ENDOCRINE PATHOLOGY

TEXT AND ATLAS

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CHAPTER

1 INTRODUCTION ANATOMY, PHYSIOPATHOLOGY

Although some ancient cultures noted biological observations grounded in endocrine function, modern understanding of endocrine glands and how they secrete hormones has evolved only in the last 300 years. Ancient Egyptian and Chinese civilizations castrated (removal of the testicles) a servile class of men called eunuchs. It was observed that eunuchs were less aggressive than other men, but the connection of this behavior to testosterone was not known until recently.

Light was shed on endocrine function during the seventeenth and eighteenth centuries by a few significant advances. Thomas Wharton (1614-1673), a seventeenth century English scientist noted the differences between ductile and ductless glands. In the 1690s, Fredrik Ruysch (1638-1731), a Dutch scientist first stated that the thyroid secreted important substances into the bloodstream. Some decades later, Theophile Bordeu (1722-1776) claimed that «emanations» were given off by some body parts that influenced functions of other body parts. [2,3,6]

In 1849, one of the greatest and early experiments performed in endocrinology was published by A. A. Berthold (1803-1861). Berthold took six young male chickens and castrated four of them. The other two were left to develop normally and used comparatively as control samples. Two of the castrated chickens were left to become chicken eunuchs. But what was done by Berthold with the other two castrated chickens is what changed endocrinology. He transplanted the testes back into these two chickens at a distant site from where they were originally. It was observed that the two castrated chickens never matured into roosters with adult combs or feathers. But the chickens, which received transplanted testes did matured into normal adult roosters. The experiment revealed that hormones that could access the bloodstream from any site would function correctly in the body and that hormones did, in fact, it travels freely in the circulation.

The same year Berthold published his findings, Thomas Addison (1793-1860), a British scientist reported one of the first well-documented endocrine diseases which was later named Addison's disease (AD). AD patients all had a gray complexion with sickly skin; they also had weak hearts and insufficient blood levels of hemoglobin necessary for oxygen transport throughout the body. At autopsy, each of the patients Addison studied was found to have diseased adrenal glands.

This disease can be controlled today if it is detected early.

The endocrine system refers to the collection of glands of an organism that secrete hormones directly into the circulatory system to be carried towards distant target organs. The phenomenon of biochemical processes' serving to regulate distant tissues by means of secretions directly into the circulatory system is called endocrine signaling. The major endocrine glands include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, parathyroid gland, and adrenal glands. The endocrine system is in contrast to the exocrine system, (endocrine shouldn't be confused with exocrine). Exocrine glands, such as sweat and salivary glands, usually secrete externally or internally via ducts, meanwhile; endocrine glands secrete hormones internally, using the bloodstream, unlike the exocrine glands which secretes its hormones to the outside of the body using ducts.

The endocrine system is an information signal system like the nervous system, yet its effects and mechanism is classifiable different. The endocrine system's effects are slow to initiate, and prolonged in their response, lasting from a few hours up to weeks. The nervous system sends information very quickly, and responses are generally short-lived.

In vertebrates, the hypothalamus is the neural control center for all endocrine systems. Endocrine diseases are common and usually occur when glands produce an incorrect amount of hormones.

The endocrine system includes all the glands of the body and the hormones produced by these glands. The glands are directly controlled by stimulation of the nervous system, as well as by chemical receptors in the blood and hormones produced by other glands. By regulating the functions of organs in the body, these glands help to maintain the body's homeostasis. Cellular metabolism, reproduction, sexual development, sugar and mineral homeostasis. Heart rate and digestion are among the many processes regulated by the actions of hormones.

The neuroendocrine system consists of cells that are a cross between traditional endocrine cells (or hormone-producing cells) and nerve cells. Neuroendocrine cells are found throughout the body in organs, such as the lungs and gastrointestinal tract, and perform specific functions, such as regulating the air and blood flow through the lungs and controlling the speed at which food moves through the gastrointestinal tract.

The endocrine system is the collection of glands that produce hormones that regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep, and mood, among other things.

The word endocrine derives from the Greek words «endo,» meaning within, and «crinis,» meaning to secrete, according to Health Mentor Online. In general, a gland selects and removes materials from the blood, processes them and secretes the finished chemical product for use somewhere in the body. The

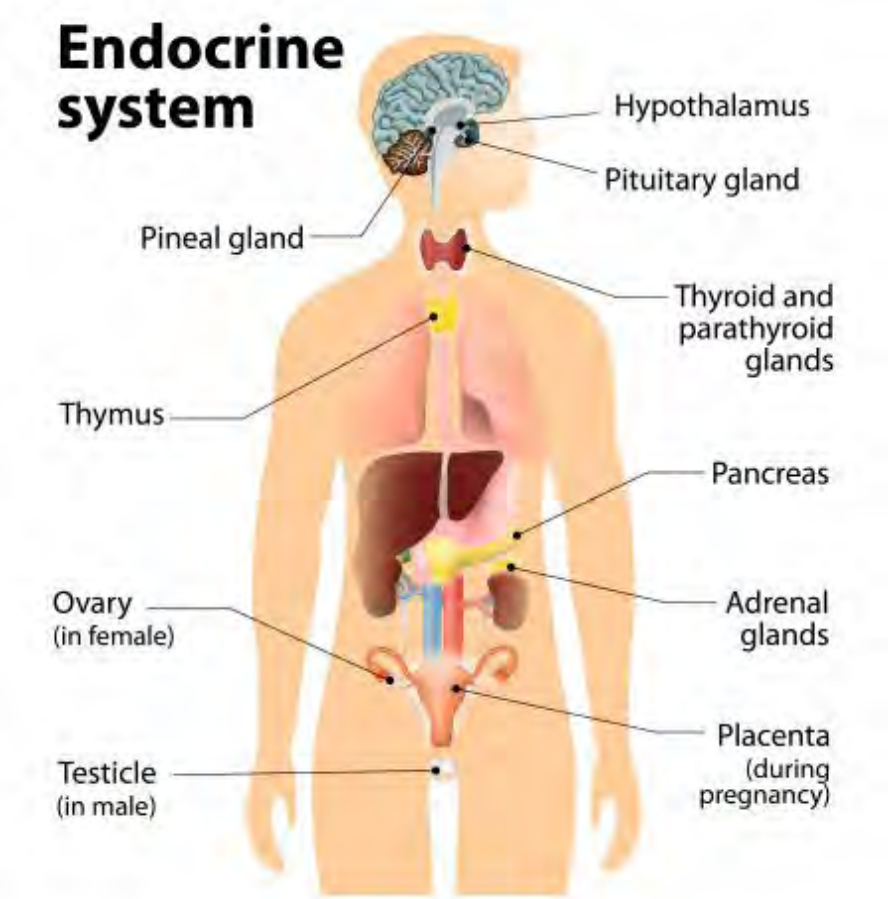
endocrine system affects almost every organ and cell in the body.

The endocrine system helps in controlling the following processes and systems: [8]

- Growth and development
- Homeostasis (the internal balance of body systems)
- Metabolism (body energy levels)
- Reproduction
- Response to stimuli (like stress or injury)

Although the hormones circulate throughout the body, each type of hormone is targeted toward certain organs and tissues. The endocrine system gets some help from organs such as the kidney, liver, heart and gonads, which have secondary endocrine functions. The kidney, for example, secretes hormones such as erythropoietin and renin.

Anatomy of the Endocrine system



Hypothalamus

The hypothalamus is one of the most evolutionarily conserved and essential regions of the mammalian brain. Indeed, the hypothalamus is the ultimate brain structure that allows mammals to maintain homeostasis, and its destruction is not compatible with life. [9]

The hypothalamus is a part of the brain located superior and anterior to the brain stem and inferior to the thalamus. It serves many different functions in the nervous system and is also responsible for the direct control of the endocrine system through the pituitary gland. The hypothalamus plays a key role in the regulation of endocrine (pituitary function), metabolic (food intake, energy balance, and water metabolism), and nonendocrine (body temperature, sleep/wake cycle) functions. Diseases involving the hypothalamus give rise to varying associations of endocrine, metabolic, neurologic, and other systemic signs and symptoms.

Causes of hypothalamic dysfunction include genetic diseases such as Prader Willi and Bardet Biedl syndromes, neoplastic lesions (e.g., craniopharyngioma) or systemic hematologic disorders such as sarcoidosis and Langerhans' cell histiocytosis, traumatic, and postirradiation brain disorders. The hypothalamus contains special cells called neurosecretory cells—neurons that secrete hormones:

- Thyrotropin-releasing hormone (TRH)
- Growth hormone-releasing hormone (GHRH)
- Growth hormone-inhibiting hormone (GHIH)
- Gonadotropin-releasing hormone (GnRH)
- Corticotropin-releasing hormone (CRH)
- Antidiuretic hormone (ADH)
- Oxytocin

Diseases of the hypothalamus comprise tumors, inflammatory and infectious diseases, and genetic disorders. Tumors found in the hypothalamus include craniopharyngioma, germinoma, teratoma, meningioma, glioma, etc. Some rare tumors that secrete hypothalamic hormones and much more rare cases of hypothalamic hormone receptor mutations. Inflammatory diseases include sarcoidosis, histiocytosis, infundibulo neurohypophysitis etc. Infectious diseases such as meningitis (tuberculous, bacterial, viral or fungal) were also found in the hypothalamus and neurohypophysis.

Malformations and hamartomas of the hypotalalmus include *Septo-optc dysplasia,* a heterogeneous condition characterized by a variable phenotype that include the classical triad of abnormalities of midline brain structure, optic nerve hypoplasia, and hypothalamic-pituitary insufficiency[17-20]. *The Hypothalamic hamartomas* are developmental, non neoplastic malformations characterized as a collection of neuronal and glial cells and myelinated fibres located within the floor of the third ventricle, tuber cinerum, or mammillary bodies. The most common symptoms are gelastic seizures characterized by spontaneous laughing, giggling and/ or smirking, or daacrystic seizures characterized by crying or grunting.[20-21]

Hypothalamic diseases cause a variety of symptoms and signs, depending on the site of the lesion. These include sexual abnormalities (hypogonadism or precocious puberty), abnormalities in water-electrolyte metabolism (diabetes insipidus, hypernatremia or hyponatremia), hypofunction of anterior pituitary, psychic disturbance, abnormalities in appetite (hyperphagia and obesity, or anorexia), emaciation, thermodysregulation, sleep disorders (e.g., narcolepsy), and sphincter disturbances. Diseases related to diabetes insipidus, hypogonadism, obesity and abnormal appetite, and the sleep disorder (narcolepsy) are described in later sections. [11,12]

Destructive lesions of the pituitary stalk cause diabetes insipidus and hypofunction of anterior pituitary except for prolactin. These include rupture after head injury, surgical transection, tumor, and granuloma. Diabetes insipidus develops, depending on the level at which the stalk has been sectioned. If the stalk is cut at the level close to the hypothalamus, diabetes insipidus almost always occurs. If it is cut at the lower level, the incidence is less.

The sellar region is the site of different pathological entities arising from the pituitary and adjacent anatomical structures, including the brain, blood vessels, nerves and meninges. The surgical pathology of this area requires the accurate identification of neoplastic lesions, including pituitary adenoma and carcinoma, craniopharyngioma, neurological neoplasms, germ cell tumors and hematological malignancies, as well as non-neoplastic lesions such as cysts, hyperplasia and inflammatory lesions. Among all these entities, primary pituitary adenomas are the most common.

Pituitary Gland

The pituitary gland, also known as the hypophysis, is a small pea-sized lump of tissue connected to the inferior portion of the hypothalamus of the brain. The pituitary gland is surrounded by many blood vessels to carry the hormones it releases throughout the body. Situated in a small depression in the sphenoid bone called the sella turcica, the pituitary gland is actually made of two completely separate structures: the posterior and anterior pituitary glands. [12]

Posterior Pituitary: The posterior pituitary gland is not glandular tissue at all, but nervous tissue instead. The posterior pituitary is a small extension of the hypothalamus through which the axons of some of the neurosecretory cells of the hypothalamus extend. These neurosecretory cells create two hormones in the hypothalamus that are stored and released by the posterior pituitary:

- Oxytocin: triggers uterine contractions during childbirth and the release of milk during breastfeeding.
- Antidiuretic hormone (ADH) or vasopressin: prevents water loss in the body by increasing the re-uptake of water in the kidneys and reducing blood flow to sweat glands.

Diseases Due to the Dysfunction in Vasopressin Secretion

- **Diabetes Insipidus**

Diabetes insipidus is a disease characterized by polydipsia and polyuria. Diabetes insipidus is caused by deficient production of vasopressin in the hypothalamus (neurogenic or central diabetes insipidus) or the deficient action of vasopressin in the renal tubular cells (nephrogenic diabetes insipidus).

- **Central Diabetes Insipidus**

Central diabetes insipidus is classified into three categories, familial, secondary, and idiopathic, according to the causes. Familial diabetes insipidus is a very rare disorder and is characterized by autosomal dominant inheritance.

Secondary diabetes insipidus is caused by tumors, infection, inflammatory diseases, infiltrative processes and trauma that damage the hypothalamic-neurohypophysial system. Tumors and inflammatory diseases in the hypothalamus and neurohypophysis are described in the following sections.

Wolfram Syndrome

Wolfram syndrome is an autosomal recessive neurodegenerative disorder associated with juvenile-onset non-immune insulin-dependent diabetes mellitus, progressive optic atrophy, sensorineural deafness, and diabetes insipidus, also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness). Patients present with diabetes mellitus followed by optic atrophy in the first decade, central diabetes insipidus and sensorineural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade. Central diabetes insipidus occurred in about 73% of the patients. A Wolfram gene (WFS1) has been mapped to chromosome 4p16.1. The WFS1 encodes an 890 amino acid protein, which is a membrane glycoprotein and localizes in the endoplasmic reticulum. WFS1 is widely expressed in the brain, including hippocampus, amygdaloid, and hypothalamus, consistent with a variety of neurological manifestations and central diabetes insipidus. Although the relationship between the WFS1 deficiency and the hypofunction of hypothalamic vasopressin neurons is not fully clarified, recent studies have shown the relationship between the WFS1 deficiency and pancreatic beta-cell loss. In pancreatic islets of wfs1-deficient mice, WFS1-deficiency increased endoplasmic reticulum stress and caused pancreatic beta-cell loss through impaired cell cycle progression and increased apoptosis.

- **Nephrogenic Diabetes Insipidus Congenital**

Nephrogenic diabetes insipidus is a hereditary disorder characterized by the inability of the kidney to concentrate urine in response to

arginine vasopressin. This disease is caused by mutations in the V2 receptor gene (X-linked recessive trait) or the gene of the renal water channel, aquaporin- 2 (AQP2) (autosomal recessive trait).

The renal V2 receptor mediates anti-diuresis by activation of adenylate cyclase in the distal parts of the nephron. In most cases, congenital nephrogenic diabetes insipidus was inherited in an X-linked recessive mode, and caused by mutations in the V2 receptor gene, which is localized to the long arm of the X chromosome. Rosenthal et al. reported a patient of congenital nephrogenic diabetes insipidus who had a deletion in the open reading frame of the V2 receptor gene, causing a frame shift and premature termination of translation in the third intracellular loop of the receptor protein.

The activation of the V2 receptor on renal collecting tubules stimulates adenylate cyclase via the stimulatory G protein (Gs) and promotes the cAMP-mediated incorporation of AQP into the luminal surface of these cells. There are at least ten members of AQP: AQP0-AQP9. AQP2 is the vasopressin sensitive water channel in renal collecting ducts.

Nephrogenic diabetes insipidus with autosomal recessive inheritance is caused by compound heterozygote or homozygosity for mutations in the AQP2 gene

Anterior Pituitary: The anterior pituitary gland is the true glandular part of the pituitary gland. The function of the anterior pituitary gland is controlled by the releasing and inhibiting hormones of the hypothalamus. The anterior pituitary produces six important hormones:

- Thyroid stimulating hormone (TSH), as its name suggests, is a tropic hormone responsible for the stimulation of the thyroid gland.
- Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex, the outer part of the adrenal gland, to produce its hormones.
- Follicle stimulating hormone (FSH) stimulates the follicle cells of the gonads to produce gametes—ova in females and sperm in males.
- Luteinizing hormone (LH) stimulates the gonads to produce sex hormones—estrogens in females and testosterone in males.
- Human growth hormone (HGH) affects many target cells throughout the body by stimulating their growth, repair, and reproduction.
- Prolactin (PRL) has many effects on the body, chief of which is that it stimulates the mammary glands of the breast to produce milk.

Pineal Gland

The pineal gland is a small pinecone-shaped mass of glandular tissue found just posterior to the thalamus of the brain. The pineal gland produces the hormone melatonin that helps to regulate the human sleep-wake cycle

known as the circadian rhythm. The activity of the pineal gland is inhibited by stimulation from the photoreceptors of the retina. This light sensitivity causes melatonin to be produced only in low light or darkness. Increased melatonin production causes humans to feel drowsy at nighttime when the pineal gland is active.

Thyroid Gland

The thyroid gland is a butterfly-shaped gland located at the base of the neck and wrapped around the lateral sides of the trachea. The thyroid gland produces three major hormones:

- Calcitonin
- Triiodothyronine (T3)
- Thyroxine (T4)

Calcitonin is released when calcium ion levels in the blood rise above a certain set point. Calcitonin functions to reduce the concentration of calcium ions in the blood by aiding the absorption of calcium into the matrix of bones. The hormones T3 and T4 work together to regulate the body's metabolic rate. Increased levels of T3 and T4 lead to increased cellular activity and energy usage in the body.

Parathyroid Glands

The parathyroid glands are four small masses of glandular tissue found on the posterior side of the thyroid gland. The parathyroid glands produce the hormone, parathyroid hormone (PTH), which is involved in calcium ion homeostasis. PTH is released from the parathyroid glands when calcium ion levels in the blood drop below a set point. PTH stimulates the osteoclasts to break down the calcium-containing bone matrix to release free calcium ions into the bloodstream. PTH also triggers the kidneys to return calcium ions filtered out of the blood back into the bloodstream so that it is conserved.

Adrenal Glands

The adrenal glands are a pair of roughly triangular glands found immediately superior to the kidneys. The adrenal glands are each made of two distinct layers, each with their unique functions: the outer adrenal cortex and inner adrenal medulla.

Adrenal cortex: The adrenal cortex produces many cortical hormones, in three classes: glucocorticoids, mineralocorticoids, and androgens.

- Glucocorticoids have many diverse functions, including the breakdown of proteins and lipids to produce glucose. Glucocorticoids also function to reduce inflammation and immune response.
- Mineralocorticoids, as their name suggests, are a group of hormones that help to regulate the concentration of mineral ions in the body.
- Androgens, such as testosterone, are produced at low levels in the adrenal cortex to regulate the growth and activity of cells

Causes of Hypothalamic Dysfunction			
Congenital Nutritional/metabolic	**Genetic (familial or sporadic cases)**	**Tumors**	**Infiltrative**
• Acquired • Developmental malformations • Anencephaly • Porencephaly • Agenesis of the corpus callosum • Septooptic dysplasia • Suprasellar arachnoid cyst • Colloid cyst of the third ventricle • Hamartoma • Aqueductal stenosis • Trauma • Intraventricular hemorrhage	• Hypothalamic hypopituitarism • Familial diabetes insipidus • Prader-Willi syndrome • Bardet-Biedl syndrome • Wolfram's syndrome • Pallister-Hall syndrome	• Primary intracranial tumors • Angioma of the third ventricle • Craniopharyngioma • Ependymoma • Ganglioneuroma • Germ cell tumors • Glioblastoma multiforme • Glioma • Hamartoma • Hemangioma • Lipoma • Lymphoma • Medulloblastoma • Meningioma • Neuroblastoma • Pinealomas • Pituitary tumors • Plasmacytoma • Sarcoma • Metastatic tumors	• Histiocytosis • Leukemia • Sarcoidosis
Functional	**Nutritional/metabolic**	**Degenerative**	**Infectious**
• Drugs • Hayek Peake syndrome • Idiopathic SIADH • Kleine Levin syndrome • Periodic syndrome of Wolff • Psychosocial deprivation syndrome	• Anorexia nervosa • Kernicterus • Wernicke Korsakoff syndrome • Weight loss	• Glial scarring • Parkinson's'	• Bacterial meningitis • Mycobacterial tuberculosis • Spirochetal syphilis
Viral	**Vascular**	**Trauma**	**Immunologic**
• Cytomegalovirus • Encephalitis • Jakob Creutzfeldt • Kuru • Poliomyelitis • Varicella	• Aneurysm • Arteriovenous malformation • Pituitary apoplexy • Subarachnoid hemorrhage • Vasculitis	• Birth injury • Head injury • Post neurosurgical	• Idiopathic diabetes insipidus • Paraneoplastic syndrome