

GENERAL PRINCIPLES OF ENDOCRINE DIAGNOSIS

A hormone is a substance secreted by a gland (or tissue) that is regulating the function of another tissue(s). Certain hormones, such as growth hormone (GH), thyroxine (T4) and insulin, influence tissue metabolism directly. Conversely, trophic hormones from the pituitary gland stimulate target endocrine glands to synthesize and secrete further hormones, which in turn partly control trophic hormone release, usually by negative feedback inhibition.

Hormones may be classified according to their structure (the following table), gland of origin, effects (kinetic, metabolic or morphogenic), nature of action (local or systemic), or mechanism of action (cell surface receptors or intracellular receptors).

Table 1: Classes of hormones based on structure.

STRUCTURAL CATEGORY	EXAMPLES
Water Soluble	
Peptides and Polypeptides	Adrenocorticotrophic hormone Antidiuretic hormone Calcitonin Glucagon Growth hormone Hypothalamic hormones Insulin Leptin Melanocyte-stimulating hormone Oxytocin Parathyroid hormone Prolactin Somatostatin Thyrotropin-releasing hormone
Glycoproteins	Follicle-stimulating hormone Luteinizing hormone Thyroid-stimulating hormone
Amines	Epinephrine Norepinephrine
Lipid Soluble	
Thyroxine (an amine but lipid soluble)	Thyroxine (both thyroxine [T4] and triiodothyronine [T3])
Steroids (cholesterol is a precursor for all steroids)	Estrogens Glucocorticoids (cortisol) Mineralocorticoids (aldosterone) Progestins (progesterone) Testosterone
Derivatives of arachidonic acid (autocrine or paracrine action)	Leukotrienes Prostacyclins Prostaglandins Thromboxanes

Although a wide variety of hormones function within the body, they share certain general characteristics:

1. Hormones have specific rates and rhythms of secretion. Hormonal rhythms are used to adapt to environmental changes, such as seasons of the year, the daily light-dark cycle, sleep, meals, and stress. The basic secretion patterns are: circadian or diurnal patterns, and pulsatile or cyclic patterns.

2. Hormone release is regulated by one or more of the following mechanisms: (i) chemical factors (endogenous such as blood glucose or calcium levels or exogenous such as drugs); (ii) endocrine factors (a hormone from one endocrine gland controlling another endocrine gland); and (iii) neural control (such as stress-induced release of catecholamines from the adrenal medulla). The endocrine and nervous systems work together to regulate responses to the internal and external environments.

3. Hormones operate within feedback systems, either positive or negative, to maintain an optimal internal environment.

4. Once hormones are released into the circulatory system, they are distributed throughout the body. Peptide or protein hormones are water soluble and circulate in free (unbound) forms. Water-soluble hormones generally have a short half-life because they are catabolized by circulating enzymes. For example, insulin has a half-life of 3 to 5 minutes and is catabolized by insulinases. Lipid-soluble hormones are transported bound to a carrier or transport protein and can remain in the blood for hours to days. Only free hormones (those not bound to the carrier protein) can signal a target cell. Because an equilibrium exists between the concentrations of free hormones and hormones bound to plasma proteins, a significant change in the concentration of binding proteins can affect the concentration of free hormones in the plasma

5. Hormones affect only cells with appropriate receptors and then act on those cells to initiate specific cell functions or activities. The sensitivity of the target cell to a particular hormone is related to the total number of receptors per cell; the more receptors, the more sensitive the cell. Low concentrations of hormone increase the number of receptors per cell, called **up-regulation**. High concentrations of hormone decrease the number of receptors, called **down-regulation**. Thus, the cell can adjust its sensitivity to the concentration of the signaling hormone.

The binding of hormones with their receptors stimulates alteration of membrane channel permeability; activating pre-existing proteins through a second-messenger system; and activating genes to cause protein synthesis.

Hormones have two general types of effects on target cells: direct and permissive. **Direct effects** are the obvious changes in cell function that specifically result from stimulation by a particular hormone. **Permissive effects** are less obvious hormone-induced changes that facilitate the maximal response or functioning of a cell. For example, insulin has a direct effect on skeletal muscle cells with insulin receptors, causing increased glucose transport into these cells. Insulin also has a permissive effect on mammary cells, facilitating the response of these cells to the direct effects of prolactin.

Some hormones have biphasic pharmacologic effects that are dependent on the concentration of the hormone. For example, low or physiologic levels of antidiuretic hormone (ADH, or arginine-vasopressin) stimulate renal tubular reabsorption of water. However, at supraphysiologic levels (i.e., those that can be achieved by exogenous administration), ADH acts as a vasoconstrictor.

Abnormalities of endocrine function

Endocrine glands may secrete excessive or deficient amounts of hormone. Abnormalities of target glands may be primary or secondary to dysfunction of the controlling mechanism, usually located in the hypothalamus or anterior pituitary gland. That is why, an important endocrine principle is that ***(an apparently 'normal' hormone result should be interpreted in the context of the associated hormone axis)***, for example a plasma PTH concentration within the reference range may be abnormal if the plasma calcium concentration is elevated.

The so-called 'dynamic' tests assess the response of the gland or the feedback mechanism, after stimulation or suppression by the administration of exogenous hormone. *Suppression tests* are used mainly for the differential diagnosis of excessive hormone secretion. The substance (or an analogue) that normally suppresses secretion by negative feedback is administered and the response is measured. Failure to suppress implies that secretion is not under normal feedback control (autonomous secretion). *Stimulation tests* are used mainly for the differential diagnosis of deficient hormone secretion. The trophic hormone that normally stimulates secretion is administered and the response is measured. A normal response excludes an abnormality of the target gland, whereas failure to respond confirms it.

It is also important to know about the assay's performance, as sometimes heterophilic interfering antibodies may cross-react with various hormones, as can certain immunoglobulins, for example macroprolactin.

HYPOTHALAMUS AND PITUITARY GLAND

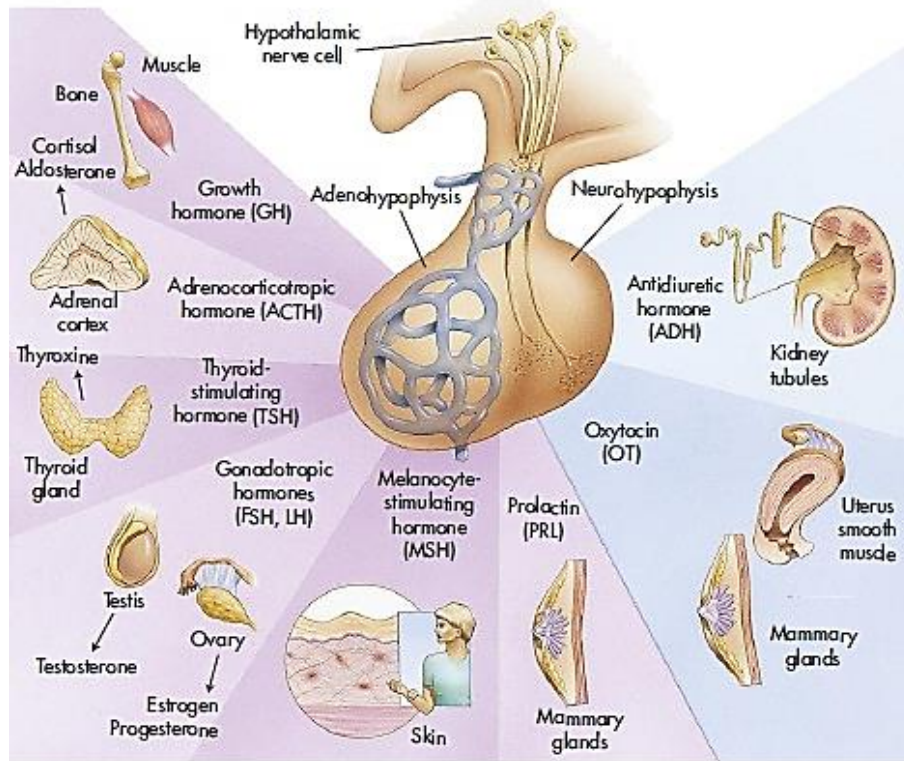
The hypothalamus is an integral part of the brain. It is a small cone-shaped structure that projects downward from the brain, ending in the pituitary stalk, a tubular connection to the pituitary gland.

The pituitary gland (*hypophysis*) has two lobes, the anterior (*adenohypophysis*) and posterior (*neurohypophysis*) lobes, which are developmentally and functionally distinct; both depend on hormones synthesized in the hypothalamus for normal function.

The hypothalamus also has extensive neural connections with the rest of the brain, and stress and some psychological disorders affect the secretion of pituitary hormones and of the hormones from other endocrine glands.

The hypothalamic-pituitary axis (HPA) forms the structural and functional basis for central integration of the neurologic and endocrine systems, creating what is called the **neuroendocrine system**.

The hypothalamus is connected to the anterior pituitary by way of portal blood vessels, whereas the hypothalamus is connected to the posterior pituitary by way of a nerve tract referred to as the *supraopticohypophysial tract*.



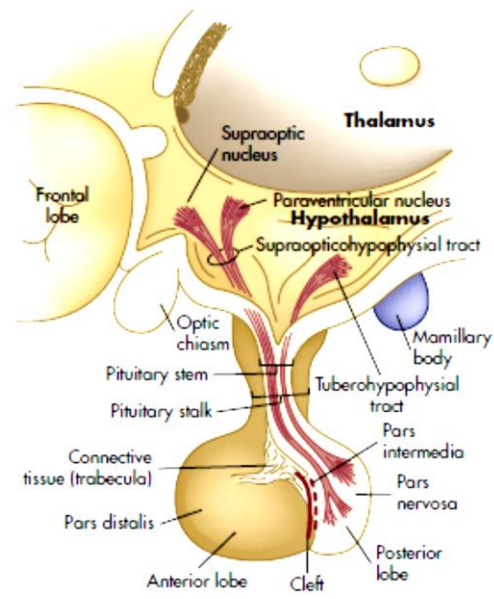
Hormones of the posterior pituitary

The posterior pituitary secretes two polypeptide hormones: (1) ADH, also called *vasopressin* or *arginine-vasopressin*; and (2) oxytocin.

These peptide hormones are similar in structure, differing by only two amino acids. They are synthesized, along with their carrier proteins (the neurophysins), in the supraoptic and paraventricular nuclei of the hypothalamus respectively.

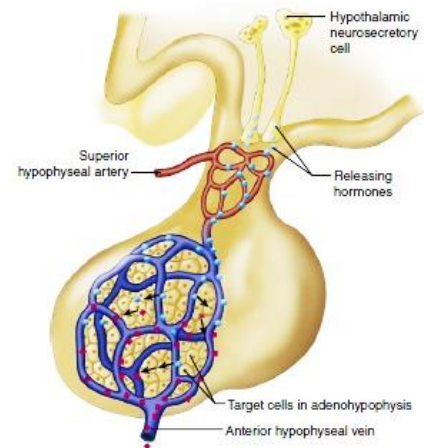
Once synthesized, these hormones and their neurophysins are packaged in secretory vesicles and are transported down the nerve fibres of the pituitary stalk to the posterior pituitary for storage. The stored hormones are released independently of each other into the bloodstream under hypothalamic control, together with neurophysin. Neurophysin has no apparent biological function and is rapidly cleared from plasma. *The posterior pituitary thus can be seen as a storage and releasing site for hormones synthesized in the hypothalamus.*

Antidiuretic hormone enhances water reabsorption from the collecting ducts in the kidneys. **Oxytocin** controls the ejection of milk from the lactating breast and may have a role in initiating uterine contractions, although normal labour can proceed in its absence. It may be used therapeutically to induce labour.



Anterior pituitary hormones

There is no direct neural connection between the hypothalamus and the anterior pituitary gland. The hypothalamus synthesizes small molecules (regulating hormones or factors) that are carried to the cells of the anterior pituitary lobe by the hypothalamic portal system. This network of capillary after passing down the pituitary stalk, divides into a second capillary network in the anterior pituitary gland, from where hypothalamic hormones stimulate or inhibit pituitary hormone secretion into the systemic circulation.



The cells of the anterior pituitary lobe can be classified simply by their staining reactions as acidophils, basophils or chromophobes. Immunohistochemistry can identify specific hormone-secreting cells.

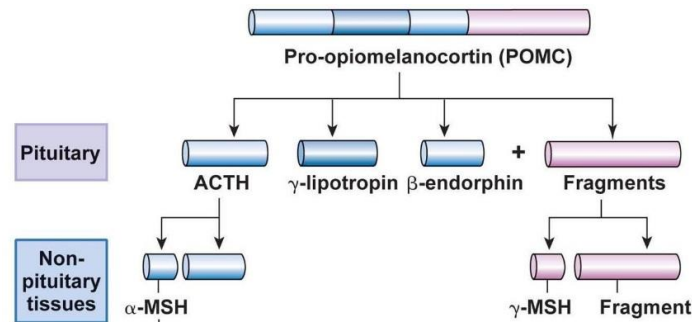
Acidophils are of two cell types:

- ✓ lactotrophs, which secrete prolactin,
- ✓ somatotrophs, which secrete GH (somatotrophin).

These hormones, which are simple polypeptides with similar amino acid sequences, mainly affect peripheral tissues directly. Stimulation and inhibition of secretion via the hypothalamus is influenced by neural stimuli.

Basophils secrete hormones that affect other endocrine glands. The hypothalamic control is mainly stimulatory. There are three cell types:

- ✓ Corticotrophs synthesize a large polypeptide (pro-opiomelanocortin), which is a precursor of both adrenocorticotrophic hormone (ACTH; corticotrophin) and β -lipotrophin. Secretion of these hormones occurs in parallel.
- Adrenocorticotrophic hormone stimulates the synthesis and secretion of steroids, other than aldosterone, from the adrenal cortex and maintains adrenal cortical growth. Part of the molecule has melanocyte-stimulating activity, and high circulating concentrations of ACTH are often associated with pigmentation.
- β -Lipotrophin is inactive until rapidly converted to endorphins. These are neurotransmitters which, because they have opiate-like effects, help control pain.



- ✓ Gonadotrophs secrete the gonadotrophins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), which act on the gonads.

- ✓ Thyrotrophs secrete TSH (thyrotrophin), which acts on the thyroid gland.

Chromophobes, once thought to be inactive, but they do contain secretory granules. Chromophobe adenomas often secrete hormones, particularly prolactin.

Control of anterior pituitary hormone secretion

Neural and feedback controls are the two most important physiological factors influencing the secretion of the anterior pituitary hormones.

Extrahypothalamic neural stimuli modify, and at times over-ride, other control mechanisms. Physical or emotional stress and mental illness may give similar findings to, and even precipitate, endocrine disease.

The stress caused by insulin-induced hypoglycaemia is used to test anterior pituitary function. Stress may also stimulate the secretion of ADH from the posterior pituitary.

Feedback control is mediated by the concentrations of circulating target-cell hormones; a rising concentration usually suppresses trophic hormone secretion. This negative feedback may directly suppress hypothalamic hormone secretion or may modify its effect on pituitary cells (long feedback loop).

The secretion of hypothalamic hormones may also be suppressed by rising concentrations of pituitary hormone (trophic hormones) in a short feedback loop.

Drugs may also stimulate or block the action of neurotransmitters, such as catecholamines, acetylcholine and serotonin, and influence the secretion of hypothalamic, and consequently pituitary hormones.

