig. 43.11. Feedback regulation of thyroid hormone levels. TRH from the hypothalamus stimulates the release of TSH from the anterior pituitary, which stimulates the release of T_3 and T_4 from the thyroid. T_4 is converted to T_3 in the liver and other cells. T_3 and T_4 inhibit the release of TSH from the anterior pituitary and of TRH from the hypothalamus.



A patient presents with the following clinical and laboratory profile: the serum free and total T_3 and T_4 and the serum TSH levels are elevated, but the patient has symptoms of mild hypothyroidism, including a diffuse, palpable goiter. What single abnormality in the pituitary-thyroid-thyroid hormone target cell axis would explain all of these findings?



A generalized (i.e., involving all of the target cells for thyroid hormone in the body), but incomplete resistance of cells to the actions of thyroid hormone could explain the profile of the patient. In Refetoff's disorder, a mutation in the portion of the gene that encodes the ligand binding domain of the β -subunit of the thyroid hormone receptor protein causes a relative resistance to the suppressive action of thyroid hormone on the secretion of TSH by the thyrotrophs of the anterior pituitary gland. Therefore, the gland releases more TSH than normal into the blood. The elevated level of TSH causes an enlargement of the thyroid gland (goiter) as well as an increase in the secretion of thyroid hormone into the blood. As a result, the serum levels of both T_3 and T_4 rise in the blood. The increase in the secretion of thyroid hormone may or may not be adequate to fully compensate for the relative resistance of the peripheral tissues to thyroid hormone. If the compensatory increase in the secretion of thyroid hormone is inadequate, the patient may develop the signs and symptoms of hypothyroidism.



When present in excess, T_3 has severe catabolic effects that increase the flow of amino acids from muscle into the blood and eventually to the liver.

comments apply to the effects of thyroid hormone on energy metabolism in individuals with normal thyroid hormone levels in the blood.

i. Effects of Thyroid Hormone on The Liver

Several of the actions of thyroid hormone affect carbohydrate and lipid metabolism in the liver. Thyroid hormone increases glycolysis and cholesterol synthesis and increases the conversion of cholesterol to bile salts. Through its action of increasing the sensitivity of the hepatocyte to the gluconeogenic and glycogenolytic actions of epinephrine, T_3 indirectly increases hepatic glucose production (permissive or facilitatory action). Because of its ability to sensitize the adipocyte to the lipolytic action of epinephrine, T_3 increases the flow of fatty acids to the liver and thereby indirectly increases hepatic triacylglycerol synthesis. The concurrent increase in the flow of glycerol to the liver (as a result of increased lipolysis) further enhances hepatic gluconeogenesis.

ii. Effects of Thyroid Hormone on The Adipocyte

T_3 has an amplifying or facilitatory effect on the lipolytic action of epinephrine on the fat cell. Yet thyroid hormone has a bipolar effect on lipid storage, because it increases the availability of glucose to the fat cell, which serves as a precursor for fatty acid and glycerol 3-phosphate synthesis. The major determinant of the rate of lipogenesis, however, is not T_3 , but rather the amount of glucose and insulin available to the adipocyte for triacylglycerol synthesis.

iii. Effects of Thyroid Hormone on Muscle

In physiologic concentrations, T_3 increases glucose uptake by muscle cells. It also stimulates protein synthesis, and, therefore, growth of muscle, through its stimulatory actions on gene expression.

In physiologic concentrations, thyroid hormone sensitizes the muscle cell to the glycogenolytic actions of epinephrine. Glycolysis in muscle is increased by this action of T_3 .

iv. Effects of Thyroid Hormone on The Pancreas

Thyroid hormone increases the sensitivity of the β cells of the pancreas to those stimuli that normally promote insulin release and is required for optimal insulin secretion.

4. CALORIGENIC EFFECTS OF THYROID HORMONE

The oxidation of fuels converts approximately 25% of the potential energy present in the foods ingested by humans to ATP. This relative inefficiency of the human "engine" leads to the production of heat as a consequence of fuel utilization. This inefficiency, in part, allows homeothermic animals to maintain a constant body temperature in spite of rapidly changing environmental conditions. The acute response to cold exposure is shivering, which is probably secondary to increased activity of the sympathetic nervous system in response to this "stressful" stimulus.

Thyroid hormone participates in this acute response by sensitizing the sympathetic nervous system to the stimulatory effect of cold exposure. The ability of T_3 to increase heat production is related to its effects on the pathways of fuel oxidation, which both generate ATP and release energy as heat. The effects of T_3 on the sympathetic nervous system increase the release of norepinephrine. Norepinephrine stimulates the uncoupling protein thermogenin in brown adipose tissue (BAT), resulting in increased heat production from the uncoupling of oxidative phosphory-

lation (see Chapter 21). Very little residual brown fat persists in normal adult human beings, however.

Norepinephrine also increases the permeability of BAT and skeletal muscle to sodium. Because an increase of intracellular Na^+ is potentially toxic to cells, Na^+, K^+ -ATPase is stimulated to transport Na^+ out of the cell in exchange for K^+ . The increased hydrolysis of ATP by Na^+, K^+ -ATPase stimulates the oxidation of fuels and the regeneration of more ATP and heat from oxidative phosphorylation. Over a longer time course, thyroid hormone also increases the level of Na^+, K^+ -ATPase and many of the enzymes of fuel oxidation. Because even at normal room temperature ATP utilization by Na^+, K^+ -ATPase accounts for 20% or more of our basal metabolic rate (BMR), changes in its activity can cause relatively large increases in heat production.

Thyroid hormone also may increase heat production by stimulating ATP utilization in futile cycles (in which reversible ATP-consuming conversions of substrate to product and back to substrate use fuels and, therefore, produce heat).

F. Gastrointestinal-Derived Hormones Affecting Fuel Metabolism

In addition to insulin and the counterregulatory hormones discussed, a variety of peptides synthesized in the endocrine cells of the pancreatic islets, or the cells of the enteric nervous system, or the endocrine cells of the stomach, small bowel and large bowel, as well as certain cells of the central and peripheral nervous system, influence fuel metabolism directly. Some of these peptides and their tissue of origin, their actions on fuel metabolism, and the factors that stimulate (or suppress) their secretion are listed in Table 43.4. In addition to these peptides, others such as gastrin, motilin, pancreatic polypeptide (PP), peptide YY (PYY), and secretin may also influence fuel metabolism but by indirect effects on the synthesis or secretion of insulin or the counterregulatory hormones (Table 43.5). For example, gastrin induces gastric acid secretion, which ultimately affects nutrient absorption and metabolism. Motilin, secreted by enteroendocrine M cells of the proximal small bowel, stimulates gastric and pancreatic enzyme secretion, which, in turn, influences nutrient digestion. Pancreatic polypeptide (PP) from the pancreatic islets reduces gastric emptying and slows upper intestinal motility. Peptide YY (PYY) from the alpha cells in the mature pancreatic islets inhibits gastric acid secretion. Finally, secretin, produced by the enteroendocrine S cells in the proximal small bowel, regulates pancreatic enzyme secretion and inhibits gastrin release and gastric acid secretion. Although not directly influencing fuel metabolism, these “gut” hormones have a significant impact on how ingested nutrients are digested and prepared for absorption. If digestion or absorption of fuels is altered through a disturbance in the delicate interplay of all of the peptides, fuel metabolism will be altered as well.

Several of these gastrointestinal peptides such as GLP-1 and GIP do not act as direct insulin secretagogues when blood glucose levels are normal but do so after a meal large enough to cause an increase in the blood glucose concentration.

The release of these peptides may explain why the modest postprandial increase in serum glucose seen in normal subjects has a relatively robust stimulatory effect on insulin release, whereas a similar glucose concentration *in vitro* elicits a significantly smaller increase in insulin secretion. Likewise, this effect (certain factors potentiating insulin release), known as the “incretin effect,” could account for the greater beta cell response seen after an oral glucose load as opposed to that seen after the administration of glucose intravenously.



In hypothyroid patients, insulin release may be suboptimal, although glucose intolerance on this basis alone is uncommon.

In hyperthyroidism, the degradation and the clearance of insulin are increased. These effects, plus the increased demand for insulin caused by the changes in glucose metabolism, may lead to varying degrees of glucose intolerance in these patients (a condition called metathyroid diabetes mellitus). The patient with uncomplicated hyperthyroidism, however, rarely develops significant diabetes mellitus.

Table 43.4. Gastrointestinal-Derived Hormones Directly Affecting Fuel Metabolism

Hormone	Primary Cell/ Tissue of Origin	Actions	Secretory Stimuli (and Inhibitors)
Amylin	Pancreatic beta cell, endocrine cells of stomach and small intestine	1. Inhibits arginine-stimulated and postprandial glucagon secretion 2. Inhibits insulin secretion	Co-secreted with insulin in response to oral nutrients
Calcitonin gene-related peptide (CGRP)	Enteric neurons and enteroendocrine cells of the rectum	Inhibits insulin secretion	Oral glucose intake and gastric acid secretion
Galanin	Nervous system, pituitary, neurons of gut, pancreas, thyroid, and adrenal gland	Inhibits secretion of insulin, somatostatin, enteroglucagon, pancreatic polypeptide, and others	Intestinal distension
Gastric inhibitory polypeptide/ glucose-dependent insulinotropic polypeptide (GIP)	Neuroendocrine K cells of duodenum and proximal jejunum	1. Increases insulin release via an "incretin" effect 2. Regulates glucose and lipid metabolism	Oral nutrient ingestion, especially long-chain fatty acids
Gastrin-releasing peptide (GRP)	Enteric nervous system and pancreas	Stimulates release of cholecystokinin; GIP, gastrin, glucagon, GLP-1, GLP-2, and somatostatin	
Ghrelin	Central nervous system, stomach, small intestine, and colon	Stimulates growth hormone release	Fasting
Glucagon	Pancreatic alpha cell, central nervous system	Primary counter-regulatory hormone that restores glucose levels in hypoglycemic state (increases glycogenolysis and gluconeogenesis as well as protein-lipid flux in liver and muscle)	Neural and humoral factors released in response to hypoglycemia
Glucagon-like peptide-1 (GLP-1)	Enteroendocrine L cells in ileum, colon, and central nervous system	1. Enhances glucose disposal after meals by inhibiting glucagon secretion and stimulating insulin secretion 2. Acts through second messengers in beta cells to increase sensitivity of these cells to glucose (an incretin)	1. Oral nutrient ingestion 2. Vagus nerve 3. GRP and GIP 4. Somatostatin inhibits secretion
Glucagon-like peptide-2 (GLP-2)	The same as for GLP-1	Stimulates intestinal hexose transport	Same as GLP-1
Neuropeptide Y	Central and peripheral nervous system, pancreatic islet cells	Inhibits glucose-stimulated insulin secretion	Oral nutrient ingestion and activation of sympathetic nervous system
Neurotensin (NT)	Small intestinal N cells (especially ileum), enteric nervous system, adrenal gland, pancreas	In brain, modulates dopamine neurotransmission and anterior pituitary secretions	1. Luminal lipid nutrients 2. GRP 3. Somatostatin inhibits secretion
Pituitary adenylate cyclase activating peptide (PACAP)	Brain, lung, and enteric nervous system	Stimulates insulin and catecholamine release	Activation of central nervous system
Somatostatin	Central nervous system, pancreatic delta cells, and enteroendocrine delta cells	1. Inhibits secretion of insulin, glucagon and PP (islets), and gastrin, secretin, GLP-1, and GLP-2 (in gut) 2. Reduces carbohydrate absorption from gut lumen	1. Luminal nutrients 2. GLP-1 3. GIP 4. PACAP 5. VIP 6. Beta-adrenergic stimulation
Vasoactive intestinal peptide (VIP)	Widely expressed in the central and peripheral nervous systems	May regulate release of insulin and pancreatic glucagon	1. Mechanical stimulation of gut 2. Activation of central and peripheral nervous systems

Table 43.5. Gastrointestinal-Derived Hormones Indirectly Affecting Fuel Metabolism

Hormone	Primary Cell/ Tissue of Origin	Actions	Secretory Stimuli (and Inhibitors)
Cholecystokinin (CCK)	Enteroendocrine I cells, enteric nerves, others	<ol style="list-style-type: none"> 1. Inhibits proximal gastric motility 2. Increases antral and pyloric contractions 3. Regulates nutrient-stimulated enzyme secretion and gallbladder contraction 4. Increases postprandial satiety 	<ol style="list-style-type: none"> 1. Oral nutrient ingestion 2. GGRP and bombesin from gut
Gastrin	Enteroendocrine G cells of the stomach, duodenal bulb, and other cells	Induces gastric acid secretion	<ol style="list-style-type: none"> 1. Luminal contents, especially aromatic amino acids, calcium, coffee, and ethanol 2. Vagus nerve stimulation; activation of beta-adrenergic and GABA neurons 3. Somatostatin inhibits secretion
Motilin	Enteroendocrine M cells in upper small bowel and other cells	<ol style="list-style-type: none"> 1. Induces phase III contractions in stomach 2. Stimulates gastric secretion and pancreatic enzyme secretion 3. Induces gallbladder contraction 	<ol style="list-style-type: none"> 4. Duodenal alkalization 5. Gastric distension 6. Secretion suppressed by nutrients in duodenum
Pancreatic polypeptide (PP)	Endocrine cells in periphery of islets in the head of the pancreas	<ol style="list-style-type: none"> 1. Reduces CCK-mediated gastric acid secretion 2. Increases intestinal transit time (slows motility) 	Stimulated by intraluminal nutrients, hypoglycemia, and vagal nerve stimulation
Peptide YY (PYY)	Enteroendocrine cells, developing pancreas; alpha cells in mature islets	<ol style="list-style-type: none"> 1. Inhibits both gastric acid secretion and gastric motility 2. Slows intestinal motility 3. Inhibits pancreatic exocrine secretion 	<ol style="list-style-type: none"> 1. Oral nutrient ingestion 2. Bile acids and fatty acids 3. Amino acids in colon
Secretin	Enteroendocrine S cells in upper small bowel	<ol style="list-style-type: none"> 1. Stimulates pancreatic and biliary bicarbonate and water secretion 2. Regulates pancreatic enzyme secretion 3. Inhibits postprandial gastric emptying, gastrin release, and gastric acid secretion 	<ol style="list-style-type: none"> 1. Gastric acid, bile salts, fatty acids, peptides, and ethanol 2. Somatostatin inhibits secretion
Tachykinins	Neurons localized in the submucous and myenteric plexuses; enterochromaffin cells in gut epithelium	<ol style="list-style-type: none"> 1. Regulates vasomotor and gastrointestinal smooth muscle contraction 2. Mucus secretion and water absorption 	Direct and indirect activation of neurons in submucosa and myenteric plexuses in gut epithelium
Thyrotropin-releasing hormone (TRH)	Enteric nervous system, colon, G cells of stomach, and pancreatic beta cell	<ol style="list-style-type: none"> 1. Suppresses hormone-stimulated gastric acid secretion 2. Inhibits cholesterol synthesis within the intestinal mucosa 	In the stomach, histamine and serotonin stimulate secretion

G. Neural Factors Controlling Insulin and Counter-regulatory Hormone Secretion

Although beyond the scope of this text, the gastrointestinal neuroendocrine system is briefly described with regard to its effects on fuel metabolism. The pancreatic islet cells are innervated by both the adrenergic and the cholinergic limbs of the autonomic nervous system. Although stimulation of both the sympathetic and the parasympathetic systems increases glucagon secretion, insulin secretion is increased by vagus nerve fibers and suppressed by sympathetic fibers via the alpha-adrenoreceptors. Evidence also suggests that the sympathetic nervous system indirectly regulates pancreatic beta cell function through stimulation or suppression of the secretion of somatostatin, beta₂-adrenergic receptor number, and the neuropeptides, neuropeptide Y and galanin.

A tightly controlled interaction between the hormonal and neural factors that control nutrient metabolism is necessary to maintain normal fuel and, hence, energy homeostasis.



To establish the diagnosis of a secretory tumor of an endocrine gland, one must first demonstrate that basal serum levels of the hormone in question are regularly elevated. More importantly, one must show that the hypersecretion of the hormone (and, hence, its elevated level in the peripheral blood) cannot be adequately inhibited by “maneuvers” that are known to suppress secretion from a normally functioning gland (i.e., one must show that the hypersecretion is “autonomous”).

To ensure that both the basal and the postsuppression levels of the specific hormone to be tested will reflect the true secretory rate of the suspected endocrine tumor, all of the known factors that can stimulate the synthesis of the hormone must be eliminated. For GH, for example, the secretagogues (stimulants to secretion) include nutritional factors; the patient’s level of activity, consciousness, and stress; and certain drugs. GH secretion is stimulated by a high-protein meal or by a low level of fatty acids or of glucose in the blood. Vigorous exercise, stage III–IV sleep, psychological and physical stress, and levodopa, clonidine, and estrogens also increase GH release.

The suppression test used to demonstrate the autonomous hypersecretion of GH involves giving the patient an oral glucose load and, subsequently, measuring GH levels. A sudden rise in blood glucose suppresses serum GH to 2 ng/mL or less in normal subjects, but not in patients with active acromegaly.

If one attempts to demonstrate autonomous hypersecretion of GH in a patient suspected of having acromegaly, therefore, before drawing the blood for both the basal (pre-glucose load) serum GH level and the post-glucose load serum GH level, one must be certain that the patient has not eaten for 6–8 hours, has not done vigorous exercise for at least 4 hours, remains fully awake during the entire testing period (in a non-stressed state to the extent possible), and has not taken any drugs known to increase GH secretion for at least 1 week.

Under these carefully controlled circumstances, if both the basal and postsuppression serum levels of the suspect hormone are elevated, one can conclude that autonomous hypersecretion is probably present. At this point, localization procedures (such as an MRI of the pituitary gland in an acromegalic suspect) are performed to further confirm the diagnosis.

CLINICAL COMMENTS



One of the functions of cortisol is to prepare the body to deal with periods of stress. In response to cortisol, the body re-sorts its fuel stores so that they can rapidly be made available for the “fight or flight” response to the alarm signal sounded by epinephrine. Cortisol causes gluconeogenic substrates to move from peripheral tissues to the liver, where they are converted to glucose and stored as glycogen. The release of epinephrine stimulates the breakdown of glycogen, increasing the supply of glucose to the blood. Thus fuel becomes available for muscle to fight or flee.

Cushing’s “disease,” the cause of **Corti Solemia’s** current problems, results from prolonged hypersecretion of ACTH from a benign pituitary tumor. ACTH stimulates the adrenal cortex to produce cortisol, and blood levels of this steroid hormone rise.

Other nonpituitary causes of Cushing’s syndrome, however, include a primary tumor of the adrenal cortex secreting excessive amounts of cortisol directly into the bloodstream. This disorder also can result from the release of ACTH from secretory nonendocrine nonpituitary neoplasms (“ectopic” ACTH syndrome). Cushing’s syndrome is often caused by excessive doses of synthetic GCs used to treat a variety of disorders because of their potent anti-inflammatory effects (iatrogenic Cushing’s syndrome).

The diabetogenic potential of chronically elevated GH levels in the blood is manifest by the significant incidence of diabetes mellitus (25%) and impaired glucose tolerance (33%) in patients with acromegaly, such as **Sam Atotrope**. Yet, under normal circumstances, physiologic concentrations of GH (as well as cortisol and thyroid hormone) have a facilitatory or permissive effect on the quantity of insulin released in response to hyperglycemia and other insulin secretagogues. This “proinsular” effect is probably intended to act as a “brake” to dampen any potentially excessive “contrain-sular” effects that increments in GH and the other counterregulatory hormones exert.

BIOCHEMICAL COMMENTS



Most hormones are present in body fluids in picomolar to nanomolar amounts, requiring highly sensitive assays to determine their concentration in the blood or urine. Radioimmunoassays (RIAs), developed in the 1960s, use an antibody, generated in animals, against a specific antigen (the hormone to be measured). Determining the concentration of the hormone in the sample involves incubating the plasma or urine sample with the antibody and then quantifying the level of antigen–antibody complex formed during the incubation by one of several techniques.

The classic RIA uses very high-affinity antibodies, which have been fixed (immobilized) on the inner surface of a test tube, a Teflon bead, or a magnetized particle. A standard curve is prepared, using a set amount of the antibody and various known concentrations of the unlabeled hormone to be measured. In addition to a known concentration of the unlabeled hormone, each tube contains the same small, carefully measured amount of radiolabeled hormone. The labeled hormone and the unlabeled hormone compete for binding to the antibody. The higher the amount of unlabeled hormone in the sample, the less radiolabeled hormone is bound. A standard curve is plotted (Fig. 43.12). The unknown sample from the patient’s blood or urine, containing the unlabeled hormone to be measured, is incubated with the immobilized antibody in the presence of the same small, carefully measured amount of radiolabeled hormone. The amount of radiolabeled hormone bound to the antibody is determined, and the standard curve is used to quantitate the amount of unlabeled hormone in the patient sample.

The same principle is used in immunoradiometric assays (IRMAs), but with this technique the antibody, rather than the antigen to be measured, is radiolabeled.

The sensitivity of RIAs can be enhanced using a “sandwich technique.” This method uses two different monoclonal antibodies (antibodies generated by a single clone of plasma cells rather than multiple clones), each of which recognizes a different specific portion of the hormone’s structure. The first antibody, attached to a solid support matrix such as a plastic culture dish, binds the hormone to be assayed. After exposure of the patient sample to this first antibody, the excess plasma is washed away, and the second antibody (which is radiolabeled) is then incubated with the first antibody–hormone complex. The amount of binding of the second (labeled) antibody to the first complex is proportional to the concentration of the hormone in the sample.

The sandwich technique can be improved even further if the second antibody is attached to an enzyme, such as alkaline phosphatase. The enzyme rapidly converts an added colorless substrate into a colored product, or a nonfluorescent substrate into a highly fluorescent product. These changes can be quantitated if the degree of change in color or fluorescence is proportional to the amount of hormone present in the patient sample. Less than a nanogram (10^{-9} g) of a protein can be measured by such an enzyme-linked immunosorbent assay (ELISA).

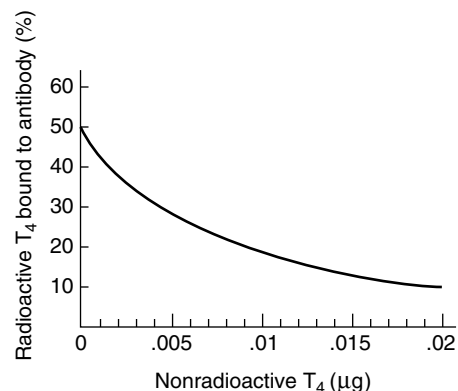


Fig. 43.12. Standard curve for a radioimmunoassay. A constant amount of radioactive T_4 is added to a series of tubes, each of which contains a different amount of nonradioactive T_4 . The amount of radioactive hormone that binds to an antibody specific for the hormone is measured and plotted against the nonradioactive hormone concentration. When more nonradioactive T_4 is present in the tube, less radioactive T_4 binds to the antibody.

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REVIEW QUESTIONS—CHAPTER 43

- As a third-year medical student, you examine your first patient. You find that he is 52 years old, has a round face, acne, and a large hump of fat on the back of his neck. He complains that he is too weak to mow his lawn. His fasting blood glucose level is 170 mg/dL (reference range = 80–100 mg/dL). Plasma cortisol levels are 62 μ g/mL (reference range = 3–31 μ g/mL). Plasma ACTH levels are 0 pg/mL (reference range = 0–100 pg/mL).

Based on the information given above, if the patient’s problem is attributable to a single cause, the most likely diagnosis is which of the following?

- Non–insulin-dependent diabetes mellitus
- Insulin-dependent diabetes mellitus
- A secretory tumor of the anterior pituitary
- A secretory tumor of the posterior pituitary
- A secretory tumor of the adrenal cortex

2. A woman was scheduled for a growth hormone suppression test. If each of the following events occurred the morning of the test, which one of the events would be most likely to cause a decrease in growth hormone levels?
- (A) She ate four large doughnuts for breakfast.
 - (B) She was on estrogen replacement therapy and took her tablets after breakfast.
 - (C) While unlocking her car, she was chased by the neighbor's vicious dog.
 - (D) She fell asleep at the start of the test and slept soundly until it was completed 1.5 hours later.
 - (E) She forgot to eat her breakfast before the test.
3. A dietary deficiency of iodine would lead to which of the following?
- (A) A direct effect on the synthesis of thyroglobulin on ribosomes
 - (B) An increased secretion of thyroid stimulatory hormone (TSH)
 - (C) Decreased production of thyrotropin releasing hormone (TRH)
 - (D) Increased heat production
 - (E) Weight loss
4. A woman whose thyroid gland was surgically removed was treated with 0.10 mg thyroxine daily (tablet form). After 3 months of treatment, serial serum TSH levels ranged between 10 and 15 MIU/mL (reference range = 0.3 – 5.0 MIU/mL). She complained of fatigue, weight gain, and hoarseness. Her dose of thyroid hormone should be adjusted in which direction?
- (A) Increased
 - (B) Decreased
 - (C) Remain the same

The next question is based on the following scenario:

A patient complains of nervousness, palpitations, sweating, and weight loss without loss of appetite, and has a goiter. Suspecting a defect in thyroid function, the physician orders a total serum T_4 . The test is performed by radioimmunoassay. The standard curve for the assay, which measures T_4 in 0.1 mL serum, is shown in Fig. 43.12. Normal levels of T_4 = 4–10 $\mu\text{g/dL}$. In an assay of 0.1 mL of the patient's serum, 15% of the radioactive T_4 was bound by the antibody.

5. According to the radioimmunoassay, the approximate blood level of T_4 is which of the following?
- (A) 0.015 $\mu\text{g/dL}$
 - (B) 0.15 $\mu\text{g/dL}$
 - (C) 15 $\mu\text{g/dL}$
 - (D) 20 $\mu\text{g/dL}$
 - (E) 30 $\mu\text{g/dL}$