10 ENDOCRINE DISORDERS

Eva M. Vivian

OBJECTIVES

After completing this chapter, the reader should be able to

- Identify patients who should be screened for diabetes mellitus and determine the diagnostic tests that should be employed
- Recognize and differentiate between the subjective and objective data consistent with a diagnosis of type 1 and type 2 diabetes mellitus and relate this data to the pathogenesis of type 1 and type 2 diabetes mellitus
- Explain the major differences between laboratory values found in diabetic ketoacidosis and in a hyperosmolar hyperglycemic state
- Identify common medications or chemicals that may induce hyperglycemia or hypoglycemia
- Describe the use of glycated hemoglobin, fasting plasma glucose, and oral glucose tolerance tests as diagnostic tools
- Describe the actions of thyroxine, triiodothyronine, and thyroid-stimulating hormone and the feedback mechanisms regulating them
- Recognize the signs and symptoms associated with abnormally high and low concentrations of thyroid hormones
- Given a case description including thyroid function test results, identify the type of thyroid disorder, and describe how tests are used to monitor and adjust related therapy

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The endocrine system consists of hormones that serve as regulators, which stimulate or inhibit a biological response to maintain homeostasis within the body. Endocrine disorders often result from a deficiency or an excess of a hormone, leading to an imbalance in the physiological functions of the body. Usually, negative feedback mechanisms regulate hormone concentrations (**Figure 10-1**). Therefore, laboratory assessment of an endocrine disorder is based on the concentrations of a plasma hormone and on the integrity of the feedback mechanism regulating that hormone. In this chapter, the relationship between a hormone (insulin) and a target substrate (glucose) serves as an example of these concepts. Evaluations of the functions of the thyroid and adrenal glands are also described. The relationships between vasopressin (antidiuretic hormone [ADH]) and serum and urine osmolality are used to demonstrate the basis for the water deprivation test in diagnosing diabetes insipidus.

GLUCOSE HOMEOSTASIS

Glucose serves as the fuel for most cellular functions and is necessary to sustain life. Carbohydrates ingested from a meal are metabolized in the body into glucose. Glucose is absorbed from the gastrointestinal (GI) tract into the bloodstream where it is utilized in skeletal muscle and brain for energy. Glucose is also stored in the liver in the form of glycogen (glycogenesis) and is converted in adipose tissue to fats and triglycerides (lipogenesis). Insulin, which is produced, stored, and released from β cells of the pancreas, facilitates these anabolic processes. The liver, skeletal muscle, brain, and adipose tissue are the main tissues affected by insulin. To induce glucose uptake, insulin must bind to specific cell-surface receptors. Most secreted insulin is taken up by the liver, while the remainder is metabolized by the kidneys. About 80% of glucose uptake is independent of insulin. These insulin-independent cells include nerve tissue, red blood cells (RBCs), mucosal cells of the GI tract, and exercising skeletal muscle.[1,2]

In the fasting state, insulin levels decrease, resulting in an increase in glycogen breakdown by the liver (glycogenolysis) and an increase in the conversion of free fatty acids to ketone bodies (lipolysis).[1,2] When glucose concentrations fall below 70 mg/dL, an event known as *hypoglycemia* occurs resulting in the release of glucagon by the pancreatic α cell. Glucagon stimulates the formation of glucose in the liver (gluconeogenesis) and glycogenolysis. Glucagon also facilitates the breakdown of stored triglycerides in adipose tissue into fatty acids (lipolysis), which can be used for energy in the liver and skeletal muscle. In addition to glucagon secretion, hypoglycemia leads to secretion of counter regulatory hormones such as epinephrine, cortisol, and growth hormone. Glucagon and, to a lesser degree, epinephrine promote an immediate breakdown of glycogen and the synthesis of glucose by the liver. Cortisol increases glucose levels by stimulating gluconeogenesis. Growth hormone inhibits the uptake of glucose by tissues when glucose levels fall below 70 mg/dL.[3,4]

Other hormones, such as amylin and incretin, affect glucose concentrations. Discovered in 1987, amylin, a β-cell hormone is cosecreted with insulin at a molar ratio of 1:20–50 in response to a glucose challenge. Amylin is a neuroendocrine hormone that complements the actions of insulin by restraining the vagus nerve-mediated rate of gastric emptying, thereby slowing intestinal carbohydrate absorption and

OBJECTIVES

- Describe the relationship between urine osmolality, serum osmolality, and antidiuretic hormone as it relates to diabetes insipidus
- Describe the laboratory tests used to diagnose Addison disease and Cushing syndrome

resulting in lower postprandial glucose (PPG) levels. This delay in gastric emptying has been found to be the same in patients with type 1 and type 2 diabetes mellitus (DM) that were without complications. Amylin also suppresses hepatic glucose output by inhibiting glucagon after ingestion of a meal.[5-8] In animal studies, amylin was found to induce postprandial satiety in direct proportion to food intake.[6] The administration of amylin has been reported to decrease food intake, thereby resulting in weight loss in patients with type 2 DM.[9,10]

Recent studies have shown that β-cell response is greater after food ingestion or when glucose is given orally versus after intravenous (IV) glucose infusion. This difference in insulin secretion has been termed the *incretin effect*, which implies that food ingestion causes the release of specific gut hormones known as *incretins* that enhance insulin secretion beyond the release caused by the rise in glucose secondary to absorption of digested nutrients.[11,12] Studies in humans and animals have shown that the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) stimulate insulin release when glucose levels are elevated.[12-14]

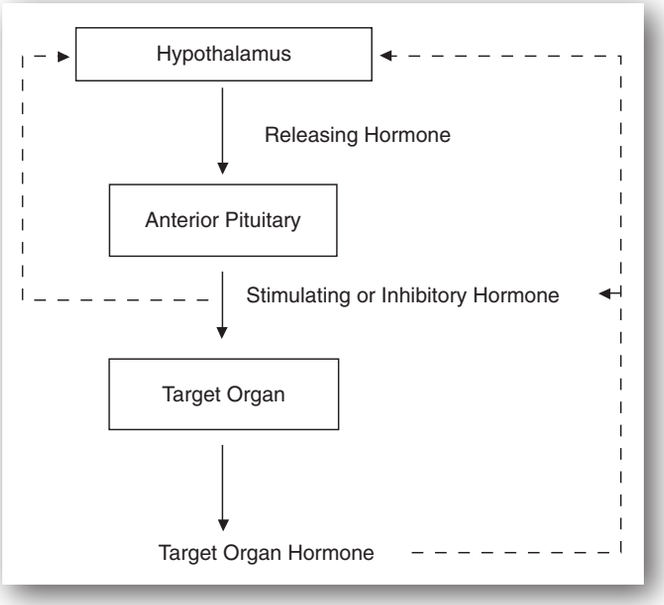

FIGURE 10-1. The hypothalamus may secrete a releasing hormone in response to low levels of stimulating, inhibitory, or target organ hormone. This releasing hormone causes the release of a stimulating or inhibitory hormone that in turn controls the release of target organ hormone.

After food is ingested, GIP is released from K cells in the proximal gut (duodenum), and GLP-1 is released from L cells in the distal gut (ileum and colon). Under normal circumstances, dipeptidyl peptidase 4 (DPP-4) rapidly degrades these incretins to their inactive forms after their release into the circulation. As a result, the plasma half-life of GIP and GLP-1 is less than five minutes.[12] GLP-1 and GIP stimulate insulin response in pancreatic β cells, and GLP-1 (but not GIP) also suppresses glucagon production in pancreatic α cells when the glucose level is elevated. The subsequent increase in glucose uptake in muscles and reduced glucose output from the liver help maintain *glucose homeostasis*. Thus, the incretins GLP-1 and GIP are important glucoregulatory hormones that positively affect glucose homeostasis by physiologically helping to regulate insulin in a glucose-dependent manner.[12,15]

The kidney contributes to glucose homeostasis primarily by the reabsorption and return of glucose to the circulation. Glucose is freely filtered by the glomerulus, and in healthy individuals approximately 180 g of glucose are filtered daily, and almost all of this is reabsorbed by the proximal tubule. Glucose reabsorption by the kidney is mediated by a class of specific glucose transport proteins, the sodium–glucose cotransporters (SGLTs). One member of this family, SGLT2, is responsible for the majority of renal glucose reabsorption and is located on the luminal side of cells in the initial part of the nephron, the early proximal convoluted tubule. Another member of this family, SGLT1, is expressed mainly in the intestine, but it is also present in skeletal muscle, heart, and based on animal studies in the late proximal tubule where it accounts for additional glucose reabsorption from the glomerular filtrate. Glucose is taken up into the cell by SGLTs and exits across the basolateral membrane into the interstitium by facilitative diffusion via the facilitative glucose transporters GLUT2 and GLUT1.[16]

In individuals without diabetes, once plasma glucose concentrations exceed approximately 180 mg/dL (the renal threshold), renal glucose reabsorption is saturated and glucose starts to appear in the urine. In hyperglycemic individuals, the renal threshold may be exceeded, and large amounts of glucose may be excreted in the urine. However, the kidneys continue to reabsorb glucose, and in patients with type 2 DM, the renal capacity to reabsorb glucose may be increased, which further contributes to hyperglycemia.[17]

In summary, glucose concentrations are affected by any factor that can influence glucose production or utilization, glucose absorption from the GI tract, glycogen catabolism, or insulin production or secretion. Fasting suppresses the rate of insulin secretion, and feasting generally increases insulin secretion. Increased insulin secretion lowers serum glucose concentrations, while decreased secretion raises glucose concentrations.[1-4]

DIABETES MELLITUS

The three most commonly encountered types of diabetes mellitus (DM) include the following:

1. Type 1 DM, formally known as *insulin-dependent DM* (IDDM)