

Endocrinology is the study of endocrine glands and their secretions. It can be a difficult topic to master because of all the mechanisms and feedback loops to understand. Yet, one way to understand the endocrine system is to break it down into smaller parts, and that is what I have attempted to accomplish in this book. **It may help to visualize each endocrine system as part of a much larger group; envision a football team with all the players (quarterback, running backs, center, guards, receivers, punter, etc.). Each of these players must perform his job properly for the team to win. If even one player is out of sync, the play may be botched, even if the other players perform flawlessly. (In endocrinology, this happens frequently, as it does in other human disorders.) The quarterback is in charge of the team, calls the plays, and provides leadership. Hopefully your endocrine system has a good quarterback, but, as in football, some turn in lackluster performances, as do some supporting players.**

Football teams often communicate plays with audible signals. **Complex organisms also require detailed communication for proper function; they have developed hormones to send messages or commands from one part of the organism to another.** Simple, one-celled organisms did not have a great need for detailed endocrine systems. But as organisms became more complex, large intercellular communication mechanisms became necessary for homeostasis.

The word “hormone” is derived from the Greek word meaning “arouse to activity.” To many lay people, the word “hormone” conjures up images of estrogen or thyroid replacement therapy. In fact, there are many types of hormones, with new ones discovered every day; some have greater significance than others.

The endocrine system sends signals to the body by secreting hormones (e.g., insulin, growth hormone, thyroxine) directly into the circulation. In contrast, the

exocrine glands secrete their substances into a duct system (e.g., sweat glands, exocrine pancreas).

The endocrine system is composed of many different glands throughout the body. The endocrine glands may be divided into two categories. The first, or “classical” glands’ functions are primarily endocrine in nature. The second, or “nonclassical” glands’ primary functions are something else, but they also secrete important substances.

The “classical” endocrine glands include the anterior pituitary, thyroid, parathyroids, adrenal cortex and medulla, gonads (testes and ovaries), and the endocrine pancreas. The primary function of these glands is to manufacture specific hormones. Some nonclassical endocrine organs and their hormones include the heart (atrial natriuretic peptide), kidney (calcitriol, renin), lymphocytes (cytokines, interleukins), GI tract (gastrin, secretin, vasoactive intestinal peptide), and many others. Many of the “classical” hormones are under the control of the hypothalamus and pituitary, which may be thought of as extensions of the nervous system. Indeed, the nervous and endocrine systems may function together quite closely (neuroendocrinology).

FUNCTION OF HORMONES

So why are hormones so important, anyway? **The first thing that an organism must have in order to survive is energy.** Food must be converted into energy, excess energy needs to be converted to storage, and stored energy must be mobilized when necessary to meet the organism’s needs. In the chapter on glucose metabolism, we will learn the effects of insulin and glucagon on the body’s metabolism and the many disorders where things go awry. Thyroid hormones are important in the regulation of the body’s metabolism. Glycogen and lipids are

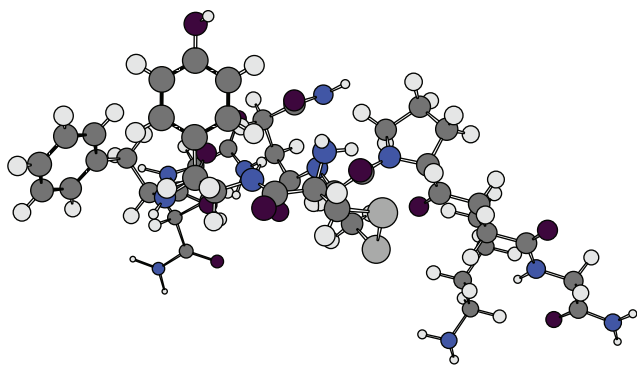
necessary to provide long-term energy needs when food is not available.

The organism must maintain its internal environment. This is not as easy as it sounds. Many hormones play a role here. Hormones such as antidiuretic hormone, aldosterone, and atrial natriuretic peptide are important in water and sodium balance. Calcium is necessary for many bodily functions, and its metabolism is regulated by parathyroid hormone and vitamin D. Several hormones, including thyroid hormones, growth hormone, and sex steroids, control growth and development. These all need to work together as a team for the body to exist in an orderly environment.

And, of course, reproduction is essential for the continued survival of any organism. Specialized reproductive organs (gonads) produce sex steroids that are necessary for spermatogenesis and ovulation (as well as normal growth and development). Gonads are under the complex control of the hypothalamic–pituitary axis (HPA).

COMPOSITION OF HORMONES

Hormones are made from a variety of different molecules. The vast majority of hormones are of the **protein** or **peptide** variety. **Proteins are chains of amino acids linked together.** Some of these peptide hormones are only a few amino acids in length; most are much larger, with some being over 200 amino acids in length. Even the very small protein vasopressin (a nonapeptide) looks quite complex.

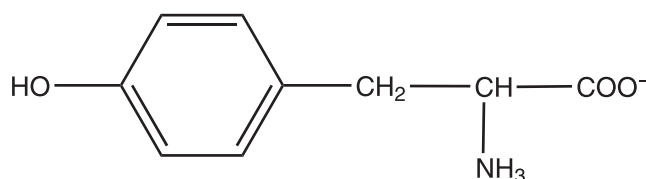


Arginine Vasopressin

Glycoproteins are sort of a hybrid hormone, consisting of a peptide hormone associated with a carbohydrate moiety. The four human glycoprotein hormones include LH (luteinizing hormone), FSH (follicle-stimulating hormone), TSH (thyroid-stimulating

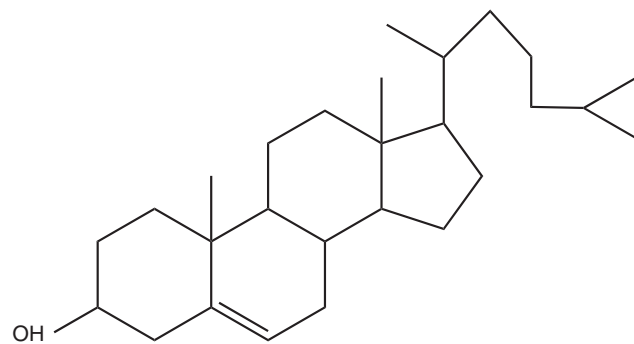
hormone or thyrotropin), and human chorionic gonadotropin (β -hCG). These hormones all share a common alpha subunit (α -SU); the β subunits differ from one to another.

Instead of being linked together to form proteins, one or two amino acids may be modified to form hormones. The amino acid tyrosine is modified to form the **catecholamines** (e.g., epinephrine and norepinephrine). While technically two amino acids joined together form a peptide, these amino acids are usually modified in some manner. The catecholamine hormones are very important in the nervous system. The thyroid or iodothyronine hormones (thyroxine, triiodothyronine) are made by joining two modified tyrosine molecules and adding several iodine atoms.



Tyrosine

Cholesterol, a molecule that we associate with atherosclerosis, is in fact essential to life. It is the precursor of steroid hormones—such as cortisol, aldosterone, estradiol, and testosterone—and sterol hormones, such as calcitriol.



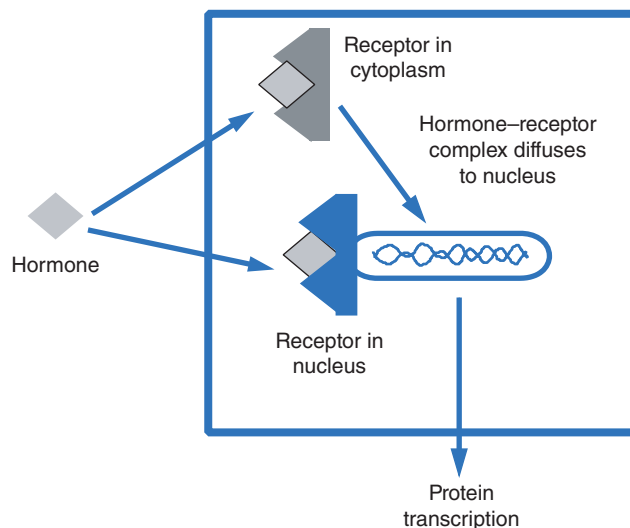
Cholesterol

Another common hormone precursor is the lowly fatty acid (the major storage component of fat), which serves as a precursor of hormones called eicosanoids. The most important eicosanoids, the **prostaglandins**, are derived from arachidonic acid. Other eicosanoids include thromboxanes, leukotrienes, and prostacyclins. They are important in smooth muscle contraction, hemostasis, inflammatory and immunologic responses, circulation, and respiratory and gastrointestinal systems.

Simple ions such as calcium also have hormone-like effects, and calcium metabolism will be discussed in Lecture 6.

HOW HORMONES WORK

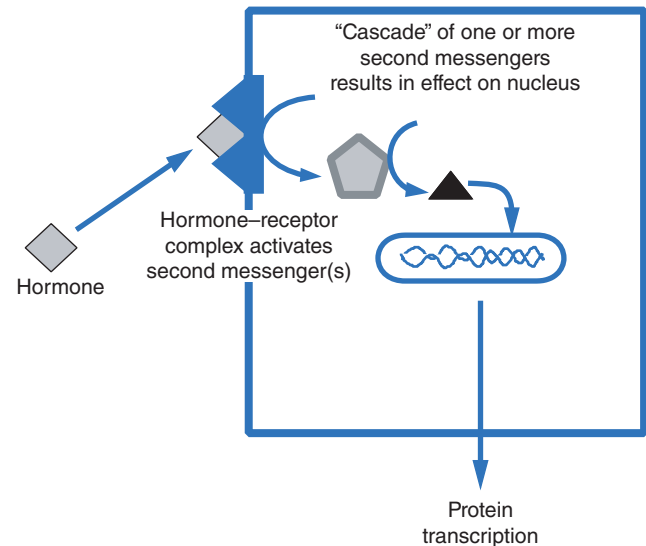
Hormones must have a way to tell the other cells what to do. The end effect of a hormone is usually at the nucleus, resulting in the production of a protein that has some effect on the cell. Some hormones go directly to the nucleus and have an effect there. These types of hormones tend to be ones that can easily traverse the cell membrane; for this to happen, the hormone usually must be “nonpolar” (non-charged). These include the steroid and iodothyronine hormones.



Hormones Interacting Directly with Nuclear or Cytoplasmic Receptors

The second class of hormones have no direct effect but instead bind to cell surface receptors, which initiates production of one or more second messengers that carry out the action. One messenger may trigger another messenger, which may trigger yet another, and so on. This concept of “multiple messengers” is called an **amplification cascade** and is the reason that some of these hormones are effective at extremely low concentrations (e.g., 10^{-12} mol/L). An analogy to the game of football would be a running back carrying the ball behind his blockers. Without the blockers, he is likely to be tackled quite quickly, ending the play abruptly; with multiple blockers, his power is “amplified” to the extent that many more yards can be gained than would have been possible

alone. **These hormones tend to be highly electrically charged, and include polypeptide, glycoprotein, and catecholamine hormones, and therefore cannot easily traverse the cell membrane.**



Hormones Interacting with Cell Surface Receptors

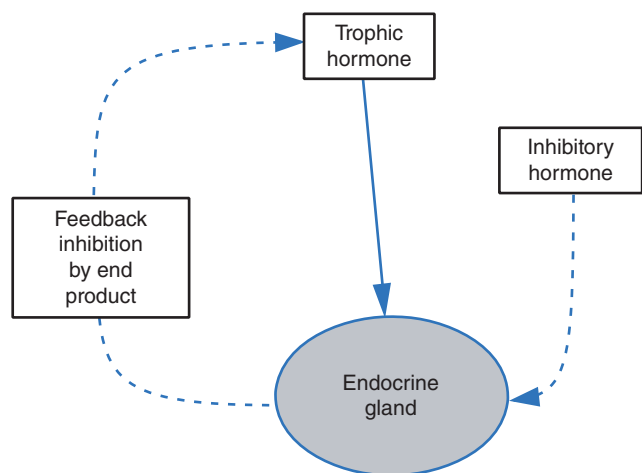
Another important difference between these hormones is how they travel in the blood. **Those that act on the nucleus directly (e.g., steroids such as sex steroids (estradiol, testosterone, and glucocorticoids)) tend to travel bound to a carrier protein.** (Interestingly, the mineralocorticoid steroids (e.g., aldosterone) do not have a binding protein.) These carrier proteins may be specific for those hormones (e.g., sex-hormone binding globulin, transcortin, thyroid-binding globulin), or may be common proteins (e.g., albumin). The hormones are often more slowly degraded if they are bound to carrier proteins, resulting in a longer half-life in serum.

The portion bound to the carrier protein is typically inactive. There is a small portion of the hormone that is not bound to the carrier protein, and this is called the active or free portion. This is clinically significant because some common conditions may result in an increase or decrease in the amount of carrier protein. This does not affect the free (active) portion, but does affect the total amount of hormone present (free + bound). Many laboratories measure the total, and not the free hormone level. Consequently, when there is a carrier protein abnormality, the total hormone may not accurately reflect the free level, which could lead to errors in diagnosis and management. Fortunately, many hormones can be measured in their free (unbound) state, which avoids this type of problem.

Peptide, glycoprotein, mineralocorticoid, and catecholamine hormones are not bound to carrier proteins and thus the type of problem mentioned above does not apply. Because they travel unbound in the plasma, they are usually degraded more quickly than the carrier-protein hormones. Some glycoproteins, because of their large carbohydrate component, are more slowly metabolized than pure peptide hormones.

HORMONAL REGULATION

Although endocrinology is very complex, the good thing is that much of it can be figured out if you understand the mechanisms. **Most hormones have another hormone that regulates its secretion; a hormone that stimulates another hormone's secretion is called a trophic or stimulatory hormone. Those that cause less of the hormone to be secreted are called inhibitory hormones.** The hormone thus secreted by the gland of interest causes a desired effect at the target gland's nucleus (e.g., production of a protein). **Once this substance reaches a desired level, it tells the trophic hormone cells to slow down and stop stimulating the endocrine organ. This causes reduction in the hormone levels by a process called feedback inhibition.** This keeps the whole system in check by preventing too much hormone from being synthesized. In effect, the end product of the endocrine organ becomes a type of indirect inhibitory hormone (by decreasing production of the trophic hormone).



Feedback Inhibition

You may compare the concept of feedback inhibition to filling up your car with gas. You go to the gas station when your gauge says that the tank is empty. Problems may arise when the gauge malfunctions (e.g., you have a full tank when it reads empty, or vice versa, resulting in inadvertently running out of fuel). When you fill up the tank, the pump should stop delivering gas when the tank is full. If it stops too soon, the tank will not be full; if it does not stop after the tank is full, gas spills out all over the place. The purpose of feedback inhibition is to keep the “gas tank” at the correct level.

When something disrupts the normal feedback mechanisms, the endocrine system goes awry and hormonal abnormalities result. Most endocrine disorders can be understood by thinking of ways that the feedback mechanisms become disordered, resulting in disruption of the endocrine system:

1. Target organ is damaged or absent and produces insufficient hormone (hypofunction), despite normal stimulatory pathways: it cannot respond to trophic hormone stimulation (primary deficiency, such as hypothyroidism due to Hashimoto's thyroiditis or thyroidectomy; i.e., the organ is damaged or absent).
2. Target organ produces too much hormone (hyperfunction—the gas pump does not stop despite the tank being full): autonomous secretion of hormone occurs despite suppressed trophic hormone (e.g., Cushing's syndrome [cortisol hypersecretion] due to autonomously functioning adrenal tumor; hyperthyroidism due to toxic nodular goiter).
3. Receptor defect/hormone resistance: desired effect not produced despite the presence of large amounts of hormone (e.g., type 2 diabetes mellitus, androgen insensitivity syndrome (testicular feminization)).
4. Excess trophic hormone that secondarily produces excess target organ hormone (e.g., Cushing's syndrome due to excess corticotropin [ACTH] production).
5. Deficiency of trophic hormone: inadequate target organ hormone produced despite structurally intact primary organ (secondary deficiency, e.g., hypopituitarism).
6. Administration of excess exogenous hormone (e.g., Cushing's syndrome due to excess corticosteroid administration).

INTERACTIONS BETWEEN THE ENDOCRINE AND IMMUNE SYSTEMS

It was recognized long ago that alterations in the immune system occur after a significant change in the endocrine milieu (e.g., gonadectomy, pregnancy). This led to the proposition that there are important interactions between the immune and endocrine systems. **Cytokines are extremely potent molecules secreted by immune cells that have significant regulatory effects on the endocrine system; in a way, they act as hormones themselves.** Hundreds of different cytokines have been isolated, and include the interleukins, tumor necrosis factors, interferons, transforming growth factors, and colony-stimulating factors. Such immune factors may either inhibit or potentiate endocrine secretion. For example, it was observed long ago that severe burn victims increased their corticosteroid and catecholamine production dramatically; much of this increase can be explained by the effects of various inflammatory factors on the adrenal cortex and medulla. **A very common condition called the euthyroid sick syndrome appears to be at least partially mediated by inflammatory products such as cytokines.** A full discussion of this topic is complex and beyond the scope of this text.

HORMONE MEASUREMENTS

Although we can measure most known hormones in the blood, the circumstances under which we measure them are very important. Random hormone levels are often of little use because many hormones are secreted in periodic or cyclical manner, with levels varying throughout the day. For example, cortisol levels are typically highest in the morning, but lower in the evening. These levels are often the opposite in a person who works the “night shift.” Totally blind individuals sometimes lose this cyclical variation, so it appears that the presence of daylight may have some influence on this phenomenon.

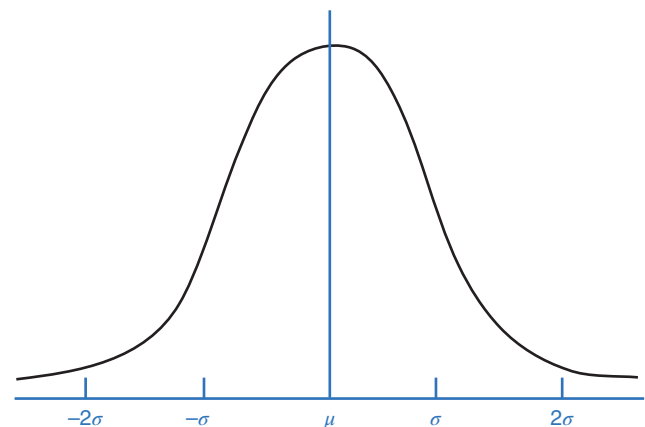
To adequately study secretion of some hormones, we must perform a “perturbation” study in which a substance is given to produce a desired result (i.e., stimulation or inhibition of the hormone’s secretion). If one is concerned about hormone deficiency, a stimulatory test is done by administering a secretagogue

(substance that provokes a hormonal response). The hormone of interest is usually measured before, and at one or more intervals after, administration of the secretagogue.

If hormonal excess is instead suspected, then a suppression or inhibitory test is performed: a substance known to suppress hormone levels is administered. For example, random growth hormone (GH) levels are often not useful in evaluating GH excess (gigantism or acromegaly) because of the episodic secretion of pituitary hormones. Since hyperglycemia is a known inhibitor of GH secretion, a glucose suppression test is possible, in which GH levels are measured before and after a large oral glucose load. In normal health, GH is suppressed; in acromegaly, secretion is autonomous and it is not suppressed.

An alternative to a provocative test may be urine collection over a long period of time (e.g., 24 h), which eliminates some of the problems associated with random hormone measurements. For example, pheochromocytomas often secrete catecholamines intermittently, making random measurements suboptimal during a quiescent period. A 24-h urine collection for catecholamines and metabolites will usually be elevated in these persons (although plasma measurements may be useful during active episodes).

One must often use caution in the interpretation of laboratory test “normal values.” Most human measurements (height, weight, intelligence, etc.) and measurements of hormone function follow the normal distribution or “bell curve”:



Normal Distribution Curve

The normal distribution curve is symmetrical about the mean (μ) or 50th percentile. One and two standard deviations (σ) above the mean correspond approximately to the 84th and 97.5th percentiles, respectively; one and two standard deviations below the mean correspond to the 16th and 2.5th percentiles, respectively. A laboratory often defines “normal ranges” as a 95% confidence interval (two standard deviations above and below the mean); this means that by definition, 5% of “normal” persons fall outside the “normal range,” and that minimally abnormal values may simply represent a normal variant.

Normal ranges may vary according to variations in population (age, gender, ethnicity, etc.). For example, “normal” TSH levels in pregnancy are significantly lower than in nonpregnant females, due to the high concentration of the glycoprotein hormone β -hCG, which has TSH-like activity at the very high concentrations found in pregnancy (so less native TSH is needed); in addition, “normal” TSH values are higher in elderly patients. Hemoglobin A_{1c} levels (an index of long-term glycemic control in diabetes) appear to be slightly higher in African Americans and Hispanic Americans (given equivalent glucose levels), due to genetic factors not related to glucose control.

In addition, “normal ranges” for some hormones may be quite wide, for example, the normal range for serum total thyroxine is approximately 5.0–12.0 $\mu\text{g}/\text{dL}$. So, it is possible for a person to have hypothyroidism with a “normal” T4 of 5.2 $\mu\text{g}/\text{dL}$; “normal” for him or her might really be 9 $\mu\text{g}/\text{dL}$. **It is often useful, therefore, to measure both the hormone of interest and the trophic hormone (called a “hormone pair”).** Indeed, many patients with low normal T4 levels have elevated TSH levels, indicating mild primary (“subclinical”) hypothyroidism. **Measuring the pair often yields more information than either hormone measurement provides alone.**

NOMENCLATURE OF ENDOCRINE DISORDERS

A normal endocrine state is denoted by the Greek prefix “eu” (e.g., euglycemia, euthyroid, eucalcemic). Hypofunctional states contain the prefix “hypo” (e.g., hypoparathyroidism, hypopituitarism); the prefix “hyper” means too much, obviously. Examples of hyperfunctional states include hyperthyroidism, hyperparathyroidism, and hyperinsulinism. These disorders

may be classified more specifically. For example, there are many causes of hyperthyroidism: Graves’ disease, toxic nodular goiter, and subacute thyroiditis. Patients with elevated glucose levels are usually said to have diabetes mellitus rather than hyperglycemia.

HYPOFUNCTION

Hormone deficiency syndromes

Endocrine deficiency occurs if the primary (target) organ functions inadequately or is absent; this is a primary deficiency disorder. Examples include hypothyroidism due to Hashimoto’s thyroiditis or thyroidectomy, Addison’s disease (primary adrenal insufficiency), and type 1 diabetes mellitus. In primary disorders, the organ’s trophic hormone level is elevated; for example, those with primary hypothyroidism have an elevated serum TSH level. The trophic hormone in this case is “beating a dead horse”—the gland does not work properly despite massive attempts to stimulate it.

Secondary deficiency disorders occur when the trophic hormone for the target organ is deficient. This occurs in hypopituitarism, in which the target organs (thyroid, adrenal, gonads) are structurally intact, but are not stimulated properly. Tertiary disorders are similar to secondary syndromes except that the deficiency is one step higher; that is, the trophic hormone for the trophic gland is deficient. An example is hypothalamic dysfunction, in which the hypothalamic hormones are made in insufficient amounts to stimulate the pituitary, and in turn, the target organs.

Antibody-mediated (autoimmune) endocrine organ destruction is the most common cause of hormone deficiency. Our bodies normally produce antibodies to defend against invaders such as viruses and bacteria. Occasionally, however, the body may produce antibodies that attack its own organs, causing destruction. The tendency for autoimmune diseases is genetically mediated, but environmental factors (i.e., exposure to an environmental “trigger”—perhaps an antigen that triggers an antibody response) seem to be a requirement as well.

Inflammatory or infiltrative disease may also result in organ destruction and hormone deficiency. Patients with inflammation of the pancreas (pancreatitis) may develop diabetes due to insufficient insulin secretion. Hemochromatosis is a relatively common genetic disorder of iron overload in which excessive iron deposits cause organ

dysfunction. This disorder may cause diabetes and adrenal insufficiency.

Large tumors in or about the target organ may destroy enough cells to cause hormone deficiency. A common example is pituitary hormone deficiency (hypopituitarism), which is often caused by the destructive effects of very large pituitary or suprasellar tumors. Destructive tumors more commonly cause secondary rather than primary endocrine deficiencies.

Hormone resistance

It is also possible for a hormone to be made in sufficient quantity, but to have inadequate effect because of resistance to the hormone. Here, the patient's hormone receptors are either absent or insufficiently sensitive to the hormone for the desired metabolic effect to occur. This appears to the clinician as a true endocrine deficiency disorder, even though normal or even increased amounts of the hormone are made. **The most common example is type 2 diabetes mellitus, in which patients are (in initial stages) insulin resistant. These patients develop elevated blood glucose levels (hyperglycemia), despite normal or even high levels of serum insulin.** Very large amounts of exogenous insulin may be required to overcome the insulin resistance.

TREATMENT OF HORMONE DEFICIENCY

Ideally, we treat deficiency syndromes by replacing the native hormone, producing normal physiologic levels. This is pretty easy for orally absorbed molecules that have a relatively long half-life (e.g., thyroxine, hydrocortisone, estradiol). Some hormones, however, are not well absorbed orally. These include most peptide hormones, which are destroyed by acids and digestive enzymes in the gastrointestinal tract. Many of these are given by injection; examples include insulin and growth hormone. Some peptides are synthetically modified to have a longer duration in the blood; these include desmopressin (a derivative of antidiuretic hormone or vasopressin which can be given orally) and octreotide (an analog of somatostatin given subcutaneously).

Other hormones such as testosterone are well absorbed orally, but are metabolized in the liver to inactive products (the "first-pass" phenomenon) before they get to the circulation, rendering them inert. These hormones must be given by injection, intranasally, or via transdermal (gel or patch) preparation.

And, even if we have the hormone to provide, it may not be possible to replace it in a precise physiological manner. The best example of this is type 1 diabetes mellitus, in which the patient is dependent on insulin injections to sustain life. Despite many technological advances, it is currently impossible to mimic insulin secretion perfectly. At best, the patient must learn to live with compromises, such as occasional hyperglycemia and hypoglycemia, which may interfere with daily living.

ENDOCRINE EXCESS SYNDROMES

As with deficiency syndromes, excess may occur in primary or secondary forms. A primary disorder occurs when the organ itself produces the excess hormone without stimulation by a trophic gland. An example is primary hyperaldosteronism caused by an autonomous adrenal tumor. A common example of a secondary excess syndrome is Cushing's disease, which is caused by increased production of adrenocorticotrophic hormone (ACTH) by a pituitary tumor. In this case, there is nothing wrong with the target organ (the adrenal gland)—it is responding as it should to excess trophic hormone. The "wide receiver" (adrenal cortex) is simply obeying the quarterback (pituitary), who has "called the wrong play."

Unlike hormone deficiency (usually caused by autoimmune diseases), hormone excess syndromes are typically caused by tumors (benign or malignant). These tumors typically arise in the organ that normally produces the hormone. **Hyperfunctioning tumors may also arise in an organ other than the one normally producing the hormone; these conditions are called paraneoplastic or ectopic ("out of place") syndromes.** We will discuss these syndromes in the final lecture.

Autoimmune syndromes only rarely cause endocrine excess as part of rather esoteric syndromes. An exception is the common condition Graves' disease, where thyroid receptor autoantibodies mimic the trophic hormone (TSH) and result in hyperthyroidism.

Another reason for hormone excess is exogenous administration of the hormone, either intentionally (iatrogenic) or by the patient without the physician's knowledge (factitious). For example, glucocorticoids are commonly used to treat transplant patients to prevent rejection. Chronic administration in past high-steroid regimens resulted in iatrogenic Cushing's syndrome. (Fortunately, current immunosuppressive regimens

today use very low steroid doses and depend on the immune-modifying actions of newer drugs targeting specific aspects of the immune process, mostly eliminating these problems.) Glucocorticoids are still used in high doses at times to treat other chronic diseases (e.g., rheumatologic and pulmonary disease).

An example of factitious hormone use is the person who wishes to lose weight by taking exogenous thyroid hormone (not prescribed by any physician), or those without diabetes who self-induce hypoglycemia with insulin or sulfonylureas. These cases are often health care workers with psychiatric problems and access to medication.

IMAGING TESTS IN ENDOCRINOLOGY

Plain X-rays (roentgenograms) are inexpensive and simple to perform, but have limited use in endocrinology. At the energy levels used for imaging, X-rays are absorbed to a great extent by molecules containing elements with high atomic numbers (Z , or number of protons in the nucleus). Such molecules appear opaque (white) on X-ray. Iodine ($Z=53$) and barium ($Z=56$) are relatively heavy elements, which is why they are commonly used as radiocontrast agents. (This use of stable iodine has nothing to do with the uses of its radioactive counterparts.) Molecules containing calcium ($Z=20$) also show up well on X-ray (think of bones, which are quite dense). Some endocrine disorders are associated with ectopic calcification and may be detected on plain X-ray. Conversely, organic molecules predominantly contain carbon, oxygen, nitrogen, sulfur, phosphorus, and hydrogen (low atomic number elements) and are thus not visualized well on conventional X-ray films.

Nuclear medicine imaging studies use radioactive substances that are administered to patients. They may be given orally (e.g., radioiodine), intravenously (technetium sulfur colloid), or inhaled (xenon). The element used is typically a radioactive counterpart (isotope) of a nonradioactive element (or one with similar chemical properties). For example, ^{123}I and ^{131}I are isotopes of the nonradioactive (stable) ^{127}I . (The superscript immediately preceding the chemical symbol indicates the mass number (A), which is the number of protons (Z) plus the number of neutrons.) Other elements do not occur in the natural compound but are similar in structure and chemical properties to the natural element. **Technetium ($^{99\text{m}}\text{Tc}$) is a synthetic transition metal with radioactive properties making it very suitable for imaging.** It is

the lowest atomic number element ($Z=43$) without any stable isotopes, and lies in the periodic table between molybdenum and ruthenium. Its low toxicity, ease of incorporation into numerous compounds, and low cost make it an all-purpose versatile radionuclide. In nuclear studies, the radioactive element is either administered in its native form or attached to a molecule that mimics the native substance.

Radionuclides may emit radiation in several ways. They may emit non-particulate energy such as photons (gamma rays), which are essentially high-energy light beams. Gamma radiation occurs after a nuclear event (e.g., β decay) that leaves the nucleus in an excited state. When the nucleus returns to its unexcited (ground) state, gamma rays are emitted from the nucleus. X-rays are exactly the same type of energy as gamma rays except that their origin is the outer electron shells rather than the nucleus when an electron passes from a higher to a lower energy state. Iodine-123 (^{123}I) and technetium are examples of pure gamma emitters.

Some radionuclides emit particulate radiation in addition to gamma rays. The nuclides of clinical interest emit beta (β) particles, which are electrons ejected from the nucleus, resulting in conversion of a neutron to a proton. β -Particles may cause significant tissue destruction, and therefore these elements are less suitable for imaging. They are used when actual destruction of tissue is desired. ^{131}I is a powerful β emitter used to destroy thyroid tissue in those with hyperthyroidism and thyroid cancer. Heavy nuclides that emit α particles (e.g., thorium, uranium, and radium) have no real clinical use in nuclear medicine. Some α -emitters have therapeutic use in targeted radioimmunotherapy.

Radionuclides disintegrate because of the very properties that make them radioactive; the half-life is the amount of time for half of the nuclide to disintegrate. Decay is exponential and the amount present at any time can be calculated if the half-life and original amount of the radionuclide are known:

$$A = A_0 e^{\frac{-0.693t}{t_{1/2}}}$$

where A = activity of the nuclide at the current time; A_0 = original activity of nuclide; t = time elapsed; $t_{1/2}$ = half-life of nuclide; and e = base of the natural logarithm (2.71828 ...).

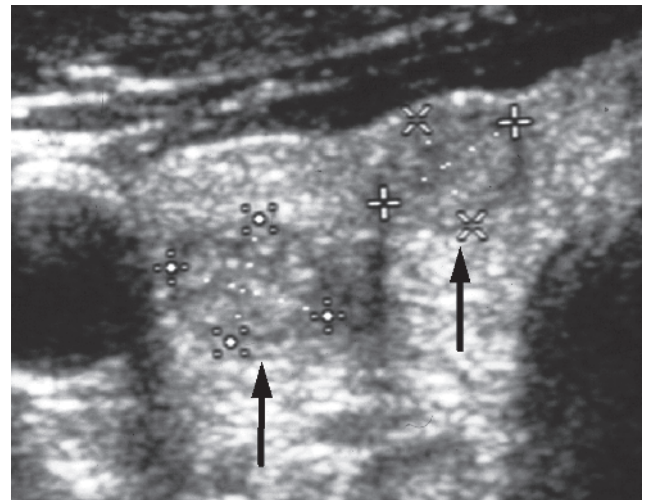
The physical amount of a radionuclide is denoted by its activity and is proportional to the number of disintegrations per second. The traditional unit of radionuclide activity is the curie (named after Marie

Curie, a prominent nuclear physicist and discoverer of polonium and radium). The amounts used in nuclear medicine are in the range of 1/1,000th curie (millicurie, mCi) or 1/1,000,000th curie (microcurie, μCi). Another unit of activity (used more commonly outside the United States) is the becquerel (Bq); $1\text{ mCi} = 37\text{ MBq}$ (megabecquerels). While activity (mCi or MBq) refers to an actual physical amount of radionuclide, the delivered dose of radiation depends on many factors, such as type of energy emitted and energy of the gamma rays, and is beyond the scope of this text. For example, 30 mCi of ^{131}I delivers approximately 100 times as much radiation as 30 mCi of ^{123}I because of the increased energy and particulate emissions of the former.

A radiation counter can detect the amount of gamma radiation emitted. It merely measures the amount of radiation coming from the patient and provides no spatial information. A radionuclide uptake may be calculated using these measurements to provide the fractional amount of nuclide accumulated at a given time. A more complex device, a gamma camera, can produce a two-dimensional image or scan of the organ radiating the energy. Gamma cameras are used to produce thyroid scan images, for example. Although nuclear medicine provides useful functional information, the scan resolution is typically far less than other imaging modalities.

Ultrasound utilizes high-frequency sound waves and takes advantage of their attenuation by various materials. Sound waves are generated by a transducer and placed in contact with the body. The sound is either reflected back to the transducer or absorbed. The distance between the transducer and the reflected echo is calculated by measuring the time between the transmitted wave and the echo. The material that absorbs sound (e.g., air) transmits little or no sound back to the transducer. Very sophisticated images can be obtained by using multiple transducers; high-speed computers collect and interpret the data in a two-dimensional form that can be displayed on a screen.

Unlike nuclear medicine, ultrasound does not expose the patient to ionizing radiation. It is also a “real-time” modality that can be used to guide procedures (e.g., fine-needle aspiration biopsy or insertion of a catheter into a difficult area). The resolution of ultrasound, however, is less than that of magnetic resonance imaging (MRI) or computed tomography (CT). Nor is ultrasound very useful for air-filled cavities (e.g., lung).



Ultrasound of Thyroid Nodule in Patient with Papillary Thyroid Carcinoma

Computed tomography (CT) uses conventional X-ray beams to produce high-resolution “cross-sections” of a body part. The patient is placed between the X-ray tube and a series of X-ray detectors, which move in a circular manner around the patient. After the detectors have completed a full circle around the patient, the data is analyzed by a computer, which reconstructs an image, a virtual “cross-section” of the area of interest. A recent development is the high-resolution (helical or spiral) CT, in which the X-ray tube and detectors move in a helical manner from one end of the area to the other, resulting in many more data points than conventional CT. Single-photon emission computed tomography (SPECT) is a hybrid of CT and nuclear medicine that uses an administered nuclear source rather than an X-ray beam for the radiation source.

Because of its speed, CT is useful for imaging large body cavities (e.g., chest, abdomen, or pelvis) that contain visceral organs. Iodine-containing contrast agents are often administered to help identify key structures. These are contraindicated in those with renal insufficiency. Many patients are allergic and require pretreatment with corticosteroids and antihistamines. These agents also interfere with radioiodine imaging of the thyroid for at least 4 weeks.

MRI takes advantage of the effect of hydrogen nuclei when exposed to a strong magnetic field. At rest, the nuclei are oriented at random. When exposed to a magnetic field, the nuclei “polarize” and oscillate at a certain frequency that is unique to each atom. Since the body is about 80% water (H_2O), there is a lot of hydrogen

to polarize. Sophisticated computer reconstruction of these faint MR signals results in detailed cross-sectional images of the body. A greater variety of imaging angles is available with MRI than CT. Another advantage is the lack of ionizing radiation. A disadvantage is the relatively long scan times compared to CT. The patient must often be enclosed, which may be difficult for those with claustrophobia. “Open” MRI units now exist in which the patient is only partially enclosed. These devices use weaker magnets, however, and may be less suitable for precise imaging of very small structures such as the pituitary. MRI strength is expressed in tesla (T) units. A unit with strength of 0.5T is relatively weak, while the strongest units have magnetic fields up to 6 T.

Positron emission tomography (PET) uses short-lived radionuclides such as fluorine-18, which can be incorporated into compounds used by the body, such as glucose; PET can therefore measure metabolic activity in tissues in addition to providing anatomic information. A positron is an electron with a positive charge. When a positron and electron strike each other, they are converted to energy by an “annihilation reaction,” which can be detected by sensors. PET has been used primarily to measure cerebral and myocardial blood flow, but has shown promise in certain endocrine applications (e.g., detection of thyroid cancer metastases). A disadvantage of PET is the extremely short half-lives of the radionuclides, mandating that they be made at the facility in a cyclotron. Another is the expense (due to the high cost of the radionuclides and equipment, it is one of the most expensive diagnostic tests available).

GENETIC TESTING IN ENDOCRINOLOGY

When insulin was discovered in the 1920s (a remarkable achievement), no one understood much about human genetics, other than the obvious (tall parents tend to have tall children, baldness runs in the family, etc.). It would be another 30 years before DNA was discovered (early 1950s), and decades before that was completely understood. To think that today we would be able to determine molecular genetic markers of disease would seem incomprehensible at that time. Yet, the number of available biomarkers increases at a rapid pace as technology develops at an exponential rate.

The discovery of new genetic markers makes it easier to diagnose diseases earlier and treat before symptoms develop. For example, family members of patients with multiple endocrine neoplasia (MEN) II once had to undergo cumbersome testing procedures for the disorders

Examples of Genetic Markers in Endocrinology

KAL-1, FGFR1	Kallmann syndrome
PHEX (phosphate-regulating endopeptidase homolog)	X-linked hypophosphatemic rickets
Glucokinase (GCK), hepatocyte nuclear factor 1 α , KCNJ11	Maturity-onset diabetes of the young (MODY)
BRAF, PPAR γ	Epithelial thyroid carcinoma
PROP1, POU1F1	Hypopituitarism
RET, VHL, SDHB	Familial pheochromocytoma/paraganglioma syndromes, multiple endocrine neoplasia II
MENIN	Multiple endocrine neoplasia I
SHOX (short stature homeobox)	Turner syndrome, other short stature syndromes

encountered in this syndrome (e.g., medullary thyroid carcinoma, pheochromocytoma). The importance of detection in potentially affected patients is immense in some circumstances (e.g., pheochromocytoma can be lethal if untreated). Instead of undergoing complex testing, measurement of the RET (rearranged during transfection) proto-oncogene can identify patients at risk, who can then undergo prophylactic surgery (e.g., thyroidectomy) if positive.

Most common endocrine diseases are still diagnosed by clinical rather than molecular genetic criteria. While some rare forms of diabetes are linked to specific genetic mutations, the most common form of type 2 diabetes is a heterogeneous disorder without identified genetic markers. The common autoimmune endocrine disorders (type 1 diabetes, Hashimoto’s thyroiditis, etc.) are linked to specific HLA haplotypes, although the penetrance is variable; we know that, for a person to develop an autoimmune endocrine disease, some environmental “trigger” must be present, as genetics are not enough. For example, in monozygotic (identical) twins, the concordance rate of type 1 diabetes is only about 50%, meaning that there is an additional, nongenetic factor that must be present for the other twin to develop the disorder.

This is all good—but remember that genetic testing is quite expensive (>\$1,000 per gene), although this cost may decrease in the future as technology improves. Therefore, it is practical today only to test patients in whom identification of a specific genetic defect would alter treatment or have impact on family members.

EPILOGUE

This lecture has laid the framework for discussion of the endocrine system. Hopefully, you now have a basic idea of how the different systems fit together. In the next several lectures, we will examine each of the “players” in detail,

discussing previous lectures as needed. Finally, we will discuss disorders of multiple endocrine glands in the last lecture.

REVIEW QUESTIONS

- A 27-year-old woman is in an automobile accident and suffers the complete transection of the pituitary stalk in a traumatic brain injury. She would have deficiency of all the following hormones except one:

 - Estradiol
 - Thyroxine
 - Cortisol
 - Aldosterone
 - Growth hormone

(d) Aldosterone secretion is regulated by the renin–angiotensin system, and not by the pituitary. All the others are dependent on normal pituitary function for proper secretion.
- In which one of the following disorders is the deficient hormone itself not used in treatment?

 - Hypoparathyroidism
 - Type 1 diabetes mellitus
 - Primary adrenal insufficiency
 - Primary hypogonadism
 - Primary hypothyroidism

(a) While synthetic PTH is available as a treatment for osteoporosis, it is not used for the treatment of hypoparathyroidism. The others are treated with insulin, glucocorticoids/mineralocorticoids, sex steroids, and thyroxine, respectively.
- In which one of the following disorders is the target organ hormone of interest *elevated* rather than *decreased*?

 - Hypoparathyroidism
 - Primary hypothyroidism due to Hashimoto’s thyroiditis
 - Primary hypothyroidism due to orchidectomy
 - Type 1 diabetes mellitus
 - Type 2 diabetes mellitus

(e) Type 2 diabetes (at least in its early stages) is a disorder of hormone resistance (to insulin, in this case), and not of deficiency. Despite elevated levels of insulin, receptor defects do not allow proper function. The others are clear cases of hormone deficiency.
- Suppressive or inhibitory tests are usually done to evaluate endocrine excess. Which one of the following is a stimulatory or provocative test used primarily to evaluate endocrine deficiency?

 - Dexamethasone test
 - Cosyntropin (synthetic ACTH) test
 - Saline infusion test
 - Glucose tolerance test

(b) Cosyntropin (1–24 ACTH) stimulates the adrenal cortex to produce cortisol, and is useful in the evaluation of adrenal insufficiency. Dexamethasone (a) is used in suppressive tests for evaluation of Cushing’s syndrome; saline infusion suppresses aldosterone levels and is used in the evaluation of hyperaldosteronism; glucose (d) suppresses growth hormone levels and is employed in the evaluation of growth hormone excess (gigantism and acromegaly).
- Which one of the following patients does not have a primary endocrine deficiency disorder?

 - A 52-year-old woman going through menopause
 - A 34-year-old man who has a thyroidectomy for thyroid cancer
 - A 16-year-old girl with new onset diabetes mellitus requiring insulin
 - A 14-year-old boy with hypopituitarism due to an intracranial tumor
 - A 47-year-old male with HIV and adrenal insufficiency due to adrenal fungal infection

(d) This patient has multiple secondary endocrine deficiencies (hypothyroidism, adrenal insufficiency, hypogonadism, etc.) due to lack of pituitary trophic hormones. The others are examples of primary deficiency disorders.

