

# THE ENDOCRINE SYSTEM

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## Learning Objectives

1. Definition of a hormone.
2. Understand the feedback mechanism that controls hormonal secretions.
3. The common features of endocrine tissues.
4. As you go through each hormone, beware of the cells that produce it, the chemical nature of the hormone, the metabolic effects of the substance, and the factors involved in stimulation/inhibition of its release.
5. The different part of the pituitary and their embryonic origins.
6. The blood supplies to the pituitary and the portal system.
7. The neurohypophysis: cells, productions controls.
8. Pars distalis of the adenohypophysis: cells, products and the feed back loops.
9. The controls exerted by the hypothalamus on the pars distalis: releasing factors and inhibiting factors.
10. The cells of the pars media, their secretions, functions and controls.
11. The organization of the adrenal gland.
12. Zona glomerulosa, the histology, steroid products, effects and controls.
13. Zona fasciculata: histology, products, effects and controls.
14. Zona reticularis: cells and products.
15. Adrenal medulla: embryonic origin, nature of secretory products and their effects on metabolism. Controls on secretion.
16. Blood supplies to the adrenal gland and the functional implications of the arrangements.
17. How to tell the histological differences between the zona reticularis from the medulla?
18. Endocrine pancreas: cell types, hormones produced, and metabolic effects.
19. The histology of thyroid follicles.
20. The pathway of thyroid hormone production and secretion.
21. The chemical nature of the follicular hormones and their metabolic effects.
22. Parafollicular C cells: embryonic origin, secretion, and effects on calcium and bone metabolism.
23. Parathyroid gland: the cells types in the organ, the hormone produced, the metabolic effects of the hormone on calcium, phosphate, and bone metabolism.
24. Pineal gland secretes melatonin, a hormone with diverse functions with influences on sexual behavior, circadian rhythm and thermoregulation.

A hormone is an organic substance, formed by specialized cells in one organ or part of the body, which is secreted at a specific time and in small amounts into tissue fluids or the vascular system. These cells are usually from endocrine organs or are modified neurons. The tissue and organ target upon which the hormone acts have receptors for the specific hormone and is generally at a distance. In instances in which the hormone acts locally upon the adjacent cells, the action is called paracrine.

Hormones are chemical messengers made up of a diversified group of chemicals. A hormone may be a protein, a glycoprotein, a steroid, a biogenic amine or a small peptide.

Although this discussion is limited to the endocrine system, you should be aware of the important interactions between the endocrine, nervous and immune systems. These three systems play significant roles in maintaining homeostasis of the body.

The main systems we will cover include the pituitary (hypothalamo-hypophyseal system), the adrenal gland, the endocrine pancreas (islets of Langerhans), the thyroid, the parathyroid and the pineal gland. Cells in the reproductive systems that produce hormones will be treated separately. Cells that produce hormones but are not arranged into organs, such as the enteroendocrine cells, are covered under the digestive systems.

Endocrine secretion is usually controlled by a feedback mechanism that may be negative or positive. Some endocrine glands use a different control mechanism, direct stimulation from the nervous system.

Two important features are common to all endocrine tissues/glands: (1) they are well endowed with blood supply; and (2) they do not have secretory ducts.

## **THE PITUITARY and the Hypothalamo-hypophyseal System**

The pituitary (a.k.a. hypophysis) lies in the sella turcica, a cavity of the sphenoid bone. During embryonic development, the hypophysis forms partly from the oral ectoderm and partly from neural tissue. The neural portion arises as an evagination from the floor of the diencephalon and extends caudally as a stalk, without detaching itself from the brain. This portion becomes the neurohypophysis. The oral component arises as an outpocketing of the ectoderm from the roof of the mouth and grows cranially as the Rathke's pouch. Eventually the pouch is pinched off from the oral cavity and the lumen of Rathke's pouch is reduced to a small slit. The oral component becomes the adenohypophysis.

The adenohypophysis has three parts: pars distalis (anterior lobe) forming the bulk of the gland, the pars intermedia (intermediate lobe), and the pars tuberalis that forms a sleeve around the median eminence.

The neurohypophysis also has three parts: the median eminence (continuous with the hypothalamus proximally), the infundibular stalk (distal continuation of the median eminence), and the neural lobe (lobus nervosus).

## Blood Supply

Two groups of blood vessels from the internal carotid artery supply the pituitary. The superior hypophyseal arteries supply the median eminence and the neural stalk. The inferior hypophyseal arteries supply mainly the neurohypophysis and a small supply to the stalk.

The superior hypophyseal arteries form a primary capillary plexus that supplies the stalk and the median eminence. They then rejoin to form veins that develop into a secondary capillary plexus in the adenohypophysis. The vessels that connect the two plexuses are called the portal venules. This is the hypophyseal portal system through which neurohormones from the median eminence gain access to and act upon the cells of the adenohypophysis. This mechanism is very important in the control of the adenohypophysis.

Blood from both the adenohypophysis and the neurohypophysis drains into the cavernous sinuses.

## Neurohypophysis

This is the part of the pituitary that developed from nerve tissue. This started as an infundibular downgrowth from the floor of the diencephalon. It remains connected with the hypothalamus. The neurohypophysis has three portions: median eminence, which is continuous with the hypothalamus proximally, the infundibular stalk, the distal continuation of the median eminence, and the neural lobe (lobus nervosus).

Peptides or small proteins are produced by collections of secretory neurons (nuclei) in the hypothalamus. Some of these hormones are transported via neuronal axons (tracts) and are stored in dilated closed ends of the axons located in the median eminence. Others are stored in the dilated ends of axons in the pars nervosa.

Thus the neurohypophysis is the area where hormones are stored and secreted but not produced. The bulk of the pars nervosa is made up of unmyelinated axons of secretory neurons from the supraoptic and paraventricular nuclei. The hormone is manufactured in the rough endoplasmic reticulum in the cell body, packaged as neurosecretory granules, and transported down the axon and stored in the dilated terminal parts. The granules contain the hormone plus a carrier protein called neurophysin. These accumulations are called Herring bodies and are located close to capillaries. The hormones are released by exocytosis as needed. The hormones enter capillaries in the plexus of pars nervosa and drain into the cavernous sinuses.

The rest of the pars nervosa contains a specific type of highly branched glial cells called pituicytes.

Hormones secreted from the Neurohypophysis are:

1. Vasopressin (ADH, arginine vasopressin, antidiuretic hormone). Prevents diuresis by increasing the permeability of kidney distal convoluted tubules and collecting ducts to water. More water is reabsorbed and the urine becomes more concentrated. This hormone also promotes vascular smooth muscle contraction.

ADH is secreted when the animal experiences dehydration. Receptors in the hypothalamus detect hemoconcentration and trigger the release of ADH.

A deficiency of ADH causes diabetes insipidus. An animal with this condition produces large quantities of very dilute urine (polyuria) and drinks large quantities of water (polydipsia).

2. Oxytocin. Induces contraction of uterine smooth muscle (myometrium) during breeding and parturition. It is also released in response to mechanical stimulation of the teat. This hormone induces contraction of the myoepithelial cells of the mammary gland leading to milk ejection (suckling reflex).

These two hormones are made up of peptides and are present in different secretory granules in different neurons. The hormones are secreted into the systemic circulation via the cavernous sinuses.

Neuroendocrine cells in the hypothalamus have either positive or negative effects on the pituitary.

The hypothalamic releasing hormones and the hypothalamic inhibiting hormones are secreted from the median eminence into the hypophyseal portal system. These neurohormones are carried to the adenohypophysis where they perform their regulatory functions.

## **Adenohypophysis**

The adenohypophysis has three parts: pars distalis (anterior lobe) forming the bulk of the gland, the pars intermedia (intermediate lobe), and the pars tuberalis that forms a sleeve around the infundibular stalk.

Hormone in the adenohypophysis are produced by the epithelial cells (remember their embryonic origin) and stored in secretory granule without a carrier protein. These hormones are released by exocytosis in a pulsatile, rhythmic or cyclic manner into the capillaries of the secondary capillary plexus. The release of these hormones is controlled by releasing factors to be described later.

### **Pars distalis**

This is formed of cords of cells interspersed with sinusoidal capillaries (fenestrated capillaries of the secondary plexus).

Classically the cells have been described as chromophobes and chromophils according to the way they stain. The chromophobes stain palely and are most likely secretory cells that have depleted their granules for the time being. The chromophils are grouped into basophils or acidophils. Most cells produce only one hormone. The exception is the gonadotropic cells that produce two hormones. Immunohistochemistry is the preferred method to demonstrate the location of a specific hormone in the organ. Of unknown function and significance are follicular cells and stellate cells.

The six hormones secreted by the cells of the adenohypophysis are:

1. Thyrotropin (thyroid stimulating hormone, TSH). Stimulates thyroid hormone synthesis, storage and secretion. In basophilic granules. A glycoprotein hormone made up of two chains. The  $\alpha$ -chain is common to TSH, LH and FSH. The  $\beta$ -chain is unique for TSH,

Positive stimulation: TRH (thyrotropin-releasing hormone, from the hypothalamus).

Negative control: Increased serum concentrations of the thyroid hormones.

2. Corticotropin (adrenocorticotrophic hormone, ACTH). Stimulates secretion of adrenal cortical hormones from the zona fasciculata and reticularis. In basophilic granules. A glycoprotein hormone.

In the corticotropes, located in the pars distalis, the prehormone proopiomelanocortin (POMC) is cleaved into ACTH,  $\beta$ -LPH (lipotropin).

ACTH (adrenocorticotropin) is secreted in a circadian manner.

Control of ACTH secretion: Positive --- hypothalamic corticotropin-releasing hormone (CRH). Negative --- high level of plasma cortisol.

$\beta$ -lipotropin has lipolytic action.

In the pars intermedia, ACTH is further cleaved into  $\alpha$ -MSH (melanotropin) and CLIP (corticotropin-like intermediate lobe peptide). In both lobes,  $\beta$ -LPH is further cleaved to  $\alpha$ -LPH and  $\beta$ -endorphin.

3. Prolactin (PL). Pulsatile secretion. Promotes and maintains milk production in the female (lactogenic, and galactopoiesis). Crop-stimulating activity in pigeon crop sacs. Has pre-lactational mammogenic activity. In acidophilic granules. A protein hormone.

Positive stimulations: PRF (prolactin-releasing factor), thyrotropin-releasing factor (TRH), both from the hypothalamus; suckling.

Secretion of prolactin controlled by inhibitory factors: dopamine and prolactin-inhibiting hormone.

4. Somatotropin (growth hormone, GH). Pulsatile secretion. Acts on growth of muscles and long bones in young via somatomedins (a.k.a. insulin-like growth factor-1, IGF-1, produced by hepatocytes). In animals of all ages, it regulates the metabolism of proteins (anabolic), carbohydrates (hyperglycemic), and lipids (catabolic) in the body. In acidophilic granules. A protein hormone.

Positive stimulations for GH release: GHRH growth hormone-releasing hormone; from hypothalamus; drop in serum IGF-1.

Negative control: Somatostatin, from hypothalamus; also by elevated blood glucose levels.

Gigantism and dwarfism, results of derangements in growth hormone secretion.

5. Follicle stimulating hormone (FSH). A glycoprotein hormone made up of two chains. The  $\alpha$  chain is common to that of FSH and TSH. The  $\beta$ -chain is specific for FSH. In basophilic granules.

Promotes ovarian follicle development and estrogen production in the female; stimulates spermatogenesis in the male.

6. Luteinizing hormone (LH). A glycoprotein hormone made up of two chains. The  $\alpha$  chain is common to that of FSH and TSH. The  $\beta$ -chain is specific for LH. In basophilic granules.

Promotes ovarian follicle maturation and progesterone secretion in the female; stimulates Leydig cells and production of androgen in the male.

FSH and LH together are called gonadotropins.

Positive stimulation for FSH: GnRH, gonadotropin-releasing hormone. Activin.

Negative control for FSH: Inhibin and estradiol.

Positive stimulation for LH: GnRH.

Negative control for LH: Testosterone and progesterone.

### Control of the Pars Distalis

The main control on the para distalis is by the hypothalamic hormones manufactures in the dorsal medial, ventral medial, and infundibular nuclei of the hypothalamus. These hormones are stored in the median eminence. These hypothalamic releasing hormones and hypothalamic inhibiting hormones travel to the pars distalis via the hypophyseal portal system and exert their effects on the cells of the adenohypophysis.

Hypothalamic Releasing and Inhibiting Hormones Include:

1. Thyrotropin-releasing hormone (TRH). Stimulates the release of thyrotropin and prolactin.
2. Corticotropin-releasing hormone (CRH). Stimulates the release of both B lipotropin and corticotropin.
3. Prolactin-inhibiting hormone (PIH). Inhibits the release of prolactin
4. Prolactin-releasing hormone (PRH). Stimulates the release of prolactin

5. Growth hormone-releasing hormone (GHRH). Stimulates release of growth hormone
6. Somatostatin (SST). Inhibits the release of growth hormone and thyrotropin.
7. Gonadotropin-releasing hormone (GnRH). Stimulates the release of FSH and LH.

A feedback mechanism exists between the adenohypophysis, its target organs, the hormones excreted by the target organs and the hypothalamus.

### **Pars tuberalis**

This is a funnel-shaped region surrounding the infundibulum of the neurohypophysis. Most of the cells in this region secrete gonadotropins.

### **Pars intermedia**

This developed from the dorsal portion of Rathke's pouch. It is usually separated from the adenohypophysis by the remains of Rathke's pouch, which is now reduced to a slit.

The main endocrine cells in the pars intermedia are the melanotropes. They secrete melanocyte-stimulating hormone (MSH). In fish, amphibians and reptiles this hormone causes the dispersion of melanosomes. In mammals it causes pigmentation of hair and may be skin. In some species, the cells also produce lipotropin (LPH).

The secretion of MSH is regulated by the melanotropin releasing factor and the melanotropin-inhibiting factor from the hypothalamus.

Depending on the species, other cell types are also found in the pars intermedia. These include typical cells of the pars distalis, follicular cells and stellate cells.

## **THE ADRENAL GLAND**

The adrenal gland has a thin connective capsule. It can be divided into a cortex, in which the parenchymal cells are arranged in cords, and a medulla, where the parenchymal cells occur in clusters.

### **The Adrenal Cortex**

This part of the adrenal gland is derived from the mesoderm. It can be divided into three or four zones based on the arrangement of the cells and their functions. Using cholesterol as a precursor, the cells of the adrenal cortex secrete steroid hormones. The steroid hormones secreted by the cells of the adrenal cortex are not stored in the cells. It appears that the steroids are manufactured and released as needed.

All zones of the cortex are highly vascularized with extensive sinusoids. These blood vessels are arranged in such a way that they drain toward the medulla. By the time the blood reaches the cells of the medulla, it may be rich in corticosteroids. This has important physiological effects on the adrenal medulla.

### **Zona glomerulosa**

This zone is found right beneath the capsule. The cells are arranged in arcs (zona arcuata) in all domestic species (horses, carnivores, pigs etc.) except in ruminants where the cells appear as clusters.

The cells have eosinophilic cytoplasm with lipid droplets. Under the electron microscope, the cytoplasm is shown to contain extensive smooth endoplasmic reticulum and mitochondria.

The cells of the zona glomerulosa secrete aldosterone, a mineralocorticoid important in the maintenance of electrolytes in the body. It causes the reabsorption of sodium in the kidney in exchange of potassium and hydrogen ions. This takes place in the distal convoluted tubules and the collecting ducts of the kidney. (This zone does not have the enzyme 17 $\alpha$ -hydroxylase, 17,20 lyase and therefore cannot produce cortisol or sex steroids).

This portion of the cortex is not under the direct influence of the adenohypophysis. It is primarily angiotensin II-dependent.

### **Zona intermedia**

This zone is not well developed in most species except in horses, dogs and cats where it is conspicuously present between the z. glomerulosa and the z. fasciculata. The cells in this zone may be reserve cells that can develop into cells of the zona fasciculata.

### **Zona fasciculata**

This is usually the widest zone in the cortex. The cells here are arranged in cords usually made up of one cell thick. The cuboidal cells contain numerous small lipid droplets in the cytoplasm. In routine histological preparations, the lipids were extracted and the cytoplasm appears vacuolated. Sinusoids run between the cords of cells exposing them to blood on two sides.

The main hormones produced in this zone are cortisone, cortisol, and corticosterone. These are glucocorticoids that have profound effects on carbohydrate metabolism (and to a lesser extent, on protein and lipid metabolism as well). In the liver, glucocorticoid has an anabolic effect and promotes the use of fatty acids, amino acids, and carbohydrates that are used in gluconeogenesis. Outside the liver, the glucocorticoids have a catabolic effect by decreasing synthetic activity and promote protein and lipid degradation. The liver then utilizes these byproducts.

The glucocorticoids also have an anti-inflammatory effect and suppress the immune system by destroying circulating lymphocytes and inhibiting cell division in lymphocyte-forming sites.

### **Zona reticularis**

The cells here are arranged in a less organized manner than those in the fasciculata. The cells have less lipid droplets but more lipofuscin pigments bodies. This zone abuts the medulla.

The cells of the reticularis produce small amounts of sex hormones.

The zona fasciculata and zona reticularis are under the influence of adrenocorticotropin (ACTH).

### **The Adrenal Medulla**

This portion of the adrenal gland is derived from the neuroectoderm and forms the “center” of the gland. It is made up of irregular cords and clusters of cells supported by a reticular fiber network. The hormones secreted by the medulla are biogenic amines and the cells are also called chromaffin cells.

The chromaffin cells are actually modified sympathetic postganglionic neurons. These cells do not have processes. Inside the cytoplasm of these cells are numerous secretory granules containing either epinephrine or norepinephrine. Also present in the granules is a protein called chromogranins, which may serve as a binding protein for the catecholamines.

Synthesis of the catecholamines starts with the conversion of tyrosine to DOPA (dihydroxyphenylalanine) by tyrosine hydroxylase. The enzyme DOPA decarboxylase converts DOPA to dopamine. Dopamine is transported into granules and then converted into norepinephrine by dopamine  $\beta$ -hydroxylase.

Epinephrine is derived from norepinephrine that leaves the granules and goes into the cytoplasm. This reaction is carried out by the enzyme phenylethanolamine N-methyltransferase (PNMT). The epinephrine thus produced is transported and stored in granules.

Different cell types secrete epinephrine and norepinephrine. In most animals the two populations of cells are mixed together. In cows, sheep, horses and pigs, epinephrine is found in larger cells located around the periphery of the medulla, and smaller cells in the center produce norepinephrine. The products are secreted into the fenestrated capillaries surrounding the cells (instead of into synapses).

Cells of the medulla are innervated by preganglionic cholinergic sympathetic neurons. Secretion of large amounts of norepinephrine and epinephrine takes place as a

response to stress. Hypertension, vasoconstriction, changes in heart rate, elevated blood glucose etc. result from the intense secretion of catecholamines into the circulation (fight or flight response). During normal activity, cells of the adrenal medulla secrete small amounts of the hormones into the blood stream.

Although not directly under the control of ACTH, the cells of the medulla nonetheless are influenced by it. Blood flowing through the sinusoids in the cortex contain glucocorticoids that can influence the metabolism of the cells in the medulla. For example, synthesis of PNMT is stimulated by glucocorticoids.

#### Blood supply to the adrenal gland

A connective capsule covers the adrenal gland. The adrenal arteries enter the capsule and form an arterial plexus.

Some of the vessels supply the capsule.

Other vessels enter the cortex and form sinusoids (straight fenestrated capillaries) in the glomerulosa and fasciculata. In the reticularis the straight sinusoids form a capillary network before entering the medulla.

A third set of arteries goes directly to the medulla without branching.

Thus the medulla is supplied by two sources of blood. The one from the sinusoid contains corticosteroids that influence the metabolism of the medullary cells. The other is directly from the arteries.

The cortex, interestingly enough, does not have veins or lymphatics.

The central vein found in the middle of the medulla drains both the cortex and the medulla.

### **ISLETS OF LANGERHANS**

The endocrine portion of the pancreas is made up of clusters of cells known as islets of Langerhans. They secrete the peptide hormones insulin and glucagon.

Each islet has a thin network of reticular fibers and may vary from several hundred to just dozens of cells. A network of fenestrated capillaries can be found in each islet. In an H&E section the islet cells stain lighter than those of the exocrine pancreas do. The ultrastructure of these cells is typical of those synthesizing peptides. A distinct cell type secretes each hormone. Classically, four cell types have been identified, alpha, beta, delta and F-cells. Immuno-histochemistry is now the preferred method to localize the various hormones secreted by the islet cells.

The hormones secreted by the islet cells are:

1. Glucagon is a peptide. It stimulates hepatic glycogenolysis and lipolysis, thus making energy stored in glycogen, fat, and protein available for use and increasing the blood glucose content. In alpha cells. Synthesized as a precursor preproglucagon and processed to glucagon. Release by exocytosis triggered by decreased in the plasma level of glucose.

2. Insulin is a 6-kDa polypeptide containing two chains. Glucose triggers both insulin release and synthesis of insulin. Insulin decreases blood glucose content and causes the storage of energy from excess nutrients (glucose, amino acids, fatty acids in blood).

Insulin is synthesized and stored in beta cells. Synthesized first as preproinsulin in the rER which gives rise to proinsulin. Proinsulin is transported to the Golgi and processed further to insulin. Mature insulin is packaged in secretory granules in the presence of zinc.

3. Somatostatin, a factor secreted by the islet, inhibits the release of insulin and glucagon through local paracrine action. In delta cells.
4. Pancreatic Polypeptide stimulates gastric secretion and inhibits intestinal mobility and bile secretion. Also inhibits the secretion of somatostatin. In F cells.

## **THYROID GLAND**

This endocrine gland, located in the cervical region, is made up of two lateral lobes united by an isthmus. It is surrounded by a connective tissue capsule and is divided into lobules by septa. The gland contains follicles that are the basic histological units of the thyroid. Each follicle consists of a simple epithelial sphere containing a gelatinous colloid. A network of fenestrated capillaries surrounds each follicle. The sizes of the follicles as well as the heights of the epithelial cells can be quite variable. These variations reflect the functional activity of the follicles.

### Follicular Cells

The epithelial cells of the thyroid follicle rest on a basal lamina. Each cell has abundant rER, large Golgi apparatus, secretory granules and lysosomes. Thus they have the characteristics of cells that synthesize, secrete, absorb and digest proteins. The cells also have distinct polarity with apical microvilli abutting the colloid.

The synthesis, storage and secretion of thyroid hormone involve some interesting convoluted steps. Thyroglobulin, a glycoprotein, is synthesized and secreted into the follicular lumen. It contains tyrosyl residues available for iodination. Thyropoxidase is also synthesized and secreted into the colloid. This enzyme is responsible for the iodination of the tyrosyl residues in thyroglobulin. In this process two iodine atoms are linked to each tyrosyl residue.

One monoiodotyrosine peptide combines with diiodotyrosine to form **T<sub>3</sub>** (triiodotyrosine). Two diiodotyrosines combine to form **T<sub>4</sub>** (thyroxine). The iodothyroglobulin is stored in the lumen until needed.

Endocytosis of the colloid (with iodinated thyroglobulin) takes place resulting in the fusion of colloid droplets with lysosomes. Proteolytic enzymes breakdown the thyroglobulin to release the active hormones: thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>).

These hormones diffuse out of the basal cytoplasm into the fenestrated capillaries surrounding the follicles.

In general, thyroxine stimulates mitochondrial respiration and oxidative phosphorylation. T<sub>3</sub> and T<sub>4</sub> increase the absorption of carbohydrates in the intestines and regulate lipid metabolism. The hormones are essential in body growth and the development of the nervous system during the fetal period. In all ages, thyroid hormone's calorigenic effects are essential to the animal.

TSH, thyroid-stimulating hormone, from the adenohypophysis regulates the follicles. In an active thyroid, the follicular cells may be cuboidal or low columnar in height. The interface between the colloid and the apical cytoplasm of the follicular cells is "scalloped" or "bubbly".

### Parafollicular Cells

These are also known as C cells (for 'clear' before we know that they contain a hormone which starts with the letter C). They are found either as clusters of cells between follicles or part of the follicular epithelium. When they are part of the epithelium, the cytoplasm of the C cells is *not* in contact with the colloid. The cells contain numerous secretory granules that contain the hormone calcitonin. The best way to demonstrate these cells is by immunohistochemistry.

Calcitonin inhibits bone resorption by osteoclasts and lowers blood calcium levels. An elevation in blood calcium concentration (hypercalcemia) triggers the secretion of calcitonin by the parafollicular cells.

Thus the calcitonin helps to maintain normal level of calcium in the blood and prevents hypercalcemia. This is antagonistic to the actions of parathyroid hormone.

## **PARATHYROID GLANDS**

These are small glands attached to or even embedded in the thyroid gland. Each gland is encased in a connective tissue capsule. Septa of connective tissue extend into the glands and merge with reticular fibers.

Two types of cells, the chief (principal) and oxyphil, form the parenchyma of the parathyroid. The clusters or cords of cells are richly endowed with capillaries.

### Chief Cells

Pale staining small cells with slight acidophilic cytoplasm. They have secretory granules containing parathyroid hormone in the cytoplasm. The amount of secretory granules in the cytoplasm determines if the cells stains are dark (active) or light (inactive).

Parathyroid hormone is a peptide derived from proparathyroid hormone that in turn came from preproparathyroid hormone.

Parathyroid hormone stimulates the reabsorption of the calcified bone matrix by osteoclasts and the release of  $\text{Ca}^{2+}$  into the blood stream. An increase in serum calcium (hypercalcemia) suppressed the release of PTH. A low level of calcium in the serum (hypocalcemia) stimulates PTH release.

Osteoclasts play critical roles in calcium metabolism. PTH stimulates the synthesis of several proteins that are essential in the differentiation and maturation of the osteoclasts:

Macrophage colony-stimulating factor (M-CSF) ligand, induces the differentiation of monocytes into immature osteoclasts.

RANKL, a cell membrane protein that interacts as a ligand with RANK receptors on the surface of immature osteoclasts. Ligand-receptor interaction induces the differentiation of osteoclast precursor into a resting osteoclast. (RANK = receptor for activation of nuclear factor kappa B).

Osteoprotegerin, a protein that blocks RANKL-RANK interaction and prevents the final differentiation of osteoclasts.

The action of calcitonin opposes that of parathyroid hormone on calcium metabolism. Absorption of calcium in the GI tract is indirectly increased when parathyroid hormone stimulates the synthesis of vitamin D. (The main function of vitamin D is to stimulate calcium absorption by the intestinal mucosa.)

Parathyroid hormone also reduces the concentration of phosphate in the blood. This is done through its action on kidney tubule (decreased absorption, increased excretion of phosphate).

Thus parathyroid hormone maintains normal levels of calcium and phosphate in the blood and prevents hypocalcemia.

### Oxyphil Cells

These cells are regularly seen in the parathyroid glands of horses and large ruminants but are less frequently encountered in other domesticated mammals. These cells are larger than chief cells and occur either singly or in clusters. The cytoplasm is rich in mitochondria and is eosinophilic. The function of this cell type is not known.

## **PINEAL GLAND**

This is an outgrowth of the roof of the diencephalon to which it is attached by a stalk. It is also called the epiphysis cerebri. The glands has a connective capsule with septa extending inward. The parenchyma is made up of pinealocytes and glial cells. There is a sinusoidal capillary network in the gland.

Pinealocytes are the main cell type in the mammalian pineal. Postganglionic nerves fibers from the cranial cervical ganglion synapse on these pinealocytes. The pinealocytes secrete melatonin (derived from tryptophan). This hormone is involved in daily and seasonal photoperiodically induced rhythms, in sexual behavior and reproduction and in thermoregulation.

Glial cells are mostly astrocytes similar to those in the rest of the central nervous system.

Calcium deposits between the cells, brain sand (corpora arenacea), are frequently encountered in the pineal gland.

### **Other Endocrine Tissues**

**Kidneys** --- produced erythropoietin, a hormone that stimulates red bone marrow to increase the production of erythrocytes.

**Heart** --- atrial natriuretic factor.

**GI tract** --- enteroendocrine products are discussed in the Digestive System.

**Placenta** --- chorionic gonadotropin, estrogen, and progesterone.

**Thymus** --- thymosin and thymopoietin.

**Gonads** --- sex hormones and related factors are discussed under Reproductive Systems.