

career CONNECTION

Endocrinologist

An endocrinologist is a medical doctor who specializes in treating disorders of the endocrine glands, hormone systems, and glucose and lipid metabolic pathways. An endocrine surgeon specializes in the surgical treatment of endocrine diseases and glands. Some of the diseases that are managed by endocrinologists: disorders of the pancreas (diabetes mellitus), disorders of the pituitary (gigantism, acromegaly, and pituitary dwarfism), disorders of the thyroid gland (goiter and Graves' disease), and disorders of the adrenal glands (Cushing's disease and Addison's disease).

Endocrinologists are required to assess patients and diagnose endocrine disorders through extensive use of laboratory tests. Many endocrine diseases are diagnosed using tests that stimulate or suppress endocrine organ functioning. Blood samples are then drawn to determine the effect of stimulating or suppressing an endocrine organ on the production of hormones. For example, to diagnose diabetes mellitus, patients are required to fast for 12 to 24 hours. They are then given a sugary drink, which stimulates the pancreas to produce insulin to decrease blood glucose levels. A blood sample is taken one to two hours after the sugar drink is consumed. If the pancreas is functioning properly, the blood glucose level will be within a normal range. Another example is the A1C test, which can be performed during blood screening. The A1C test measures average blood glucose levels over the past two to three months by examining how well the blood glucose is being managed over a long time.

Once a disease has been diagnosed, endocrinologists can prescribe lifestyle changes and/or medications to treat the disease. Some cases of diabetes mellitus can be managed by exercise, weight loss, and a healthy diet; in other cases, medications may be required to enhance insulin release. If the disease cannot be controlled by these means, the endocrinologist may prescribe insulin injections.

In addition to clinical practice, endocrinologists may also be involved in primary research and development activities. For example, ongoing islet transplant research is investigating how healthy pancreas islet cells may be transplanted into diabetic patients. Successful islet transplants may allow patients to stop taking insulin injections.

37.2 | How Hormones Work

By the end of this section, you will be able to do the following:

- Explain how hormones work
- Discuss the role of different types of hormone receptors

Hormones mediate changes in target cells by binding to specific **hormone receptors**. In this way, even though hormones circulate throughout the body and come into contact with many different cell types, they only affect cells that possess the necessary receptors. Receptors for a specific hormone may be found on many different cells or may be limited to a small number of specialized cells. For example, thyroid hormones act on many different tissue types, stimulating metabolic activity throughout the body. Cells can have many receptors for the same hormone but often also possess receptors for different types of hormones. The number of receptors that respond to a hormone determines the cell's sensitivity to that hormone, and the resulting cellular response. Additionally, the number of receptors that respond to a hormone can change over time, resulting in increased or decreased cell sensitivity. In **up-regulation**, the number of receptors increases in response to rising hormone levels, making the cell more sensitive to the hormone and allowing for more cellular activity. When the number of receptors decreases in response to rising hormone levels, called **down-regulation**, cellular activity is reduced.

Receptor binding alters cellular activity and results in an increase or decrease in normal body processes. Depending on the location of the protein receptor on the target cell and the chemical structure of the hormone, hormones can mediate changes directly by binding to **intracellular hormone receptors** and modulating gene transcription, or indirectly by binding to cell surface receptors and stimulating signaling pathways.

Intracellular Hormone Receptors

Lipid-derived (soluble) hormones such as steroid hormones diffuse across the membranes of the endocrine cell. Once outside the cell, they bind to transport proteins that keep them soluble in the bloodstream. At the target cell, the hormones are released from the carrier protein and diffuse across the lipid bilayer of the plasma membrane of cells. The steroid hormones pass through the plasma membrane of a target cell and adhere to intracellular receptors residing in the cytoplasm or in the nucleus. The cell signaling pathways induced by the steroid hormones regulate specific genes on the cell's DNA. The hormones and receptor complex act as transcription regulators by increasing or decreasing the synthesis of mRNA molecules of specific genes. This, in turn, determines the amount of corresponding protein that is synthesized by altering gene expression. This protein can be used either to change the structure of the cell or to produce enzymes that catalyze chemical reactions. In this way, the steroid hormone regulates specific cell processes as illustrated in **Figure 37.5**.

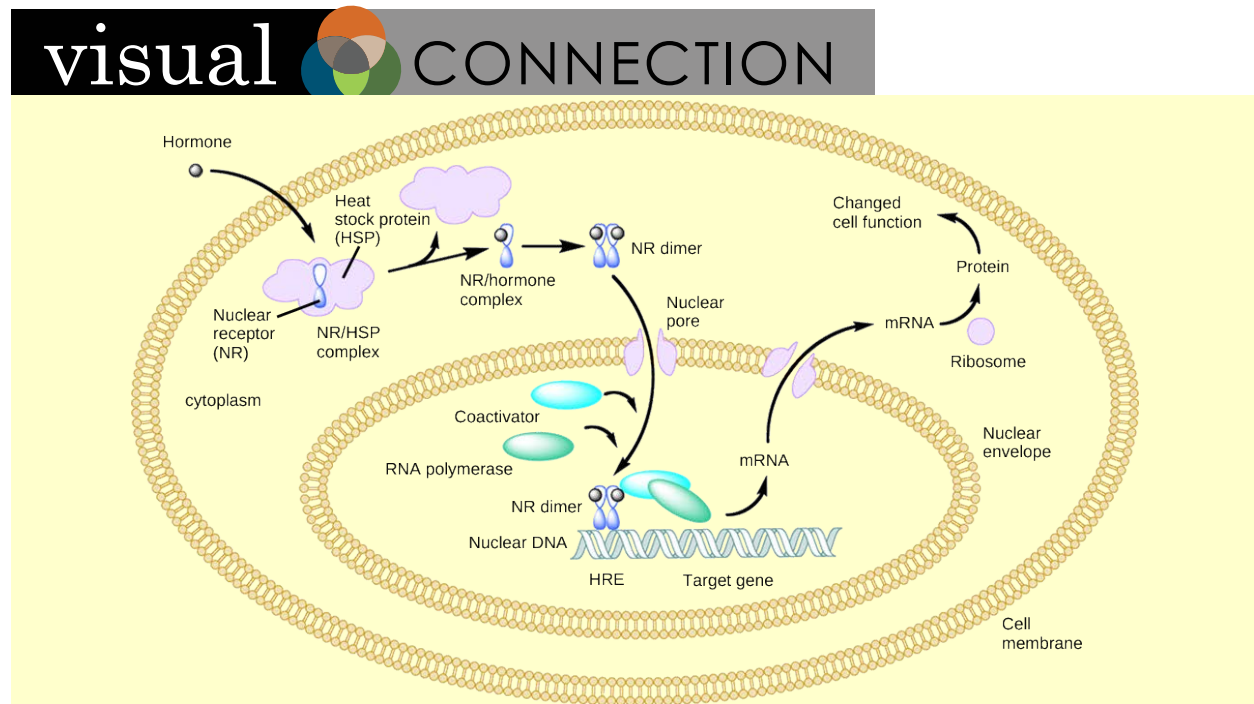


Figure 37.5 An intracellular nuclear receptor (NR) is located in the cytoplasm bound to a heat shock protein (HSP). Upon hormone binding, the receptor dissociates from the heat shock protein and translocates to the nucleus. In the nucleus, the hormone-receptor complex binds to a DNA sequence called a hormone response element (HRE), which triggers gene transcription and translation. The corresponding protein product can then mediate changes in cell function.

Heat shock proteins (HSP) are so named because they help refold misfolded proteins. In response to increased temperature (a “heat shock”), heat shock proteins are activated by release from the NR/HSP complex. At the same time, transcription of HSP genes is activated. Why do you think the cell responds to a heat shock by increasing the activity of proteins that help refold misfolded proteins?

Other lipid-soluble hormones that are not steroid hormones, such as vitamin D and thyroxine, have receptors located in the nucleus. The hormones diffuse across both the plasma membrane and the nuclear envelope, then bind to receptors in the nucleus. The hormone-receptor complex stimulates transcription of specific genes.

Plasma Membrane Hormone Receptors

Amino acid derived hormones and polypeptide hormones are not lipid-derived (lipid-soluble) and therefore cannot diffuse through the plasma membrane of cells. Lipid insoluble hormones bind to receptors on the outer surface of the plasma membrane, via **plasma membrane hormone receptors**. Unlike steroid hormones, lipid insoluble hormones do not directly affect the target cell because they cannot enter the cell and act directly on DNA. Binding of these hormones to a cell surface receptor results in activation of a signaling pathway; this triggers intracellular activity and carries out the specific effects associated with the hormone. In this way, nothing

passes through the cell membrane; the hormone that binds at the surface remains at the surface of the cell while the intracellular product remains inside the cell. The hormone that initiates the signaling pathway is called a **first messenger**, which activates a second messenger in the cytoplasm, as illustrated in **Figure 37.6**.

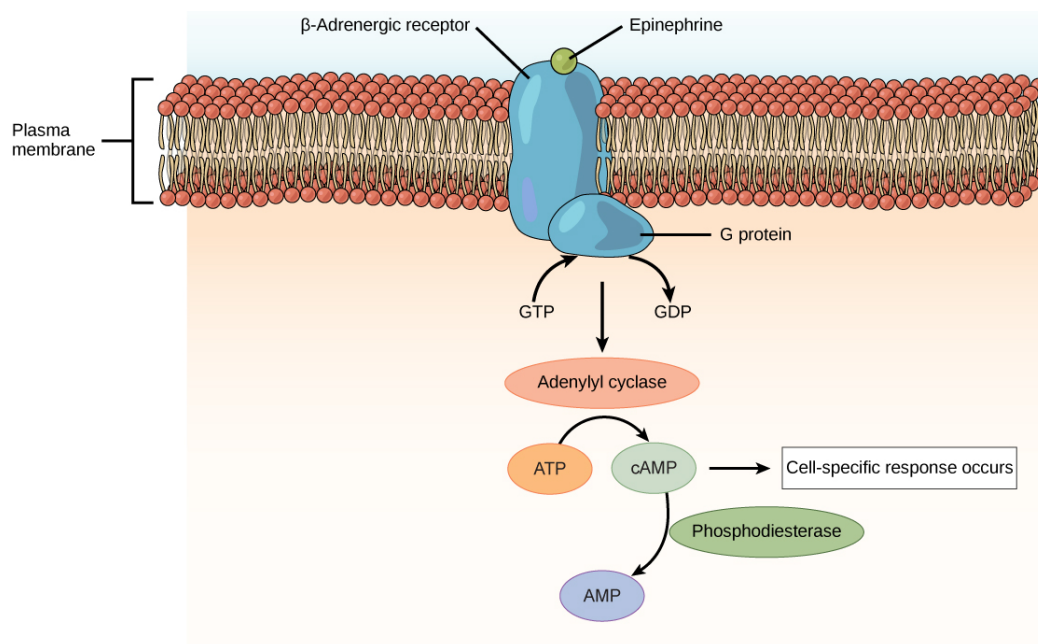


Figure 37.6 The amino acid-derived hormones epinephrine and norepinephrine bind to beta-adrenergic receptors on the plasma membrane of cells. Hormone binding to receptor activates a G-protein, which in turn activates adenylyl cyclase, converting ATP to cAMP. cAMP is a second messenger that mediates a cell-specific response. An enzyme called phosphodiesterase breaks down cAMP, terminating the signal.

One very important second messenger is cyclic AMP (cAMP). When a hormone binds to its membrane receptor, a **G-protein** that is associated with the receptor is activated; G-proteins are proteins separate from receptors that are found in the cell membrane. When a hormone is not bound to the receptor, the G-protein is inactive and is bound to guanosine diphosphate, or GDP. When a hormone binds to the receptor, the G-protein is activated by binding guanosine triphosphate, or GTP, in place of GDP. After binding, GTP is hydrolysed by the G-protein into GDP and becomes inactive.

The activated G-protein in turn activates a membrane-bound enzyme called **adenylyl cyclase**. Adenylyl cyclase catalyzes the conversion of ATP to cAMP. cAMP, in turn, activates a group of proteins called protein kinases, which transfer a phosphate group from ATP to a substrate molecule in a process called phosphorylation. The phosphorylation of a substrate molecule changes its structural orientation, thereby activating it. These activated molecules can then mediate changes in cellular processes.

The effect of a hormone is amplified as the signaling pathway progresses. The binding of a hormone at a single receptor causes the activation of many G-proteins, which activates adenylyl cyclase. Each molecule of adenylyl cyclase then triggers the formation of many molecules of cAMP. Further amplification occurs as protein kinases, once activated by cAMP, can catalyze many reactions. In this way, a small amount of hormone can trigger the formation of a large amount of cellular product. To stop hormone activity, cAMP is deactivated by the cytoplasmic enzyme **phosphodiesterase**, or PDE. PDE is always present in the cell and breaks down cAMP to control hormone activity, preventing overproduction of cellular products.

The specific response of a cell to a lipid insoluble hormone depends on the type of receptors that are present on the cell membrane and the substrate molecules present in the cell cytoplasm. Cellular responses to hormone binding of a receptor include altering membrane permeability and metabolic pathways, stimulating synthesis of proteins and enzymes, and activating hormone release.