Chapter 10. Endocrine Integration of Energy and Electrolyte Balance

Objectives

- Identify the normal range of plasma glucose concentrations and the hormonal regulation of its metabolism, storage, and mobilization.
- Identify the specific roles of insulin, glucagon, glucocorticoids, catecholamines, growth hormone, and thyroid hormone in the regulation of energy substrate utilization, storage, and mobilization.
- Describe the hormonal regulation of energy substrate metabolism during the fed and fasted states and understand the consequences of its dysregulation.
- Identify the mechanisms involved in the maintenance of long-term energy balance.
- Identify the normal range of dietary sodium intake, its body distribution, and routes of excretion. Explain the roles of antidiuretic hormone, aldosterone, angiotensin, and atrial natriuretic hormone in the regulation of sodium balance.
- Identify the normal range of dietary potassium intake, its body distribution, and routes of excretion. Explain the hormonal regulation of plasma potassium concentration, distribution, and balance in the acute and chronic settings.
- Identify the normal range of dietary calcium intake, its body distribution, and routes of excretion. Explain the hormonal regulation of plasma calcium concentration through bone resorption, renal excretion, and intestinal absorption.
- Identify the normal range of dietary phosphate intake, its body distribution, and routes of excretion. Explain the hormonal regulation of plasma phosphate concentration through exchange with bone, renal excretion, and dietary intake and absorption.

Endocrine Integration of Energy and Electrolyte Balance: Introduction

In the first chapter, several of the key functions of the endocrine system that maintain homeostasis were outlined. Subsequent chapters described the specific physiologic effects of individual hormones, the mechanisms that regulate their production and release, and the consequences of isolated excess or deficiency. The presentation of this material would not be complete without an attempt to integrate some of these actions into the overall regulation of specific functions. Although a complete description of the integrative control of physiologic function is beyond the scope of this book, this chapter integrates many of the concepts already presented. It describes how the different arms of the neuroendocrine system interact to regulate and maintain basic functions, which include energy substrate balance, blood volume and blood pressure, and preservation of bone mineral density (BMD). Finally, it presents an integrated discussion of the neuroendocrine mechanisms involved in mediating the stress response.

Neuroendocrine Regulation of Energy Storage, Mobilization, and Utilization
Two distinct phases directly related to the ingestion of a meal alternate throughout the day in the regulation of energy metabolism. The fed state reflects overall anabolic metabolism, during which energy is stored in the form of energy-rich compounds (adenosine triphosphate [ATP], phosphocreatinine), glycogen, fat, and proteins. The fasted or catabolic phase is the period during which endogenous energy sources are utilized.

The anabolic and catabolic phases alternate to preserve adequate glucose supply to the brain as well as sufficient energy to maintain body functions, such as thermoregulation (maintaining a constant core temperature), food digestion, and physical activity. The 2 hormones at the core of maintaining this balance are insulin and glucagon (see Chapter 7); in particular, their ratio plays a critical role in the dynamic regulation of substrate metabolism (summarized in Table 10–1). However, several other established and newly discovered hormones participate in the regulation of energy metabolism to different extents, according to age, sex, nutritional state, and metabolic demands of the individual.

Table 10–1. Regulation of Metabolic Processes by Insulin/Glucagon Ratios

<table>
<thead>
<tr>
<th>Anabolic ↑ I : G</th>
<th>Metabolic process</th>
<th>Catabolic ↓ I : G</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>Glycogen synthesis (liver and muscle)</td>
<td>↓</td>
</tr>
<tr>
<td>↓</td>
<td>Glycogen breakdown</td>
<td>↑</td>
</tr>
<tr>
<td>↓</td>
<td>Gluconeogenesis</td>
<td>↑</td>
</tr>
<tr>
<td>↑</td>
<td>Triglyceride synthesis (hepatocytes and adipose tissue)</td>
<td>↓</td>
</tr>
<tr>
<td>↑</td>
<td>Muscle protein synthesis</td>
<td>↓</td>
</tr>
<tr>
<td>↑</td>
<td>Lipogenesis and triglyceride formation</td>
<td>↓</td>
</tr>
<tr>
<td>↓</td>
<td>Lipolysis</td>
<td>↑</td>
</tr>
<tr>
<td>↓</td>
<td>Free fatty acid oxidation</td>
<td>↑</td>
</tr>
<tr>
<td>↓</td>
<td>Ketone body formation</td>
<td>↑</td>
</tr>
<tr>
<td>↓</td>
<td>Muscle proteolysis</td>
<td>↑</td>
</tr>
</tbody>
</table>

G, glucagon; I, insulin.

The autonomic nervous system interacts with the endocrine system in the modulation of glucose and fat metabolism. Hence, the system is in fact under neuroendocrine regulation. The autonomic nervous system exerts its effects both directly and indirectly. For example, activation of the sympathetic nervous system through norepinephrine release directly stimulates skeletal muscle glycogenolysis and hepatic glucose output. The indirect effects of the autonomic nervous system are exemplified by sympathetic activation of the adrenal medulla (see Chapter 6), stimulating the release of epinephrine. Epinephrine stimulates the pancreatic release of glucagon and suppresses the release of insulin, resulting in an increase in the glucagon to insulin ratio and an overall increase in hepatic glucose production.

To simplify the discussion of the neuroendocrine regulation of substrate metabolism, a brief summary of overall substrate regulation and the principal hormones involved will be presented as they pertain to the fed (anabolic) and fasted (catabolic) states.

**Neuroendocrine Regulation of Energy Metabolism during the Fed State**

**Glucose**

Blood glucose regulation occurs through interactions among hormonal, neural, and hepatic autoregulatory mechanisms. As described in detail in Chapter 7, the pancreatic hormones insulin and glucagon play central roles in the tight control of blood glucose concentrations. Following a meal
(postprandial state), in response to the increase in pancreatic insulin release, glucose uptake is increased in muscle, fat, and the hepatosplanchnic bed; hepatic glucose output is suppressed; and glycogen synthesis is increased.

Glucose disposal by insulin-sensitive tissues is regulated initially by an increase in glucose transport and enzyme phosphorylation leading to the activation of glycogen synthase, phosphofructokinase, and pyruvate dehydrogenase (see Figure 7–5). The majority of insulin-stimulated glucose taken up is stored as glycogen. Hormonally induced changes in intracellular fructose 2,6-bisphosphate concentrations play a key role in muscle glycolytic flux and both glycolytic and gluconeogenic flux in the liver.

Fat

Most of the body's energy reserve is stored in adipose tissue in the form of triglycerides. During periods of caloric excess or abundance, fat is stored in the form of triacylglycerol in the adipocytes. The principal hormone involved in lipogenesis is insulin, through activation of lipogenic and glycolytic enzymes. Opposing the effects of insulin are growth hormone (GH; discussed in Chapter 3) and leptin (described later), which inhibit lipogenesis (Figure 10–1). The balance between lipogenesis and lipolysis followed by fatty acid oxidation determines the overall accumulation of body fat.

![Figure 10–1.](image)

Relevance to health & disease
- Excess fat storage
  - Metabolic syndrome
  - Insulin resistance
  - ↑ Risk of cardiovascular disease
- Excess proteolysis
  - Loss of lean body mass
  - ↑ Disease morbidity & mortality
- Diseases of glycogen storage or degradation
  - Liver: hypoglycemia
  - Muscle: weakness

Hormonal factors controlling fat, protein, and carbohydrate (CHO) stores and balance. Adipose, protein, and carbohydrate (CHO in the form of glycogen) stores are the result of balanced synthesis and degradation under hormonal regulation by insulin (INS), growth hormone (GH), leptin, testosterone (T), epinephrine (Epi), thyroid hormone (TH), insulin-like growth factor 1 (IGF-1), and cortisol (Cort). Excess, deficiencies, or impaired regulation of adipose, protein, and carbohydrate stores have direct implications on health and disease as illustrated above.
Protein

The whole-body protein pool, as well as that of individual tissues, is determined by the balance between protein synthesis and degradation (see Figure 10–1). These in turn are principally regulated by interactions among hormonal, nutritional, neural, and inflammatory mediators. Hormonally, regulation of protein metabolism is predominantly under the influence of insulin, GH, and insulin-like growth factor-1 (IGF-1). During the fed state, insulin acts primarily to inhibit proteolysis, and GH stimulates protein synthesis. IGF-1 has antiproteolytic effects during the postabsorptive state that progress to stimulation of protein synthesis in the fed state or when amino acids are provided. GH and testosterone are of particular importance during growth and development, as well as during adulthood and senescence. Thyroid hormones are also required for normal growth and development. Thyroid hormones stimulate bone growth indirectly by increasing secretion of GH and IGF-1 and directly by activating gene transcription.

Neuroendocrine Regulation of Energy Metabolism during the Fasted State

During the fasted postabsorptive state, catabolism of stored energy sources provides the energy required for bodily functions. The total amount of energy produced per unit of time by a given individual is referred to as the metabolic rate. The amount of energy expended by an awake, resting individual, measured 12–14 hours following the last meal, at normal (or thermoneutral) body temperature is called the basal metabolic rate (BMR). The BMR is the amount of energy required to maintain breathing, brain activity, enzymatic activity, and other functions without any physical movement of the individual. Any deviation from the basal condition, such as changes in body temperature (fever or hypothermia), the level of activity of the individual (exercise or sleeping), or time from the last meal (fed or fasted), will affect the metabolic rate. In addition, BMR can be directly affected by hormone action, particularly thyroid hormones, which increase body temperature and increase Na⁺/K⁺-adenosine triphosphatase (ATPase) activity, resulting in an increase in the BMR. In a healthy individual, BMR averages 2000 kcal/d. Hence, the recommended dietary allowance of calories is derived from the BMR, age, sex, and level of activity of any given individual. The BMR can be estimated clinically by measuring the amount of oxygen consumed with the use of indirect calorimetry.

Glucose

In the resting postabsorptive state, release of glucose from the liver through glycogenolysis and gluconeogenesis is the key regulated process. During fasting, hepatic glucose production is increased and peripheral glucose utilization is inhibited. Initially, hepatic glucose output is derived from breakdown of hepatic glycogen stores (a maximum of 70–80 g in humans) through glycogenolysis. Following an overnight fast, glycogenolysis provides approximately 50% of the overall hepatic glucose output. As hepatic glycogen stores are depleted during a period of prolonged fasting (approximately 60 hours), the contribution of glycogenolysis to hepatic glucose output becomes negligible, with hepatic gluconeogenesis predominating. Glycogenolysis depends on the relative activities of glycogen synthase and phosphorylase, the latter being the more important (see Figure 7–5). Gluconeogenesis is regulated by the activities of fructose-1,6-diphosphatase, phosphoenolpyruvate carboxykinase, pyruvate kinase, and pyruvate dehydrogenase, and by the availability of the principal gluconeogenic precursors, lactate, glycerol, glutamine, and alanine.

A smaller, yet significant amount (approximately 25%) of systemic glucose production in the postabsorptive state is derived from renal gluconeogenesis. The proximal tubule cells produce glucose at a rate similar to that of glucose utilization by the renal medulla. Overall, the kidney is not a net producer of glucose. Thus, in the postabsorptive state, blood glucose homeostasis is the result of hormonal regulation of glycogenolysis, gluconeogenesis, and glucose uptake.
Fat

The amount of energy stored as triglycerides in adipose tissue is substantial. For example, an adult with 15 kg of body fat has enough energy to support the whole body energy requirements (8.37 MJ; 2000 kcal) for about 2 months. After an overnight fast, most of the resting energy requirement is provided by oxidation of fatty acids derived from adipose tissue. Lipolysis in adipose tissue is mostly dependent on the concentrations of hormones (epinephrine stimulates lipolysis, and insulin inhibits lipolysis). During a period of acute energy deprivation or prolonged starvation, lipolysis mobilizes triglycerides, providing nonesterified fatty acids as energy substrates for tissues such as muscle, heart, and liver; and substrates for glucose (glycerol) and lipoprotein (free fatty acids) synthesis to the liver. Unlike most other tissues, the brain cannot utilize fatty acids for energy when blood glucose levels become compromised. In this case, ketone bodies (discussed in Chapter 7) provide the brain with an alternative source of energy, amounting to nearly two-thirds of the brain’s energy needs during periods of prolonged fasting and starvation.

The release of glycerol and free fatty acids from adipose tissue is under negative regulation by insulin and is stimulated primarily by catecholamines (see Chapter 7). During fasting, plasma insulin levels decrease and plasma GH and glucagon both increase. As the fasting period progresses, or more frequently during periods of acute glucose deficiency (insulin-induced hypoglycemia) or increased energy demand (as with strenuous exercise), catecholamines play an important role in the stimulation of lipolysis.

Protein

Unlike excess fat and glucose, which are stored as fat and glycogen in adipose tissue, liver, and muscle, there is no storage pool for body protein. Therefore, under catabolic conditions, essential proteins are degraded. Glucagon, cortisol, and epinephrine together favor muscle protein breakdown and hepatic amino acid uptake, some of which can be utilized for gluconeogenesis (see Figure 10–1). The effects of glucagon are predominantly mediated through increased hepatic uptake of amino acids. Epinephrine increases production of the gluconeogenic amino acid alanine by muscle and its uptake by the splanchnic bed. Prolonged changes in either the protein synthetic or degradative processes (or both) leading to loss of lean body mass have been shown to increase morbidity and mortality from several diseases, including cancer and acquired immunodeficiency syndrome (AIDS).

Counterregulatory Hormone Effects

Glucagon

Glucagon plays a primary role in energy metabolism. This hormone primarily stimulates hepatic glycogenolysis, as well as gluconeogenesis resulting in an overall increase in hepatic glucose output.

Growth Hormone and Cortisol

GH and cortisol facilitate glucose production and limit glucose utilization, but neither of them plays a critical role in the acute counterregulatory response to a hypoglycemic episode. Their effects are not immediate (delayed for approximately 6 hours); thus, they are mostly involved in defense against prolonged hypoglycemia. Cortisol contributes to the regulation of gluconeogenic substrate supply through permissive effects on the lipolytic action of catecholamines and GH in adipose tissue and on the glycogenolytic action of catecholamines in skeletal muscle. In addition, it induces hepatic enzymatic gene expression required for enhanced gluconeogenic rates and exerts permissive effects on the stimulation of gluconeogenesis in the liver by glucagon and epinephrine.
Epinephrine

Epinephrine stimulates hepatic glycogenolysis and hepatic and renal gluconeogenesis, largely by mobilizing gluconeogenic precursors including lactate, alanine, glutamine, and glycerol from adipose and muscle stores. Epinephrine also limits glucose utilization by insulin-sensitive tissues. Epinephrine helps increase hepatic glucose output and together with glucagon acts within minutes to increase plasma glucose concentrations.

The increased activation of the sympathetic nervous system and the associated release of epinephrine and norepinephrine suppress pancreatic insulin release and stimulate glucagon release leading to an increased glucagon to insulin ratio. Thus, stimulation of glycogenolysis and inhibition of glycogen synthesis by glucagon and epinephrine as well as the glucagon-stimulated hepatic gluconeogenesis proceed unopposed.

Neuroendocrine Regulation of Energy Metabolism during Extreme Conditions

Counterregulation to Hypoglycemia

The contribution of the activation of the autonomic nervous system is easier understood when described in the context of acute and severe hypoglycemia. Because of the clear advantages of glycemic control in preventing organ injury in diabetic patients, tight regulation of plasma glucose levels is desired and recommended in this patient population. However, the most prevalent problem associated with tight glycemic control is the development of insulin-induced hypoglycemia. The decrease in plasma glucose concentrations (hypoglycemia) within and below the physiologic postabsorptive concentration range of approximately 70–110 mg/dL (3.9–6.1 mmol/L) triggers the activation of a counterregulatory neuroendocrine response. Acute insulin-induced hypoglycemia increases neuronal activity in the nucleus tractus solitarius and lateral hypothalamic glucosensors, resulting in increased sympathetic activity.

Enhanced sympathetic activity suppresses pancreatic insulin release and stimulates glucagon and epinephrine release, leading to increased hepatic glucose output. The additional release of GH and cortisol also contribute to the increase in hepatic glucose output and the suppression of tissue glucose uptake, partly through an increase in tissue fatty acid oxidation. As plasma glucose levels are restored, peripheral glucose sensors in the portal vein, small intestine, and liver decrease firing. This afferent signal is transmitted to the hypothalamus and to the nucleus solitarius in the medulla through the vagus nerve, conveying information on the prevailing peripheral glucose levels. The hypothalamus integrates these signals and initiates an appropriate response through the inhibition of hepatic and adrenal nerve activity, with consequently decreased release of adrenomedullary catecholamines, removing the inhibition on pancreatic insulin release and thus allowing hyperglycemia to induce pancreatic insulin secretion. Thus, in this system, glucose acts as a feedback signal contributing to integration of the neuroendocrine mechanisms that regulate its homeostasis.

Regulation of Energy Metabolism during Exercise

The neuroendocrine response to exercise is targeted to provide for the increased energy demands of the exercising muscle and includes activation of the sympathetic nervous system, release of GH, activation of the hypothalamic-pituitary-adrenal axis with consequent release of catecholamines and cortisol, suppression of insulin release, and stimulation of glucagon release (Figure 10–2). This neuroendocrine response stimulates lipolysis, and hepatic and muscle glycogenolysis leading to an increase in free fatty acids, gluconeogenic substrate mobilization, and hepatic glucose output (because of an increase in both gluconeogenesis and glycogenolysis). Both hepatic and skeletal
muscle glycogenolysis are stimulated by the increase in catecholamine release. However, because muscle lacks glucose-6-phosphatase, the glucose-6-phosphate produced by muscle glycogenolysis is either oxidized in muscle cells or released into the circulation as lactate. The increased lactate delivered to the liver is then used for hepatic gluconeogenesis. Hepatic glycogenolysis predominates during intense exercise, but gluconeogenesis contributes substantially to the increased hepatic glucose output during prolonged exercise as the liver glycogen stores decline and the supply of gluconeogenic precursors increases. As exercise intensity increases from mild to moderate and intense, energy substrate selection switches from lipid to carbohydrate dependence. GH and cortisol contribute only minimally to the exercise-induced increase in liver glucose output.

Figure 10–2.
Neuroendocrine response to exercise. The principal pathways activated by stress are the hypothalamic-pituitary-adrenal axis and sympathetic nervous system resulting in the increased release of corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), catecholamines, endorphins, and growth hormone (GH). In the periphery, increased production and release of cortisol, glucagon and catecholamines, and suppressed release of insulin favor an overall catabolic response. Stimulation of hepatic glycogenolysis and gluconeogenesis, muscle glycogenolysis, and adipose
tissue lipolysis ensure the production and mobilization of energy stores to sustain the enhanced metabolic demands of the individual. Reproductive and growth functions are inhibited, conserving energy to sustain fundamental processes that ensure survival. ACTH, adrenocorticotropic hormone; ATP, adenosine triphosphate; FA, fatty acid; FFA, free fatty acid; SNS, sympathetic nervous system.

Skeletal muscle is the main site of oxidation of fatty acids, and endogenous triacylglycerols represent an important source of energy both at rest and during low- and moderate-intensity exercise. During moderate-intensity exercise, lipolysis increases approximately 3-fold, mainly because of an increase in β-adrenergic stimulation, leading to an increased release of glycerol (used as a hepatic gluconeogenic substrate) and fatty acids into the circulation. The increase in adipose tissue and muscle blood flow facilitates the delivery of fatty acids to skeletal muscle for oxidation. In combination, the decrease in insulin and enhanced sympathetic stimulation, result in increased lipolysis and triacylglycerol oxidation; which serves as the main energy substrate for muscle. As the intensity of exercise increases, fat oxidation increases further until exercise intensities reach approximately 65% maximum oxygen consumption (VO₂ max). After this point, the rate of fat oxidation declines, most likely because of reduced fatty acid delivery from adipose tissue to muscle.

The contribution of amino acid oxidation to total energy expenditure is negligible during short-term intense exercise and accounts for 3–6% of the total ATP supplied during prolonged exercise in humans. Although it is not quantitatively important regarding energy supply, the intermediary metabolism of several amino acids, notably glutamate, alanine, and the branched-chain amino acids, influences the availability of tricarboxylic acid cycle intermediates. Sustained dynamic exercise stimulates amino acid oxidation, chiefly of the branched-chain amino acids, and ammonia production in proportion to exercise intensity. If the exercise is intense enough, it causes a net loss of muscle protein (as a result of decreased protein synthesis, increased breakdown, or both); some of the amino acids are oxidized as energy, whereas the rest provide substrates for gluconeogenesis and possibly for acid-base regulation.

**Maintenance of Long-Term Energy Balance and Fat Storage**

The neuroendocrine mechanisms involved in maintaining energy balance have been described earlier. Furthermore, the hormonal regulation of the 2 principal energy stores in the body—hepatic glycogen and adipose tissue triglycerides—has been outlined. The balanced transition from fed to fasted and the consumption of adequate energy commensurate with the level of physical activity of a given individual ensure that adequate energy reserves are available for short-term increases in metabolic demands, such as those described for exercise. An imbalance in either energy intake or expenditure leads to 1 of 2 extremes: loss of lean body mass or wasting syndrome resulting from an overall catabolic state, or obesity resulting from a combination of excess caloric intake and decreased physical activity. The salient features of these 2 conditions are described below.

**Catabolic State**

When the fasted state is prolonged into a state of starvation, or under conditions of increased energy substrate demands, the contributions of the counterregulatory hormones cortisol, epinephrine, norepinephrine, and glucagon become evident, favoring overall catabolic effects. During such conditions, insulin effects are practically abolished. Because of the important anabolic effects of insulin, it follows that the metabolic responses that predominate are those that lead to catabolism of stored energy (glycogenolysis, lipolysis) and of lean tissues (muscle proteolysis), leading to loss of lean body mass, or wasting. It is important to note that energy metabolism can be pushed to a starvation-like state not only by discontinuation of food intake, in the classic sense of starvation, but also during conditions of stress, such as from a surgical intervention, cancer, severe infection, sepsis, burns, and traumatic injury. Under these conditions, additional factors such as inflammatory cytokines (eg, tumor necrosis factor [TNF], interleukins 1 and 6) interact with mediators of the neuroendocrine
response. In addition, the production of GH, IGF-1, and the respective binding proteins becomes dysregulated, also contributing to the lack of anabolic processes and dominance of catabolic responses. Overall, the increased release of stress hormones and proinflammatory cytokines and the impairment in the release and action of insulin and growth factors, in association with altered release of androgens, lead to an overall catabolic response that affects the liver, adipose tissue, muscle, and, in extreme circumstances, visceral tissues. The deleterious impact of the loss of lean body mass on survival from disease underscores the relevance of understanding the hormonal mechanisms involved in the regulation of energy metabolism and their importance in the management of the critically ill patient.

**Obesity**

Obesity is defined as a significant increase above the ideal weight (the weight that maximizes life expectancy). The increase in body mass index (BMI), an indicator of the adiposity or fatness that accompanies obesity, has become an important health problem for the developed world. Life expectancy is reduced when body mass index is significantly increased above the ideal level. Obesity is associated with an increased risk of diabetes, dyslipidemia, hypertension, heart disease, diabetes, and cancer. Approximately 20% of the US population is considered obese, according to the definition of the World Health Organization (Table 10–2).

**Table 10–2. Classification of Overweight According to the World Health Organization**

<table>
<thead>
<tr>
<th>BMI (kg/m²)*</th>
<th>Definition</th>
<th>WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>Thin</td>
<td></td>
</tr>
<tr>
<td>18.5–24.9</td>
<td>Healthy or normal</td>
<td></td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>Overweight</td>
<td>Grade 1 overweight</td>
</tr>
<tr>
<td>30.0–39.9</td>
<td>Obese</td>
<td>Grade 2 overweight</td>
</tr>
<tr>
<td>=40.0</td>
<td>Morbidly obese</td>
<td>Grade 3 overweight</td>
</tr>
</tbody>
</table>

BMI, body mass index; WHO, World Health Organization.

*BMI is defined as mass in kilograms divided by the square of the height in meters.

Body weight and the excess weight gain leading to obesity are determined by interactions among genetic, environmental, and psychosocial factors that affect the physiologic mediators of energy intake and expenditure, several of which pertain to the endocrine system. The altered balance between energy intake and energy expenditure leads to excess weight gain and obesity. Energy expended by the individual can be in the form of work (physical activity) or heat production (thermogenesis), which can be affected by environmental temperature, diet, and the neuroendocrine system (catecholamines and thyroid hormone). The uncoupling of ATP production from mitochondrial respiration dissipates heat and affects the efficiency with which the body utilizes energy substrates. The expression of proteins involved in this process (uncoupling protein-1 expressed in brown adipose tissue and uncoupling protein-3 in skeletal muscle) is modulated by catecholamines, thyroid hormones, and leptin. Studies are currently under way to establish their roles in the regulation of BMR and in the development of obesity.

The role of genetics in the predisposition to obesity has been demonstrated convincingly. Susceptibility genes that increase the risk of developing obesity have been identified, and their relevance has been shown in studies in which pairs of twins were exposed to periods of positive and negative energy balance. The differences in the rate of weight gain, the proportion of weight gained, and the sites of fat deposition showed greater similarity within pairs than between pairs, indicating a close genetic relationship. Although a clear correlation between energy expenditure and weight gain has not been demonstrated, increasing physical activity; which represents 20%–50% of total energy
expenditure, has been actively promoted as an approach to prevent obesity and improve insulin responsiveness. Environmental factors are also thought to unmask genetic tendencies toward obesity.

From the standpoint of endocrine physiology, it is important to note that the responsiveness to hormones that regulate lipolysis varies according to the distribution of fat depots. The lipolytic response to norepinephrine is greater in abdominal than in gluteal or femoral adipose tissue in both men and women. The exaggerated release of free fatty acids from abdominal adipocytes directly into the portal system, an increased hepatic gluconeogenesis, and hepatic glucose release, and hyperinsulinemia are hallmarks of patients with upper-body obesity. The endocrine properties of the different fat pads may be more important than the anatomic location of the fat pad. The severity of medical complications is more closely related to body fat distribution; being greater in individuals with upper-body obesity than those with an excess total body fat. Differential fat deposition leading to upper-body or abdominal obesity is reflected in a high waist-hip ratio, an index used for predicting risks associated with fat accumulation. The presence of visceral obesity, insulin resistance, dyslipidemia, and hypertension is collectively termed the **metabolic syndrome** or **syndrome X**.

Excess energy intake in relation to the energy expended by the organism leads to the accumulation of fat. The fat mass itself is determined by the balance between breakdown (lipolysis) and synthesis (lipogenesis) (see Figure 10–1). The sympathetic nervous system is the principal stimulator of lipolysis, leading to a decrease in fat stores, particularly when the energy demands of the individual are increased. When intake exceeds energy utilization, lipogenesis occurs in liver and adipose tissue. Lipogenesis is influenced by diet (increased by carbohydrate-rich diets) and hormones (principally GH, insulin, and leptin) through modification of transcription factors (e.g., peroxisome proliferator-activated receptor γ [PPAR-γ]). The main hormones involved in fat storage are insulin (which stimulates lipogenesis), and GH and leptin (which reduce lipogenesis). The transcription factor PPAR, the target for the insulin sensitizer thiazolidinedione drugs (see Chapter 7), affects gene transcription of several enzymes involved in glucose and fat metabolism and is involved in preadipocyte differentiation into mature fat cells. Other hormones involved in the regulation of body fat stores include testosterone, dehydroepiandrosterone, and thyroid hormone.

**Regulation of Energy Intake**

Regulation of energy intake is mediated by several factors. Central integration of peripheral signals, including those mediated by mechanoreceptors and chemoreceptors, signals the presence and energy density of food in the gastrointestinal tract. Hypothalamic glucose sensors monitor fluctuations in circulating glucose concentrations. Hormones signal the central release of peptides that regulate appetite and satiety. Two hormones that have been identified as crucial in the long-term regulation of energy balance are insulin (see Chapter 7) and leptin, the product of the *ob* gene (discussed later). Both hormones are released in proportion to body fat. They are transported into the brain, where they modulate the expression of hypothalamic neuropeptides known to regulate feeding behavior and body weight, resulting in inhibition of food intake and increase in energy expenditure. Although insulin release is directly correlated to meals; that of leptin does not correlate with food intake but reflects body fat mass.

**Hypothalamic Integration**

The hypothalamus receives innervation from several areas, notably the nucleus tractus solitarius (NTS) and area postrema in the brainstem. These areas relay many neural and hormonal signals from the gastrointestinal tract. Mechanical stretch receptors sense stretch of the stomach and other areas of the intestine. The principal hormone associated with control of satiety is the peptide cholecystokinin (CCK). CCK, is released from the duodenum in response to the presence of lipids or protein in the intestinal lumen (see Figure 10–2). This hormone acts via local sensory receptors in the duodenum sending signals to the brain regarding the intestinal nutritional content. The NTS also relays taste
information to the hypothalamus and other centers. Other signals regarding smell, sight, memory of food, and the social context under which it is ingested are also integrated and may also influence energy intake by modulating output from the hypothalamus. Integration of these signals results in the activation of gene expression of mediators implicated in the regulation of satiety and development of obesity. These genes control thermogenesis (uncoupling proteins), hormone synthesis (ghrelin, leptin, and CCK and adiponectin), and neurotransmitter (neuropeptide Y) availability, as summarized in Table 10–3.

Table 10–3. Mediators Implicated in Regulation of Energy Balance

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Regulation and target effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Released in the duodenum during a meal. Stimulates the vagus nerve projecting to the NTS and signals within the hypothalamus to induce satiety.</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Produced primarily by the stomach. Levels increase before meals and decrease following a meal. Stimulates growth hormone release, increases food intake. Overall has anti-leptin action. Plasma levels are low in obese patients.</td>
</tr>
<tr>
<td>PYY3–36</td>
<td>Member of the NPY family, released in the distal small intestine and colon in response to food. Blood levels remain elevated between meals. Reduces food intake.</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Peptide produced in the intestinal cells in response to high intestinal luminal glucose concentrations. Amplifies glucose-induced insulin release from the β-cell.</td>
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<tr>
<td>Adipose tissue</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (AdipoQ)</td>
<td>Increases insulin sensitivity and tissue fat oxidation, resulting in reduced circulating fatty acid levels and reduced intramyocellular and liver triglyceride content. Levels decreased in obese patients; plasma levels correlate negatively with triglycerides.</td>
</tr>
<tr>
<td>Acylation-stimulating protein</td>
<td>Stimulates triglyceride synthesis in adipocytes, resulting in more rapid postprandial lipid clearance. Stimulates translocation of glucose transporters to the cell surface.</td>
</tr>
<tr>
<td>Leptin</td>
<td>Secreted by fat cells in proportion to fat stores. Acts on hypothalamic neurons to decrease food intake. Leptin is necessary for maturation of the reproductive axis.</td>
</tr>
<tr>
<td>Resistin</td>
<td>Peptide hormone induced during adipogenesis. It antagonizes insulin action.</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td></td>
</tr>
<tr>
<td>NPY</td>
<td>Produced by hypothalamic neurons that express AgRP. Release is under leptin, insulin, and cortisol regulation. Stimulates food intake via the NPY5 receptor.</td>
</tr>
<tr>
<td>α-MSH</td>
<td>Product of POMC in hypothalamic neuronal subset under leptin regulation. Decreases food intake through melanocortin-4 receptors in the hypothalamus.</td>
</tr>
<tr>
<td>CART</td>
<td>Peptide produced by hypothalamic POMC-expressing neurons stimulated by leptin and amphetamines. Reduces food intake.</td>
</tr>
<tr>
<td>AgRP</td>
<td>Released from hypothalamic NPY-expressing neurons. Inhibits neuronal melanocortin-4 receptors and increases food intake.</td>
</tr>
<tr>
<td>Orexins (A and B)</td>
<td>Produced by neurons in the lateral hypothalamus perifornical area. Regulated by glucose, leptin, NPY, and POMC neurons. They stimulate food intake.</td>
</tr>
</tbody>
</table>

AdipoQ, adipocyte complement-related protein of 30 kDa; AgRP, agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; GI, gastrointestinal; GLP-1, glucagon-like Peptide 1; MSH, melanocyte-stimulating hormone; NTS, nucleus tractus solitarius; PYY, polypeptide YY; POMC, proopiocortin.

The relative contributions of these mediators to the regulation of caloric intake, energy expenditure, body weight, and fat mass are not completely understood. However, important new discoveries, such
as the secretory function of adipose tissue, have provided new insight into potential factors contributing to obesity. Adipose tissue is now classified not just as an energy storage tissue but as an endocrine tissue participating in a complex network regulating energy homeostasis, glucose and lipid metabolism, vascular homeostasis, immune response, and even reproduction. Among the hormones identified that are produced by adipose tissue are leptin, cytokines (TNF-α, interleukin 6), adipin and acylation-stimulating protein, angiotensinogen, plasminogen activator inhibitor-1, adiponectin, resistin, and steroid hormones (see Table 10–3). Secretion of almost all of these hormones and cytokines is dysregulated as a consequence of both excess and deficiency in the mass of adipose tissue, suggesting that they are involved in the pathophysiology of both obesity and cachexia. Of particular interest are the contributions of the proinflammatory cytokines to the development of insulin resistance in obese individuals and the potential role of leptin as a regulator of fat mass.

TNF produced by adipose tissue has been implicated in producing insulin insensitivity, both indirectly and directly. Indirectly, TNF stimulates stress hormone production. Directly, TNF decreases insulin-induced receptor substrate 1 tyrosine phosphorylation and its association with the downstream signaling mediators (phosphatidylinositol trisphosphate kinase), and it also inhibits PPAR. These pathways and their role in the regulation of intermediary metabolism and regulation of fat mass are currently under intense investigation.

Leptin

Leptin is a peptide hormone produced predominantly in adipose tissue. Leptin is thought to serve as an indicator of energy stores (lipostat), as well as a modulator of energy balance. The specific effects of leptin on fat metabolism are as follows:

- Decrease in fat storage
- Increase in sympathetic-mediated energy expenditure
- Increase in expression of uncoupling proteins
- Decrease in triglyceride content by increasing fatty acid oxidation
- Decrease in activity and expression of esterification and lipogenic enzymes
- Decrease in lipogenic activity of insulin, favoring lipolysis

The release of leptin into the circulation is pulsatile. Plasma concentrations follow a circadian rhythm, and are highest between midnight and early morning and lowest in the early to midafternoon. These changes in leptin plasma concentrations are not influenced by meal ingestion or meal-induced increases in the circulating insulin concentration. The overall effect of leptin is to deplete fat stores and promote leanness in a feedback regulatory system. In this feedback loop, leptin functions as a sensor that monitors the level of energy stores (adipose tissue mass). The signal is received and integrated by hypothalamic neurons, and an effector response, most likely involving modulation of appetite centers and sympathetic nervous system activity, regulates the 2 main determinants of energy balance: intake and expenditure.

The effects of leptin are mediated through the leptin receptor, located throughout the central nervous system and peripheral tissues. Leptin binding to its receptor activates gene transcription on hypothalamic neurons resulting in reduced expression of 2 orexigenic (feeding-inducing) neuropeptides, neuropeptide Y (NPY) and agouti-related peptide (AgRP); and enhanced expression of 2 anorexigenic peptides, α-melanocyte-stimulating (α-MSH) hormone and cocaine- and amphetamine-regulated transcript (CART). Thus, leptin-induced inhibition of food intake results from both the suppression of orexigenic and the induction of anorexigenic neuropeptides (Figure 10–3).
Hypothalamic integration of energy intake. The hypothalamus receives innervation from several areas, notably the nucleus tractus solitarius and area postrema in the brainstem, that relay many neural and hormonal signals from the gastrointestinal tract, such as mechanical signals indicating stretch of the stomach and other areas of the intestine, and hormonal signals indicating the presence of food in the gut, such as cholecystokinin. Additional signals regarding smell, sight, memory of food, and the social context under which it is ingested are also integrated and may also influence energy intake by modulating output from the hypothalamus. Hormones also alter hypothalamic gene expression resulting in modulation of energy intake. Leptin and insulin decrease appetite by inhibiting the production of neuropeptide Y (NPY) and agouti-related protein (AgRP), while stimulating melanocortin-producing neurons in the arcuate-nucleus region of the hypothalamus. NPY and AgRP stimulate eating, and melanocortins inhibit eating. Ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurons. PYY\textsubscript{3–36}, released from the colon, inhibits these neurons and transiently decreases appetite. Integration of these signals results in the activation of gene expression of mediators implicated in the regulation of satiety, control of thermogenesis, and energy expenditure. CART, cocaine- and amphetamine-regulated transcript; α-MSH, α-melanocyte-stimulating; PYY, polypeptide YY.

The role of leptin in humans appears to be mostly one of adaptation to low energy intake rather than a brake on overconsumption and obesity. Leptin concentrations decrease during fasting and energy-restricted diets, independent of body fat changes, stimulating an increase in food intake before body energy stores become depleted. Because leptin levels do not increase in response to individual meals, it is not thought to serve as a meal-related satiety signal. Finally, it is notable that obese individuals have high plasma leptin concentrations that do not result in the expected reduction in food intake and increase in energy expenditure, suggesting that obesity may be related to leptin resistance and not leptin deficiency.

Congenital leptin deficiency is a rare autosomal recessive disease resulting from mutations in the leptin gene. Affected individuals are markedly obese mainly because of increased food intake (hyperphagia) and have inadequate gonadotropin-releasing hormone (GnRH) release, manifesting in
hypogonadotropic hypogonadism characterized by failure to reach puberty, including absence of growth spurt, secondary sex characteristics, and menarche.

Ghrelin

Ghrelin is a hormone produced by the enteroendocrine cells of the stomach, and to lesser extent by the placenta, pituitary, and hypothalamus. Circulating levels of ghrelin decrease during meals and are highest in the fasted state. Ghrelin levels are decreased in obese individuals and increased in individuals consuming low-calorie diets, involved in chronic strenuous exercise, and with cancer anorexia and anorexia nervosa. In humans, ghrelin has been shown to be a potent GH secretagogue and appetite stimulant.

Electrolyte Balance

Regulation of Sodium Balance

Sodium is the primary electrolyte that regulates extracellular fluid (ECF) levels and osmolarity in the body. Sodium is an essential mineral required for the integrity of multiple organ functions, particularly through the regulation of fluid balance and ultimately the regulation of blood pressure. It is essential for maintaining hydration, water balance, osmotic equilibrium, plasma volume, and acid-base balance and for preserving nerve impulses and muscle contractions. Sodium concentration determines the ECF tonicity, which reflects the balance between sodium and water in the ECF. The osmolarity (the amount of solute per unit volume) of bodily fluids is tightly regulated by balancing the intake and excretion of sodium with those of water. Extreme variation in osmolarity causes cells to shrink or swell, damaging or destroying cellular structure and disrupting normal cellular function.

Regulation of extracellular Na\(^+\) concentration controls the distribution of water between the ECF and intracellular fluid (ICF) and maintains cell volume, ensuring normal physiologic function. Sodium is maintained in the ECF by the action of Na\(^+\)/K\(^+\)-ATPase, whereas water crosses cell membranes through ubiquitously expressed aquaporins (maintaining ICF and ECF isotonicity). Water balance is maintained by matching the amount of water consumed in food and drink (and generated by metabolism) to the volume of water excreted. Consumption is regulated by central nervous system stimulation of thirst and salt craving, whereas excretion is principally regulated hormonally at the kidney. Additional loss of water (1 L/d) occurs through the skin, lungs, and feces.

The overall mass of Na\(^+\) is under aldosterone regulation, whereas the Na\(^+\) concentration in plasma is under antidiuretic hormone (ADH) regulation. Thus, low Na\(^+\) concentrations do not necessarily mean that total Na\(^+\) mass is low. In chronic heart failure, osmolarity can be low, yet Na\(^+\) mass can be high because of excess water and Na\(^+\) in the ECF, with greater increases in total body water than in Na\(^+\) mass.

Intake, Distribution, and Excretion of Sodium

Sodium concentrations average 140 mmol/L in plasma and 10 mmol/L intracellularly. The concentration of sodium in gut secretions and sweat is similar to that in the ICF (10–50 mmol/L). Sodium concentrations and intravascular volume are physiologically controlled in parallel. For a given amount of total-body water, intravascular volume is determined by sodium concentrations, which control the distribution between ICF and ECF.
The minimum recommended intake of sodium is 500 mg/d; which is markedly exceeded by the average diet in the United States (average 4–5 g/d). One teaspoon of table salt contains approximately 6 g of sodium chloride (2.3 mg of sodium). Sodium intake is usually considered to be unregulated; however, specific hypothalamic areas are involved in salt appetite, although their physiology is not completely understood.

Sodium balance is maintained primarily through hormonal regulation of renal sodium excretion. Fecal loss is small (0.8–8 mmol/d) even when sodium intake is high. Skin loss is small except under conditions of excessive sweating. Small changes in percentage renal reabsorption of sodium cause a large change in the amount of sodium excreted. The total amount of filtered sodium load (about 25,200 mmol/d) is equal to the glomerular filtration rate (180 L/d) multiplied by plasma sodium concentrations (140 mmol/L). Therefore, to maintain sodium balance on a dietary intake of 150 mmol/d, a total of 25,050 mmol (ie, 99.4% of the filtered load) must be reabsorbed. Approximately 60%–70% of the filtered sodium is reabsorbed in the proximal tubule. An additional 20%–30% of filtered sodium is reabsorbed in the ascending limb of the loop of Henle. Sodium reabsorption in the thick ascending limb is passive, down an electrical gradient set up by the active transport of chloride ions, and is the site of inhibition by loop diuretics. Thus, a significant (80%–95%) obligatory reabsorption of filtered sodium occurs in the renal tubule before reaching the distal tubule, preventing large renal sodium losses. The majority of the remaining sodium (5%–10%) is reabsorbed in the distal tubule and collecting duct. It is here that the finer regulation of sodium excretion through aldosterone occurs, and this is the site of inhibition by the diuretic hydrochlorothiazide (see Chapter 6).

Hormonal Regulation of Sodium and Water Balance

The system that controls total-body water is a negative feedback homeostatic mechanism, of which thirst and ADH are the major effectors. Two stimuli regulate the system: tonicity of the ECF through osmoreceptors, and intravascular volume through stretch or baroreceptors. As discussed in Chapter 3, the system works primarily to maintain intravascular volume and to a lesser extent to maintain tonicity. Thirst is stimulated by an increase in tonicity (1%–2% changes are sufficient to elicit thirst) and by reductions in the ECF volume. Water intake is inhibited by hypotonicity and ECF volume expansion.

Sudden decreases in blood volume are sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles (Figure 10–4; see Figure 2–7). These mechanoreceptors respond to decreased stretch resulting from decreases in systemic arterial pressure, stroke volume, renal perfusion, or peripheral vascular resistance by triggering an increase in sympathetic outflow from the central nervous system, activation of the renin-angiotensin-aldosterone system, and nonosmotic release of arginine vasopressin (AVP or ADH), as well as stimulation of thirst. Low blood pressure results in decreased renal perfusion pressure and lower glomerular filtration rates, which stimulate the release of renin from juxtaglomerular cells in the afferent and efferent arterioles. Renin is an enzyme synthesized in the juxtaglomerular cells of the kidney that cleaves angiotensinogen (a peptide produced by the liver) to angiotensin I, which is later converted by angiotensin-converting enzyme to angiotensin II. This renin-angiotensin system is part of an extremely powerful feedback system for long-term control of blood pressure and volume homeostasis. Together, angiotensin II, aldosterone, and ADH produce vasoconstriction, and renal retention of Na⁺ and water.

Figure 10–4.
Neuroendocrine control of blood volume. Sudden decreases in blood volume are sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles triggering an increase in sympathetic (SNS) outflow from the central nervous system, activation of the renin-angiotensin-aldosterone (RAS) system, and the nonosmotic release of arginine vasopressin (AVP), as well as the stimulation of thirst. The decrease in renal perfusion pressure and glomerular filtration rates, stimulate the release of renin, the enzyme responsible for angiotensinogen conversion to angiotensin I (later converted by angiotensin-converting enzyme [ACE] to angiotensin II). Angiotensin II, aldosterone, and antidiuretic hormone (ADH) produce vasoconstriction, venoconstriction, and renal retention of Na\(^+\) and water.

**Antidiuretic Hormone**

ADH directly controls water excretion by the kidneys (see Chapter 2). ADH secretion and compensatory thirst are stimulated by hypothalamic osmoreceptors and by decreased stimulation of aortic and carotid stretch receptors. Release of ADH is inhibited by increased stretch of mechanoreceptors (stretch receptors) in the atria of the heart. ADH stimulates insertion of aquaporins into the cell membrane, increases water reabsorption in the collecting ducts, and concentrates excreted urine.

**Angiotensin II**

Angiotensin II elevates blood pressure by several mechanisms, including direct vasoconstriction, potentiation of the activity of the sympathetic nervous system at both the central and peripheral levels, stimulation of aldosterone synthesis and release with consequent sodium reabsorption by the kidney.
stimulation of ADH release and increased water retention, intrarenal efferent arteriolar constriction (which maintains glomerular filtration rate when renal perfusion is impaired, also known as “glomerular tubular feedback”). Because of the effectiveness of the renin-angiotensin system in regulating blood pressure, blockade of the system with angiotensin-converting enzyme inhibitors offers a powerful therapeutic tool in diseases such as hypertension and congestive heart failure.

**Aldosterone**

Aldosterone increases sodium reabsorption and potassium excretion in the distal tubule and the collecting duct of the nephron, playing a central role in determining total-body Na\(^+\) mass, and thus long-term blood pressure regulation. Aldosterone release from the adrenals is under positive regulation by Angiotensin II.

**Atrial Natriuretic Peptide (ANP)**

ANP is a 28-amino-acid peptide, synthesized primarily in cardiac atrial cells, and released in response to atrial stretch via mechanosensitive ion channels. Release of ANP is increased by volume expansion, immersion in water up to the neck, changing from the standing to the supine position, exercise, and sympathetic stimulation. ANP binds to transmembrane receptors with cytoplasmic domains that are guanylyl cyclases. The effects of ANP are to increase glomerular filtration rate and decrease proximal tubular sodium reabsorption leading to increased natriuresis. Additional effects of ANP include inhibition of renin, aldosterone, and AVP release, and vasodilation.

Integrity of the arterial circulation, as determined by cardiac output and peripheral vascular resistance, is the primary determinant of renal sodium and water excretion in health and disease. Specifically, either a primary decrease in cardiac output or arterial vasodilatation causes arterial underfilling, which results in the activation of neurohumoral reflexes that stimulate sodium and water retention. The renal excretion of sodium and water normally parallels sodium and water intake, so that an increase in plasma and blood volume is associated with increased renal sodium and water excretion. The increase in blood volume results in pressure diuresis and natriuresis (loss of water and sodium), restoring blood volume to normal.

**Abnormalities in Sodium and Water Balance**

Abnormalities in sodium and water balance can be classified into 4 categories. Excess Na\(^+\) is characterized by expansion of the ECF volume and frequently by low effective circulating blood volume (ie, heart failure, hypoalbuminemia, renal insufficiency). Deficit in Na\(^+\) is characterized by reduced ECF volume. Excess water is caused by either excess intake or enhanced ADH release and is manifested by hyponatremia and hyponatremia. Water deficit is caused by lack of intake or excess loss (renal and nonrenal) and is manifested by hypervolemia and hypervolemia.

**Regulation of Potassium Balance**

Potassium is the most abundant cation in the body and the main intracellular electrolyte. Most (98%) of the potassium in the body is sequestered within cells. The ratio of extracellular to intracellular potassium (1:10) is the major determinant of resting membrane potential and is maintained by a Na\(^+\)/K\(^+\)-ATPase. Serum potassium levels range between 3.6 and 5.0 mmol/L. Small losses (1%, or 35 mmol) of total-body potassium content can seriously disturb the delicate balance between intracellular and extracellular potassium and can result in profound physiologic changes. Because only a small percentage of the total-body stores is present in the ECF, hypokalemia (serum levels less than 3.6
mmol/L) is not necessarily synonymous with whole-body potassium deficiency. Manifestations of hypokalemia include generalized muscle weakness, paralytic ileus, and cardiac arrhythmias.

### Intake, Distribution, and Excretion of Potassium

The minimum daily requirement of potassium is approximately 1600–2000 mg (40–50 mmol or mEq). The daily intake of potassium in the western diet is approximately 80–120 mmol. Only a small fraction (10%) of potassium is excreted through the gastrointestinal tract. The majority is excreted by the kidney, accounting for 90% of daily potassium losses. Thus, the kidney is responsible for long-term potassium homeostasis, as well as for regulating the serum potassium concentration. On a short-term basis, serum potassium is also regulated by the shift of potassium between the ICF and ECF. This short-term regulation of serum potassium is principally controlled by insulin and catecholamines through regulation of the transcellular distribution of potassium. Dietary potassium, which is rapidly absorbed by the gut, increases serum potassium transiently. The release of insulin and catecholamines during a meal quickly shifts the potassium into the cells.

Potassium excretion by the kidney is tightly regulated and is determined primarily by events beyond the early distal tubule, where either reabsorption or secretion of K⁺ can occur. The filtered K⁺ (approximately 700–800 mmol/d) is largely reabsorbed by proximal nephron segments, including the proximal convoluted tubules and thick loop of Henle. Only approximately 10% of filtered K⁺ reaches the distal convoluted tubule. Excretion of K⁺ occurs mainly through secretion by distal segments, predominantly the distal convoluted tubule and the collecting duct, and is mediated primarily by apical membrane K⁺ channels in the principal cells. Potassium excretion almost always exceeds the amount delivered to the early distal tubule (except under conditions of sustained K⁺ depletion), indicating that the rate of secretion is the key determinant of K⁺ excretion. The principal site for the regulation of K⁺ excretion is the distal tubule, where secretion is indirectly but tightly coupled to sodium reabsorption via the amiloride-sensitive sodium channel, and under regulation by aldosterone. Increased sodium reabsorption increases potassium secretion, whereas decreased sodium reabsorption decreases K⁺ secretion. Any condition that decreases the activity of renal K⁺ channels results in hyperkalemia (eg, amiloride intake or aldosterone deficiency), whereas increased activity results in hypokalemia (eg, primary aldosteronism or Liddle syndrome; see Chapter 6). Because the kidney is the major regulator of K⁺ homeostasis, renal dysfunction results in abnormal levels of serum K⁺.

Potassium contributes to regulation of its balance by stimulating aldosterone secretion by the glomerulosa cells of the adrenal cortex (Figure 10–5). This effect is facilitated by angiotensin II released in response to activation of the renin-angiotensin system when renal perfusion pressure is decreased. Aldosterone enhances renal and colonic K⁺ secretion, promoting the loss of K⁺ in the urine and stool. Sustained hyperkalemia does not occur in individuals with normal renal function despite marked increases in potassium intake because of an adaptive change in distal tubular K⁺ secretion, such that intake is matched by rapid and equivalent increases in K⁺ excretion. The mechanisms involved in the chronic adaptation to increased levels of K⁺ include changes in apical K⁺ and Na⁺ conductance and in basolateral Na⁺/K⁺-ATPase pump activity, an increase in apical Na⁺ delivery and reabsorption, and an increase in K⁺ excretion per nephron to match K⁺ intake.

Figure 10–5.
An increase in extracellular fluid potassium concentration stimulates the secretion of aldosterone and a decrease inhibits its secretion. Aldosterone promotes potassium excretion through its effects on
Na⁺/K⁺-adenosine triphosphatase (ATPase) and epithelial sodium and potassium channels in collecting-duct cells. Angiotensin II has a synergistic effect on the stimulation of aldosterone production induced by hyperkalemia. Insulin stimulates entry of K⁺ into the cell through the activation of the electroneutral Na⁺/K⁺ antiporter. The increase in intracellular Na⁺ produced by insulin triggers the activation of the electrogenic Na⁺/K⁺-ATPase, which extrudes Na⁺ from the cell in exchange for K⁺. Catecholamines (β-adrenergic receptor stimulation) increase cellular potassium uptake by stimulating cell membrane Na⁺/K⁺-ATPase. Stimulation of the α-adrenergic receptor produces a shift of K⁺ out of the cell. (Modified, with permission, from Gennari F. Current concepts: hypokalemia. N Engl J Med. 1998;339:451. Copyright © Massachusetts Medical Society. All rights reserved.)

Hormonal Regulation of Potassium Balance

Total-body stores of potassium and its cellular distribution in the body are closely regulated by key hormones.

Aldosterone

Aldosterone is the major regulator of body stores of potassium through its effect on the excretion of potassium by the kidney. Aldosterone increases the synthesis and activity of Na⁺/K⁺-ATPase in the basolateral membrane of the distal tubule, promoting the exchange of cytosolic Na⁺ for K⁺. The overall result is an increase in Na⁺ reabsorption and an increase in K⁺ excretion.

Insulin stimulates entry of K⁺ into the cell through activation of the electroneutral Na⁺/H⁺ antiporter, leading to Na⁺ influx. The increase in intracellular Na⁺ produced by insulin triggers the activation of the electrogenic Na⁺/K⁺-ATPase, which extrudes Na⁺ from the cell in exchange for K⁺. The treatment of patients with diabetic ketoacidosis with high insulin doses produces a significant influx of K⁺ into the cells that may result in hypokalemia, manifested by changes in the electrocardiogram.

Catecholamines

Catecholamines (β-adrenergic receptor stimulation) increase cellular K⁺ uptake by stimulating cell membrane Na⁺/K⁺-ATPase. Indirectly, catecholamines stimulate glycogenolysis, resulting in an increase in plasma glucose concentrations, release of insulin from the pancreas, and insulin-mediated effects on K⁺ redistribution. Stimulation of the α-adrenergic receptor shifts K⁺ out of the cell and can also affect K⁺ distribution through inhibition of pancreatic insulin release.

Insulin and catecholamines are both stimulated by the ingestion of glucose- and K⁺-rich foods, thereby maintaining K⁺ homeostasis despite large dietary intake. These hormones are essential in moving K⁺ primarily into the intracellular compartment of the liver and striated muscle cells.

Acid-Base and Osmolar Regulation of Potassium Distribution
Intracellular K⁺ homeostasis is also affected by changes in acid-base balance and osmolarity. Sudden changes in plasma osmolarity redistribute water between the ICF and ECF. This movement of water out of a cell creates a solvent drag phenomenon, pulling K⁺ out of the cell and therefore increasing serum K⁺. Similarly, metabolic acidosis caused by a loss of bicarbonate or a gain in hydrogen ion concentration [H⁺] leads to a shift of K⁺ across cell membranes and hyperkalemia. However, integrity of renal function and stimulation of aldosterone release rapidly correct this imbalance. These examples do not entail net changes in body K⁺. In contrast, in diabetic ketoacidosis, there is a net loss of K⁺ from the body because of osmotic diuresis, despite elevations in ECF K⁺ concentrations (hyperkalemia), because of insulin deficiency. Following aggressive insulin treatment, hypokalemia becomes apparent. Opposite effects are observed during alkalosis. In metabolic alkalosis, the excess bicarbonate causes H⁺ in the ECF to decrease, leading to entry of Na⁺ into the cell in exchange for H⁺. Na⁺ is pumped out of the cell by the Na⁺/K⁺-ATPase in exchange for K⁺ movement into the cell creating a shift of K⁺ into the cells.

Low serum K⁺ concentration (hypokalemia; less than 3.6 mmol/L) is perhaps the most common electrolyte abnormality encountered in clinical practice. Hypokalemia is almost always the result of K⁺ depletion induced by abnormal fluid losses (ie, vomiting, colonic diarrhea, profuse sweating, diuretic use, or nasogastric suction). Patients present with muscle weakness and changes in the electrocardiogram. More rarely, hypokalemia occurs because of an abrupt shift of K⁺ from the ECF into cells, frequently as an effect of prescription drugs.

**Regulation of Calcium Balance**

Serum calcium concentrations are tightly regulated and concentrations are held constant at 1 mmol of ionized calcium or 10 mg/dL of total calcium. Calcium accounts for 1%–2% of adult human body weight, with the majority (99%) found in bones and teeth. Calcium helps maintain the cell membrane electrical potential and is involved in signaling mechanisms, enzymatic activity, coagulation cascade, neurotransmitter release, and intercellular communication. Because of its role in these and other critical functions, its tight regulation is important in preventing diseases such as osteoporosis, renal and heart disease, and hypertension.

**Intake, Distribution, and Excretion of Calcium**

The recommended calcium intake varies with age, sex, and reproductive stage. Higher intakes are recommended for children, adolescents, pregnant and lactating mothers, postmenopausal women, and the elderly (1200–1500 mg/d) than for healthy adults up to age 65 years (1000 mg/d). A positive correlation between protein intake and urinary calcium has been established. This relationship may explain the apparently higher calcium requirement of the diet in the developed world as compared with that of underdeveloped countries. The catabolism of dietary protein generates ammonium ion and sulfates from sulfur-containing amino acids, leading to the acidification of plasma. This decrease in pH triggers bone resorption to supply buffers such as citrate and carbonate, with the consequent release of calcium into the circulation, resulting in calciuria.

**Hormonal Regulation of Calcium Balance**

Calcium homeostasis is maintained by the complex interaction of several hormones, particularly vitamin D, parathyroid hormone (PTH), and calcitonin (see Chapter 4). Because the major reservoir
for calcium is the bone, and this is the pool of calcium that is involved in actively maintaining serum plasma concentrations within a normal range, the factors that influence bone metabolism such as estrogen, growth factors, glucocorticoids, thyroid hormone, and cytokines also contribute significantly to the overall metabolic control of Ca^{2+} stores. However, it is important to note that it is the “free” calcium in serum that is under tight hormonal regulation, principally by PTH.

Parathyroid Hormone

PTH activates 25-hydroxyvitamin D-1α-hydroxylase, the enzyme that converts 25-hydroxyvitamin D to the active form of 1,25-dihydroxyvitamin D [1,25(OH)_{2}D]. PTH also stimulates renal reabsorption of calcium.

Vitamin D

1,25(OH)_{2}D increases dietary Ca^{2+} absorption in the small intestine and increases osteoblast activity, resulting in stimulation of osteoclast-mediated resorption. Vitamin D plays an important role in differentiation of the promyelocyte to the osteoclast precursor to mature osteoclast through osteoblast-generated osteoclast differentiation factor (see Chapter 5). These effects of vitamin D on bone resorption coupled with formation as part of the bone-remodeling process result in calcium mobilization by the skeleton into the plasma compartment. Both PTH and vitamin D are required for this system to operate. In the distal renal tubule, PTH and vitamin D act in concert to produce virtually complete reabsorption of the filtered load of calcium. These sources of calcium cause an increase in serum calcium, which, through feedback inhibition at the parathyroid gland, decreases PTH secretion (see Chapter 5).

Calcitonin

Calcitonin counteracts the effects of PTH and vitamin D. It prevents hypercalcemia by directly inhibiting osteoclast activity, thereby reducing calcium mobilization and release from the skeleton.

Hormonal Regulation of Phosphate Balance

Phosphorus in the form of phosphate (H_{2}PO_{4}^{-}), accounts for more than 50% of bone mineral mass. Osteoblasts are unique among all other cell types in that they create a mineral trap (calcium-phosphate) in bone matrix after it has been deposited. This trap depletes the ECF around the osteoblast of both calcium and phosphorus, and if the local concentration of phosphorus drops too low, osteoblasts become phosphorus starved. Throughout the body, phosphorus is found as a component of nucleic acids, phospholipids, signaling molecules (inositol 1,4,5-trisphosphate, phosphatidylinositol 4,5-bisphosphate), and cofactors involved in cellular energy metabolism (ATP, guanosine triphosphate), playing numerous vital roles in cell function. Most food products, whether plant or animal, contain relatively abundant quantities of phosphates. Normal balanced diets provide 800–1500 mg of phosphorus per day. The skeleton contains 85% of the body’s phosphorus; the rest is distributed in the ECF and ICF (0.5–0.8 g). Total extracellular phosphorus (about 12 mg/dL) is found in an ionized form and a nonionized form (8.5 mg/dL is in the organic form and 3.5 mg/dL is in the inorganic form). The inorganic form may be found ionized or free (50%); complexed with Ca^{2+}, Mg^{2+}, and Na^{+} (35%); or bound to protein (15%).

Phosphate homeostasis is maintained by intestinal absorption, renal excretion, balance of phosphate exchange in and out of the cells, and their hormonal regulation. Because of its critical role in energy-
requiring physiologic functions, the extracellular phosphate concentration is maintained in a narrow range, principally through regulation of urinary excretion. When renal function is compromised, impaired phosphate excretion by the kidney leads to hyperphosphatemia and the stimulation of PTH release from the parathyroid gland (Figure 10–6).

![Phosphate Balance Diagram](image)

Phosphate balance in chronic renal failure. When renal function is compromised, impaired phosphate excretion by the kidney leads to hyperphosphatemia. Hyperphosphatemia stimulates parathyroid hormone (PTH) release from the parathyroid gland and also stimulates release of fibroblast growth factor 23 (FGF23), which in turn suppresses activity of 1α-hydroxylase and vitamin D activation. Decreased 1,25(OH)2D allows for increased PTH release as well. PTH stimulates bone resorption and release of calcium phosphate. Because of the impairment in renal function, PTH is unable to stimulate calcium reabsorption, phosphate excretion, or vitamin D activation. Management of these patients requires supplementation with calcium, control of dietary phosphate intake, and vitamin D supplementation.

Following intestinal absorption from the diet, most phosphate undergoes urinary excretion. Under normal physiologic conditions, urinary phosphate excretion corresponds roughly to phosphate intake and absorption from the upper small intestine. Alterations in extracellular phosphate concentrations lead to rapid adjustments in renal excretion and slower and less regulated adjustments in intestinal absorption. Under normal physiologic conditions, approximately 80%–90% of the filtered load of phosphate is reabsorbed primarily in the proximal tubules, with higher rates of reabsorption at early segments. Low dietary phosphate intake can lead to almost 100% reabsorption of filtered phosphate, whereas high dietary phosphate intake decreases proximal tubular reabsorption.

Phosphate excretion by the kidney is stimulated by PTH through the inhibition of brush-border membrane Na+/PO42−-cotransport activity. Phosphate reabsorption in the proximal tubule can also be decreased by fibroblast growth factor 23 (FGF23), a peptide produced in osteoblasts and osteocytes.
FGF23 suppresses the 1-hydroxylase responsible for synthesis of 1,25(OH)$_2$D and decreases renal phosphate reabsorption through reduction of the expression of the sodium phosphate cotransporters in the kidney and intestine. FGF23 production is stimulated by 1,25(OH)$_2$D and by high phosphate levels. Abnormalities in FGF23 are linked to genetic diseases such as autosomal dominant hypophosphatemic rickets.

Phosphate reabsorption by the kidney is increased by vitamin D and insulin through stimulation of brush-border membrane Na$^+/PO_4^{2-}$ cotransport and inhibition of the phosphaturic action of PTH. Vitamin D also regulates intestinal phosphate absorption by stimulating the brush-border membrane Na$^+/PO_4^{2-}$ cotransport in the upper small intestine. Thus, PTH promotes phosphate excretion, whereas vitamin D and insulin promote phosphate renal reabsorption and intestinal absorption. Vitamin D deficiency leads to increased phosphate renal excretion and decreased intestinal phosphate and Ca$^{2+}$ absorption, resulting in a severe loss of both Ca$^{2+}$ and phosphate from bone (the major site of both of these mineral stores) because of enhanced PTH activity, resulting in loss of bone mineral and osteomalacia. This is in contrast to osteoporosis induced by Ca$^{2+}$ deficiency.

**Neuroendocrine Regulation of the Stress Response**

Alterations in the environment or in the host that require adaptation involve the synchronized interaction of virtually all aspects of neuroendocrine function that have been described. The process of adaptation to a biologic, psychosocial, or environmental insult to the host is referred to as the stress response; in the acute setting, it is also termed the “fight or flight” response. It is now clear that in modern life, this stress response can be chronic, with a significant cost to the health of the individual. This wear and tear of chronic adaptation to daily stressors constitutes the allostatic load of the individual; it is the “pathologic” chronic homeostasis through which we achieve stability at the expense of psychosocial and physical well being.

Chronic activation of the mechanisms that restore homeostasis results in excessive and, in some cases, inadequate responses that ultimately alter the function of virtually all organ systems (eg, hypertension, autoimmune disorders, metabolic syndrome) (Figure 10–7). Many of the effects of this dysregulated state are mediated by chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, producing marked alterations in endocrine function, such as the following:

Figure 10–7.
The chronic activation of the mechanisms that restore homeostasis results alterations in function in virtually all organ systems. The short-term activation of these stress response mechanisms ensures that energy substrates are available to meet the increased metabolic demands of the individual. However, prolonged duration and increased magnitude of their activity leads to erosion of lean body mass and tissue injury. GH, growth hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal axis; IGF-1, insulin-like growth factor 1; SNS, sympathetic nervous system; TSH, thyroid-stimulating hormone.

Inhibition of Reproduction Function

Enhanced release of corticotropin-releasing hormone (CRH) and β-endorphin suppresses GnRH release directly and indirectly through the release of glucocorticoids. Elevated glucocorticoids suppress the release of GnRH, luteinizing hormone, and follicle-stimulating hormone, and produce gonadotropin resistance at the gonads. This suppression in gonadal function is evident in patients with anorexia nervosa and extreme athletes.

Inhibition of the GH–IGF-1 Axis
Chronic activation of the HPA axis suppresses GH release and inhibits the effects of IGF-1 at target tissues.

**Suppression of Thyroid Function**

CRH and cortisol suppress the production of thyroid-stimulating hormone and inhibit the activity of peripheral 5'-deiodinase, leading to the euthyroid sick syndrome.

**Dysregulation of Energy Substrate Metabolism**

An increase in catecholamines stimulates lipolysis and decreases triglyceride synthesis in white adipose tissue. In the liver, increased epinephrine levels stimulate hepatic glycogenolysis and, together with high cortisol levels, increase hepatic glucose output. High cortisol levels resulting from activation of the HPA increase gluconeogenesis, produce insulin resistance in peripheral tissues, inhibit the lipolytic action of GH, and inhibit bone osteoblastic activation (remodeling) by sex steroids. This leads to increases in visceral adiposity and loss of BMD and lean body mass. This aspect of the stress response may be of particular importance in the treatment of diabetic patients during stressful periods such as surgery or infection.

**Alterations in the Immune Response**

The significant rise in circulating cortisol levels affects virtually all aspects of the immune response, including cytokine production, leukocyte trafficking and recruitment, and production of chemokines. Overall, glucocorticoids exert an anti-inflammatory response and increase the risk of infections. CRH may have direct proinflammatory effects on cells of the immune system. Activation of the autonomic nervous system also affects the immune response through effects on neutrophil demargination and cytokine production.

Short-term activation of these stress response mechanisms ensures that energy substrates are available to meet the increased metabolic demands of the individual. However, prolonged duration and increased magnitude of these activities lead to erosion of lean body mass and tissue injury. Nevertheless, impaired activation or lack of responsiveness of the HPA and autonomic nervous system can also be deleterious, as in the case of the critically ill patient. Thus, the overall regulation of the neuroendocrine responses that mediate the physiologic functions involved in maintaining and restoring homeostasis is critically important in situations such as illness, trauma, surgery, or fasting.

**Key Concepts**

1. **Energy substrate mobilization, utilization, and storage are under neuroendocrine regulation.**
2. **Hepatic glycogen and adipose tissue triglycerides are the principal sites of energy storage.**
3. **The central nervous system integrates the counterregulatory response to acute decreases in energy substrate availability.**
4. **Regulation of sodium balance determines blood volume and blood pressure control.**
The kidney is responsible for long-term potassium homeostasis and serum potassium concentration.

Insulin and catecholamines regulate the cellular distribution of potassium.

Serum calcium levels are tightly regulated through hormone-mediated effects on bone.

Phosphate is regulated principally through effects on renal excretion.

Suggested Readings


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Hormonal factors controlling fat, protein, and carbohydrate (CHO) stores and balance. Adipose, protein, and carbohydrate (CHO in the form of glycogen) stores are the result of balanced synthesis and degradation under hormonal regulation by insulin (INS), growth hormone (GH), leptin, testosterone (T), epinephrine (Epi), thyroid hormone (TH), insulin-like growth factor 1 (IGF-1), and cortisol (Cort). Excess, deficiencies, or impaired regulation of adipose, protein, and carbohydrate stores have direct implications on health and disease as illustrated above.

Neuroendocrine response to exercise. The principal pathways activated by stress are the hypothalamic-pituitary-adrenal axis and sympathetic nervous system resulting in the increased release of corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), catecholamines,
endorphins, and growth hormone (GH). In the periphery, increased production and release of cortisol, glucagon and catecholamines, and suppressed release of insulin favor an overall catabolic response. Stimulation of hepatic glycogenolysis and gluconeogenesis, muscle glycogenolysis, and adipose tissue lipolysis ensure the production and mobilization of energy stores to sustain the enhanced metabolic demands of the individual. Reproductive and growth functions are inhibited, conserving energy to sustain fundamental processes that ensure survival. ACTH, adrenocorticotropic hormone; ATP, adenosine triphosphate; FA, fatty acid; FFA, free fatty acid; SNS, sympathetic nervous system.

Hypothalamic integration of energy intake. The hypothalamus receives innervation from several areas, notably the nucleus tractus solitarius and area postrema in the brainstem, that relay many neural and hormonal signals from the gastrointestinal tract, such as mechanical signals indicating stretch of the stomach and other areas of the intestine, and hormonal signals indicating the presence of food in the gut, such as cholecystokinin. Additional signals regarding smell, sight, memory of food, and the social context under which it is ingested are also integrated and may also influence energy intake by modulating output from the hypothalamus. Hormones also alter hypothalamic gene expression resulting in modulation of energy intake. Leptin and insulin decrease appetite by inhibiting the production of neuropeptide Y (NPY) and agouti-related protein (AgRP), while stimulating melanocortin-producing neurons in the arcuate-nucleus region of the hypothalamus. NPY and AgRP stimulate eating, and melanocortins inhibit eating. Ghrelin stimulates appetite by activating the NPY/AgRP-expressing neurons. PYY3-36, released from the colon, inhibits these neurons and transiently decreases appetite. Integration of these signals results in the activation of gene expression of mediators implicated in the regulation of satiety, control of thermogenesis, and energy expenditure. CART, cocaine- and amphetamine-regulated transcript; α-MSH, α-melanocyte-stimulating; PYY, polypeptide YY.

Neuroendocrine control of blood volume. Sudden decreases in blood volume are sensed by mechanoreceptors in the left ventricle, carotid sinus, aortic arch, and renal afferent arterioles triggering an increase in sympathetic (SNS) outflow from the central nervous system, activation of the renin-angiotensin-aldosterone (RAS) system, and the nonosmotic release of arginine vasopressin (AVP), as well as the stimulation of thirst. The decrease in renal perfusion pressure and glomerular filtration rates, stimulate the release of renin, the enzyme responsible for angiotensinogen conversion to angiotensin I (later converted by angiotensin-converting enzyme [ACE] to angiotensin II). Angiotensin II, aldosterone, and antidiuretic hormone (ADH) produce vasoconstriction, venoconstriction, and renal retention of Na⁺ and water.

An increase in extracellular fluid potassium concentration stimulates the secretion of aldosterone and a decrease inhibits its secretion. Aldosterone promotes potassium excretion through its effects on Na⁺/K⁺-adenosine triphosphatase (ATPase) and epithelial sodium and potassium channels in collecting-duct cells. Angiotensin II has a synergistic effect on the stimulation of aldosterone production induced by hyperkalemia. Insulin stimulates entry of K⁺ into the cell through the activation of the electroneutral Na⁺/K⁺ antiporter. The increase in intracellular Na⁺ produced by insulin triggers the activation of the electrogenic Na⁺/K⁺-ATPase, which extrudes Na⁺ from the cell in exchange for K⁺. Catecholamines (β-adrenergic receptor stimulation) increase cellular potassium uptake by stimulating cell membrane Na⁺/K⁺-ATPase. Stimulation of the α-adrenergic receptor produces a shift of K⁺ out of the cell. (Modified, with permission, from Gennari F. Current concepts: hypokalemia. N Engl J Med. 1998;339:451. Copyright © Massachusetts Medical Society. All rights reserved.)

Phosphate balance in chronic renal failure. When renal function is compromised, impaired phosphate excretion by the kidney leads to hyperphosphatemia. Hyperphosphatemia stimulates parathyroid hormone (PTH) release from the parathyroid gland and also stimulates release of fibroblast growth factor 23 (FGF23), which in turn suppresses activity of 1α-hydroxylase and vitamin D activation.
Decreased 1,25(OH)\textsubscript{2}D allows for increased PTH release as well. PTH stimulates bone resorption and release of calcium phosphate. Because of the impairment in renal function, PTH is unable to stimulate calcium reabsorption, phosphate excretion, or vitamin D activation. Management of these patients requires supplementation with calcium, control of dietary phosphate intake, and vitamin D supplementation.

The chronic activation of the mechanisms that restore homeostasis results alterations in function in virtually all organ systems. The short-term activation of these stress response mechanisms ensures that energy substrates are available to meet the increased metabolic demands of the individual. However, prolonged duration and increased magnitude of their activity leads to erosion of lean body mass and tissue injury. GH, growth hormone; GnRH, gonadotropin-releasing hormone; HPA, hypothalamic-pituitary-adrenal axis; IGF-1, insulin-like growth factor 1; SNS, sympathetic nervous system; TSH, thyroid-stimulating hormone.