Endocrinology Review – Adrenal and Thyroid Disorders

LINDA S. GORMAN, JANELLE M. CHIASERA

LEARNING OBJECTIVES

1. Define endocrinology and list the major endocrine glands of the body.
2. Explain how feedback (positive and negative) promotes maintenance of normal levels of hormones.
3. Differentiate between steroid and peptide hormones with regard to their mechanism of action.
4. Provide examples of peptide and steroid hormones.
5. Explain how endocrine disorders are categorized.

ABBREVIATIONS: ACTH - adrenocorticotropic hormone; ADH - antidiuretic hormone; CRH – corticotropin releasing hormone; DHEA – dehydroepiandrosterone; FSH - follicle stimulating hormone; GHRH - growth hormone releasing hormone; GnRH – gonadotropin releasing hormone; HPT - hypothalamus, pituitary, target gland; LH - luteinizing hormone; MBST - membrane-bound signal transducer; SRE - steroid response element; TRH - thyrotropin releasing hormone; TSH - thyroid stimulating hormone

INDEX TERMS: Endocrine Glands, Hormones, Hydrocortosone, Hypoalamo-hypophyseal System, Pituitary-Adrenal System, Stress

Clin Lab Sci 2013;26(2):107

Linda S. Gorman, PhD, MLS (ASCP)[CM], University of Kentucky, Lexington, KY

Janelle M. Chiasera, PhD, MT (ASCP), University of Alabama at Birmingham, Birmingham, Alabama

Address for Correspondence: Linda S. Gorman, PhD, MLS (ASCP)[CM], CLS Education Co-ordinator, Associate Professor, 900 S. Limestone Ave, Rm 126G CTW, University of Kentucky, Lexington, KY 40536-0200, (859)-218-0855, lsgorm0@uky.edu

This article represents the first of three articles focusing on the endocrine system. The first article will provide you with fundamental theory regarding the endocrine system that will serve as a basis for understanding the next two articles focusing on two specific endocrine glands, the thyroid and adrenal glands.

Endocrinology is the branch of medical science that deals with the endocrine system, a system that consists of several glands located in different parts of the body that secrete hormones directly into the bloodstream. Although every organ system in the body may respond to hormones, endocrinology focuses specifically on endocrine glands whose primary function is hormone secretion. Major endocrine glands include the pituitary (anterior and posterior), hypothalamus, thyroid, parathyroid, pineal, pancreas, adrenal (cortex and medulla), and gonads (ovaries and testes). Figure 1 shows the various locations of endocrine glands.

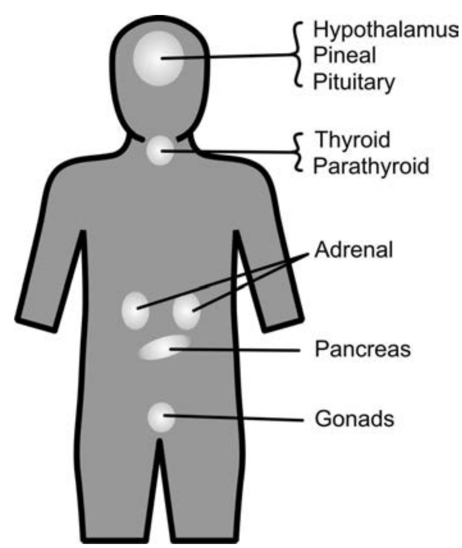

Figure 1. Location of the Major Endocrine Glands. Image reprinted with permission of John Nagy.

The HPT Axis

The endocrine system is part of the body's extracellular communication system that links the brain to various parts of the body and acts to control body metabolism, growth and development, and reproduction. The production and circulating levels of hormones are controlled by means of a feedback process that links the hypothalamus to the pituitary and the pituitary to a target gland. This linkage is referred to as the hypothalamus, pituitary, target gland (HPT) axis.[1,2] Refer to Figure 2.

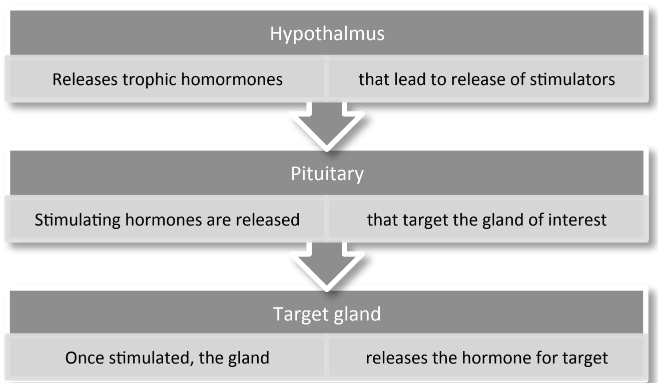

Figure 2. Hypothalamus, Pituitary, Target Gland (HPT) axis

In general terms, hormones are produced by specialized glands in one part of the body and travel through the bloodstream to result in a biological effect at a distant site. The hypothalamus is considered to be the "master gland" of this axis as it takes signals from cortical inputs, autonomic function, and other environmental triggers and delivers signals (via releasing hormones) to target cell types in the pituitary gland. The pituitary gland responds by releasing hormones that act on target glands to produce specific target gland hormones. For example, thyrotrophin releasing hormone (TRH) produced by the hypothalamus acts on thyrotroph cells of the pituitary gland to produce thyroid stimulating hormone (TSH). Thyroid stimulating hormone acts directly on the thyroid gland (target gland) to produce thyroid hormones. Refer to Table 1 for other examples of releasing hormones and their effect on pituitary and target glands.[1,2]

The hypothalamus gland is located in the brain above the brain stem and below the thalamus.[3] In humans, the hypothalamus is the size of an almond. Its functions include releasing the trophic hormones called "releasing hormones". These trophic hormones span from Thyrotropin Releasing Hormone (TRH), which affects the release of thyroid hormones, Corticotropin Releasing Hormone (CRH), which affects adrenal hormones, to ones that foster sexual characteristics (Gonadotropin Releasing Hormone) and growth (Growth Hormone Releasing Hormone). Our focus here is on the thyroid and adrenal glands so we will leave the other hypothalamic hormones for others to discuss. (Figure 2, Table 1.)

Table 1. Releasing Hormones and Their Effect on Pituitary and Target Glands

Hypothalamic Hormone	Cellular Target/Pituitary Gland Hormone	Target Gland/Target Gland Hormone(s)
Corticotropin Releasing Hormone (CRH)	Corticotroph/ ACTH	Adrenal gland (Cortisol)
Thyrotropin Releasing Hormone (TRH)	Thyrotroph/TSH	Thyroid Gland/ T3 and T4
Growth Hormone Releasing Hormone (GHRH)	Somatotroph/GH	All tissues
Gonadotropin Releasing Hormone (GnRH)	Gonadotroph/ LH and FSH	Gonads/Testosterone and Estrogen

In the hypothalamus the tropic releasing hormones come from neurons in the anterior hypothalamus and are released thru the portal veins to the pituitary sinusoids. The hypothalamic hormones stimulate the selective pituitary release of hormones, often called "stimulating hormones".[4] The pituitary stalk links the posterior pituitary with the part of the hypothalamus that secretes anti-diuretic hormone (ADH) and oxytocin.[4] These hormones are associated with the posterior pituitary and not of interest here.

The Thyrotrophic releasing hormone (TRH) and Corticotrophic releasing hormones of the hypothalamus are released into the hypothalamic portal vein system that is separate from the general human circulatory system. These releasing hormones can travel thru the portal veins to the pituitary without being evident in the venous blood.[4] Once the tropic hormones enter the pituitary sinusoids they can stimulate the pituitary to produce/secrete specific stimulating hormones, such as Thyroid Stimulating Hormone (TSH) if the hypothalamus sends TRH or Adenocorticotropic hormone (ACTH) if the hypothalamus sends CRH. (Figures 3 and 4)

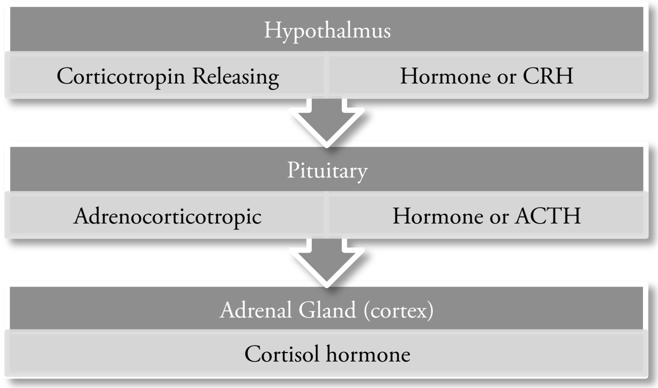

Figure 3. Adrenal gland stimulation to produce cortisol hormone.

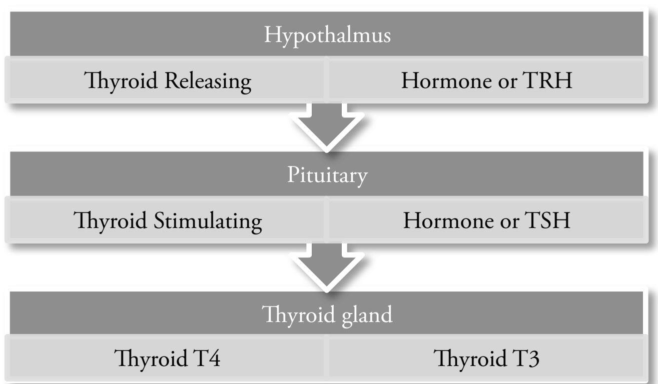

Figure 4. Thyroid stimulation by TSH to produce thyroid hormones T4 and T3.

The Pituitary

The pituitary gland, with its stimulating hormones, is like a bus stop or railroad station. The pituitary takes in the messages from hypothalamic released hormones and responds by sending out its own stimulating hormones. By itself the pituitary is the size of a pea[5] and is located between the two optic nerves in the brain. This gland has 2 compartments with the anterior section made of individual cells that can produce individual stimulating hormones such as TSH, ACTH, LH/FSH, or Growth hormone. These anterior pituitary stimulating cells are individualized in their function. The 5 functional units of the anterior pituitary can be thought of as individual sections that do their job of producing only one type of stimulating hormone per functional unit. The posterior section takes what has been sent to it from the hypothalamus, namely ADH and oxytocin and sends these hormones into the blood circulation so they can exert their respective affects.

Mechanism of Action

All hormones act on their specific glands/tissues through receptors located on the surface or within the cytosol of the cell. The binding between the hormones and the receptor serves as an initial signal resulting in a cascade of events that result in the production of a protein. Hormones are divided into two broad categories, peptide (water soluble) and steroid (water insoluble). Refer to Table 2. While all hormones react with receptors, their mechanism of action varies depending on how they are categorized. Because they are water soluble, peptide hormones must interact with receptors that are located at the surface of the cell. Once bound to its receptor, the hormone receptor complex activates a membrane-bound signal transducer (MBST). Often this signal transducer is guanine nucleotide-binding regulatory protein, also called the G-protein complex. The MBST is coupled to the adenylate cyclase and phospholipase enzyme systems and once activated results in the production of a peptide hormone. Due to their water insoluble nature, steroid hormones may diffuse across the surface of the cell membrane and bind to their receptors in either the cytoplasmic or nuclear fractions of the cells. Once the steroid hormone binds to its receptor, the receptor undergoes a conformational change resulting in activation of the entire hormone receptor complex. The activated complex has an increased affinity for chromatin at a site referred to as the steroid response element (SRE). The SRE binding ultimately causes the production of the nuclear product--a specific protein.[6,7] Peptide hormones are synthesized as preprohormones and are packaged into secretory vesicles providing a ready available storage pool of hormones to draw from. Steroid hormones, on the other hand, are all produced from cholesterol and are available bound to proteins. Because they are protein bound their action takes longer to initiate; however, once initiated their action is sustained due to the increased half life from being protein bound.

Hormone Regulation and Transport

A unique feature of the endocrine system is that all hormones are controlled through positive and negative feedback systems. This feedback system involves two production units. The hormones from one unit usually cause the second unit to increase its hormone production. The second unit's hormones then feed back to the first unit to control any further output from the first unit. It is through this feedback loop that the hu-

Table 2. Peptide and Steroid Hormones (note: this is not an exhaustive list of all endocrine hormones).

Hormone Category	Hormones
Peptide	Thyroid Stimulating Hormone
	Follicle Stimulating Hormones
	Luteinizing Hormone
	Prolactin
	Growth Hormone
	Parathyroid Hormone
	Adrenocorticotropic Hormone
	Thyroid Hormones
	Pancreatic hormones
Steroid	Testosterone
	Dehydroepiandrosterone sulfate
	Estrogens
	Progesterone
	Cortisol
	Aldosterone

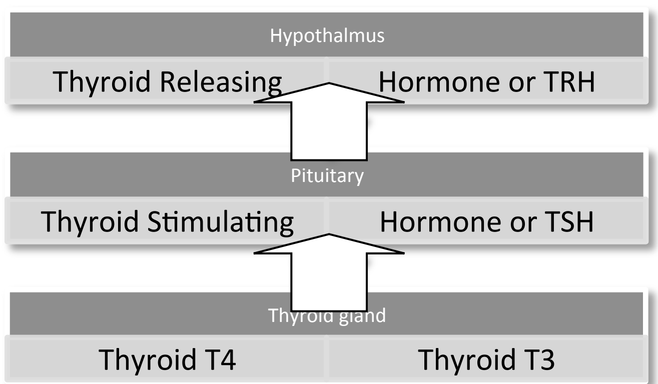

Figure 5. Thyroid hormone acting as Negative feedback to Pituitary and Hypothalmus.

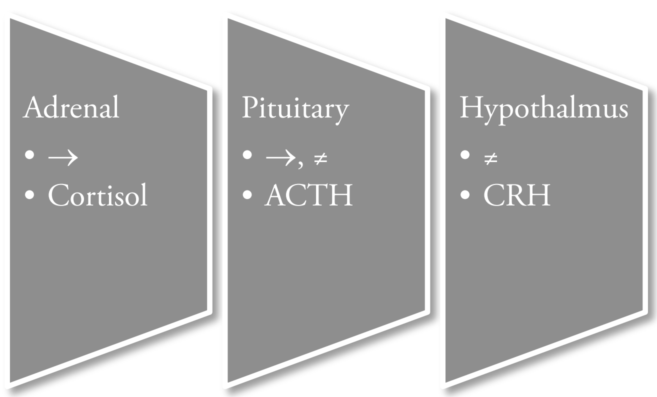

Figure 6. Cortisol Negative Feedback Mechanism inhibits the Pituitary and Hypothalmus secretions of stimulation.

man body is able to maintain normal levels of circulating hormones. Various textbooks[1,2,4] and articles[3,5,7] on hormones refer to the "negative feedback" mechanism as the predominant mechanism by which endocrine hormones are regulated in the human body. Figures 5 and 6 are included here to help demonstrate the negative feedback mechanism as it applies to the thyroid and adrenal gland in humans.

Negative feedback mechanisms are used to prevent overproduction of hormones from the gland and to inhibit the releasing and stimulating hormones produced from the hypothalamus and pituitary, respectively. Figure 6 shows the negative feedback loop for the adrenal gland. Cortisol from the adrenal gland is circulated in the blood back to the hypothalamus and pituitary so that inhibition of the ACTH and CRH will occur. As long as the level of cortisol hormone is meeting the body's needs the pituitary and hypothalamus will not stimulate the adrenal gland. Once the cortisol level becomes low or inadequate in the function of this hormone the osmotic stimulation to the brain will cause the hypothalamus CRH to be released, stimulating the pituitary to release ACTH and leading to the adrenal glands release of cortisol once again.

Pituitary and hypothalamic hormones are stimulated to be released in a minute-by-minute pulsatile fashion. In addition to the pulsatile feature, pituitary hormones also exhibit a biorhythmic pattern. Biorhythms with a 24 hour time span are referred to as circadian (diurnal). The circadian (diurnal) cycle is controlled by both light cycles and sleep patterns and therefore any disruption to light cycles and/or sleep patterns may alter the normal diurnal cycle of hormones. While pituitary hormones exhibit circadian rhythm, this rhythm will differ depending on the pituitary hormone produced. For example, highest concentrations of adrenocorticotrophic hormone (ACTH) are seen at 0800 with lowest concentrations seen at midnight. Highest concentrations of Thyroid Stimulating Hormone (TSH) are seen just before midnight and lowest levels are seen midday. The pulsatile and diurnal features of endocrine hormones warrant closer consideration when interpreting their concentrations in light of making a clinical diagnosis.[1,2]

Steroid hormones circulate in the body bound to proteins or in the free form. Bound hormones are either high or low affinity protein bound hormones. Several proteins serve as carriers of hormones including general hormone binders such as albumin and prealbumin and high affinity specific binders such as thyroid binding globulin. Refer to Table 3 for a list of hormone transport proteins. It is important to note that some steroid hormones lack a specific binding protein such as dehydroepiandrosterone (DHEA). In this case, DHEA is sulfated to increase its solubility and promote its transport without a specific protein.[1,2]

Table 3 Transport Proteins for Hormones and Their Bioavailability

Transport Protein	Hormones	Binding Strength/Availability
Albumin	All	Weak/Bioavailable
Prealbumin	All	Weak/Bioavailable
Cortisol Binding Globulin	Cortisol	Strong/Not bioavailable
Thyroid Binding Globulin	T3 and T4	Strong/Not bioavailable
Thyroxine Binding Prealbumin	T4	Strong/Not bioavailable
Sex Hormone Binding Globulin	Sex Hormones	Strong/Not bioavailable

Pathology and Testing

Diseases in the endocrine system are categorized using two processes 1) by the level of circulating hormone and 2) by the endocrine gland causing the disorder. Diseases categorized by the level of circulating hormones are categorized as either hyper or hypo. Disorders causing increased levels of thyroid hormones in circulation are categorized as hyperthyroidism while those resulting in low levels of circulating thyroid hormones are categorized as hypothyroidism. Diseases categorized by the gland causing the disorder are categorized as primary when the disorder is caused by the target gland, secondary when the gland causing the disorder is the pituitary gland, and tertiary when the gland causing the disorder is the hypothalamus. Using the example above, when a disorder involving the thyroid gland is caused by the target gland itself (the thyroid) and results in elevated levels of thyroid hormones this disorder is referred to as primary hyperthyroidism. When a disorder involving the thyroid gland is caused by an abnormality with the pituitary gland and results in elevated levels of thyroid hormones this disorder is referred to as secondary hyperthyroidism.[1,2]

Specific endocrine organ pathologies are beyond the scope of this article. Testing for the diagnosis of disorders involving the endocrine system is complex due to the overlapping signs and symptoms produced. Testing may include basal levels of hormones and/or provocative testing including stimulation and/or suppression tests. The pathology surrounding and the details of diagnosing thyroid and adrenal disorders are being covered in the two associated articles.

Summary

The endocrine system comprises part of the body's communication system that links the brain to its organs and functions to control metabolism, growth & development and reproduction. Control of this system is predominantly through a complex feedback system that works to maintain homeostasis. When there is disruption to an endocrine gland or to the feedback system, it can lead to endocrine disturbance. Due to the complexity of the endocrine system, diagnosis and interpretation of endocrine pathology can be challenging.

REFERENCES:

1. Clines GA, Demers LM. General Endocrinology. In: Kaplan LA, Pesce AJ. eds. Clinical Chemistry: Theory, Analysis, Correlation. 5th ed. St. Louis:Mosby Inc.;2010:929-47.
2. Kleerekoper M. Hormones. In: Burtis CA, Ashwood ER, Bruns DE. eds. Tietz Fundamentals of Clinical Chemistry. 6th ed. Philadelphia:W.B. Saunders Company;2008:837.
3. Ananya, M. Nov 5,2012 (hypothalamus) http://www.news-medical.net/health/What-is-the-Hypothalamus.aspx. Accessed 2013 January 28
4. Jones, RE, In:Michael L. Bishop,Edward P. Fody, Larry E. Schoeff,eds. , Clinical Chemistry: Techniques, Principles, Correlations, 6th ed. Philadelphia: Lippincott, Williams and Wilkins; 2010:445-55.
5. Neurosurgery Department. What is the pituitary gland © 2001-12 Department of Neurosurgery, University of Pittsburgh, http://www.neurosurgery.pitt.edu/minc/skullbase/pituitary/index.html. Accessed 2013 January 8
6. Alberts B, Johnson A, Lewis J, et al. Molecular biology of the cell. 4th ed. New York: Garland Science; 2002. Signaling through G-Protein-Linked Cell-Surface Receptors. Available from: http://www.ncbi.nlm.nih.gov/books/NBK26912/ Accessed 2013 February 25
7. Chan L, O'Malley BW. Mechanism of action of sex steroid hormones. N Engl J Med 1976;294:1322-8.