ANAT D502 – Basic Histology

Endocrine System
Revised 11.9.15

Reading Assignment: Chapter 21: Endocrine Organs; pay special attention to Folders 21.2, 21.3, 21.4 and 21.5

Recommended recreational reading (for when the semester is over):

Outline
I. Prolegomenon
II. Concepts
III. Introduction
IV. Hormones and receptors
V. Hypophysis [cerebri] (pituitary gland)
VI. Epiphysis cerebri (pineal gland or body)
VII. Thyroid gland
VIII. Parathyroid glands
IX. Endocrine pancreas
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I. Prolegomenon

II. Concepts

Endocrine is one of those terms (maddening to students) that have multiple meanings. Specifically, endocrine can refer to (1) a class of glands or to (2) a type of hormonal action.

Recall that glands can be broadly classified as exocrine and endocrine. Exocrine glands secrete their products externally while endocrine glands secrete their products internally. As such, most endocrine glands contain extensive capillary beds.

Endocrine gland secretions are called hormones and the action of these hormones is classified on the basis of their target cells and working distance as (1) autocrine, (2) paracrine or (ready?) (3) endocrine. These actions can be described as follows:
- autocrine – hormone acts locally on the releasing cell and adjacent like-members
- paracrine – hormone acts locally or within an organ system on non-like cells (e.g., enteroendocrine cells of the gut)
- endocrine – hormone acts distantly via fluid transport (i.e., blood, lymph or CSF) on non-like cells

Thus endocrine can refer to a class of glands or a type of action. [Thus also, oxymoronically, there can be endocrine glands that lack endocrine action.] How do you know which meaning is intended? By context.
III. Introduction

Homeostasis is the [unconscious] maintenance of a constant internal environment by the organism (Claude Bernard’s “internal milieu”). Homeostasis is accomplished by two interconnected systems: (1) the autonomic nervous system (sympathetic, parasympathetic and enteric) which communicates via nerve impulses resulting in rapid, but typically short-lived responses; and (2) the endocrine system which communicates via hormones resulting in a slower, but more prolonged response.

Both systems (ANS and endocrine) coordinate activity between organs and organ systems to maintain homeostasis. Similarly, both systems are highly integrated (interwoven) with one another. Control of the ANS and much of the endocrine system is centered in the hypothalamus of the brain; in turn, the hypothalamus is the site of action of many hormones (e.g., the thyroid hormones T3 and T4).

The endocrine system consists of the following three elements:

1. endocrine cells and glands
2. hormones - 100+ chemical messengers secreted by endocrine cells into the intercellular (extracellular) space where they may act locally (autocrine and paracrine) or be transmitted by adjacent circulatory systems (blood, CSF, lymph) to act distantly (endocrine)
3. target cells – only cells possessing the proper receptors will respond to hormones; this is what gives the endocrine system its specificity.

N.B. Almost all organs of the body contain endocrine cells and thus are functionally, at least in part, endocrine organs. Indeed, the largest collection of endocrine cells is the combined cells of the gastroenteropancreatic (GEP) system which are involved in digestion. Today, we’ll examine organs whose function is primarily, but not exclusively, endocrinial. The astute student will recall that the rules of anatomical nomenclature prefer that glands, arteries, tracts and ganglia be named for their location (toponymy). Thus it is not surprising, with one exception, these glandular organs take their primary name from their location.

IV. Hormones and receptors

Hormones are chemically divided into 3 classes of compounds: (1) steroids, (2) protein hormones (small peptides, proteins and glycoproteins), and (3) amino acid analogous and derivatives.
Steroids are cholesterol-derived compounds. They are water insoluble thus (1) don’t require cell membrane receptors (i.e., they will diffuse through the cell membrane) but (2) do require carrier proteins for transport through the circulatory system. Examples include the sex hormones and cortisols.

Protein hormones (comprising small peptides, proteins and glycoproteins) are water-soluble thus (1) they don’t require carrier proteins for circulatory system transport but (2) do require cell membrane receptors to enter their target cells.

Amino acid analogues and derivatives include (1) catecholamines (e.g., epinephrine, norepinephrine) that act like the protein hormones and (2) thyroid hormones that act like steroids.

Cell signaling pathways

Individual hormones do not act on all cells of the body (universal or non-specific action), rather they act on a specific subset of cells. This specificity is accomplished through hormone-specific receptors located either on the cell surface or intracellularly.

Cell surface receptors interact with the catecholamine and water-soluble hormones. Binding of a hormone to its corresponding cell surface receptor activates a secondary messenger system (e.g., cAMP, IP3, etc.) within the cell that amplifies the signal and alters cell activity. The cells’ response to such signals is relatively fast (seconds to minutes).

Intracellular receptors interact with steroid and thyroid hormones. Binding of these hormones to their corresponding intracellular receptor results in DNA binding that alters transcription. This response is relatively slow, taking hours to days to effect.

Note, however that this dichotomy in hormone action is not absolute (remember that there’s only one absolute in biology), and that many water-soluble hormones also act to alter transcriptional activity (e.g., many hormones of the adenohypophysis).

V. Hypophysis [cerebri] (pituitary gland)

As its names suggests, the hypophysis is found beneath the brain resting within a bony crypt formed by the sphenoid bone. Anatomically and functionally it is divided into an posterior neurohypophysis and anterior adenohypophysis. The hypophysis develops from the union of two ectodermal invaginations: (1) the infundibulum, derived from the neuroectoderm of the brain (specifically the diencephalon) and that gives rise to the neurohypophysis; and (2) Rathke’s pouch, derived from oral ectoderm and that gives rise to the adenohypophysis.

The neurohypophysis contains nerve axons and support cells (pituicytes); it is comprised of three parts:
1. median eminence – forms the connection to the hypothalamus.
2. infundibular stalk (or infundibulum) - projects into the hypophyseal fossa connecting the median eminence to the pars nervosa.
3. pars nervosa – the expanded distal portion containing the neurosececretory axons of the hypothalamo-hypophyseal tract.

The adenohypophysis contains secretory cells and is also
comprised of three parts:
1. pars distalis – forms the thickened, anterior wall.
2. pars intermedia – forms the division between pars nervosa and pars distalis; it is the remnant of the lumen of Rathke’s pouch and appears as a series of colloidal filled cysts.
3. pars tuberalis – is a dorsal extension along the infundibular stalk.

Blood supply

Branches from the internal carotid supply arterial blood to all regions of the hypophysis except the pars distalis which lacks an arterial blood supply. Vascular perfusion of the pars distalis is supplied by the hypothalamo-hypophyseal portal system (described below). All regions of the hypophysis drain to the hypophyseal veins which are part of the systemic ( caval) venous circulation.

The hypothalamo-hypophyseal portal system arises from capillary bends in both the median eminence and infundibulum of the neurohypophysis and drains via venules to capillary beds in the pars distalis of the adenohypophysis. This portal system carries neuroendocrine secretions (i.e., regulating hormones) from hypothalamic neurons to the cells of the pars distalis to regulate their activity.

Neurohypophysis

The pars nervosa contains the non-myelinated axons (why not-myelinated?) and nerve terminals of the hypothalamo-hypophyseal tract (as opposed to the portal system). The cells bodies of these fibers lie in the supraoptic (SO) and paraventricular (PV) nuclei of the hypothalamus. The nerve terminals of these cells are atypical in that they are (1) non-synaptic and (2) secrete hormones rather than neurotransmitters. These hormones are stored in granules at the nerve terminal and are visible in the light microscope as Herring bodies. The pars nervosa also contains fibroblasts, mast cells and support cells (glia) called pituicytes.

The neurons of the SO and PV nuclei synthesize and secrete two polypeptide hormones, ADH and oxytocin. ADH (anti-diuretic hormone or vasopressin) acts through cell membrane receptors to conserve water by (1) increasing water resorption by the renal collecting ducts, (2) decreasing eccrine gland secretion, and (3) increasing blood pressure by vascular smooth muscle contraction (how might this work to retain water?). Oxytocin also acts via cell membrane receptors to (1) stimulate smooth muscle contractions of the uterus during parturition, menstruation and copulation, and (2) stimulate contraction of mammary myoepithelial cells resulting in milk expression; secretion of oxytocin for the latter is initiated by the infants sucking.

The other two regions of the neurohypophysis, the median eminence and infundibulum, also contain neurosecretory nerve endings from hypothalamic neurons but from nuclei other than SO and PV. The hormones secreted in these regions enter the hypothalamo-hypophyseal portal system and regulate the endocrine cells of the adenohypophysis. The names of these hypothalamic hormones describe their action and include:
1. Growth hormone-releasing hormone (GHRH) – stimulates release of GH
2. Somatostatin – inhibits release of GH and TSH
3. Corticotropin-releasing hormone (CRH) – stimulates release of ACTH
4. Gonadotropin-releasing hormone (GRH) – stimulates FSH and LH release
5. Thyrotropin-releasing hormone (TRH) – stimulates release of TSH and PRL
6. Dopamine (prolactin inhibiting hormone) – inhibits release of PRL

Adenohypophysis (glandular hypophysis)

The pars distalis forms the bulk of the glandular portion of the hypophysis and is an elaboration (thickening) of the anterior wall of Rathke’s pouch. It is comprised of 3 cell types names for their staining properties: acidophils, basophils, (where else have you seen cells called basophils?) and chromophobes. [Chromophobes are acidophils or basophils that have recently released their secretory granules and thus lost their staining profile.] These cells are arranged in cords which are interwoven with capillaries. The
pars intermedia is the remnant of the lumen of Rathke’s pouch and contains colloid-filled cysts as well as sporadic chromophobes and basophils. The pars tuberalis is simply an extension of the cells of the pars distalis around the infundibulum but also contains the venules of the hypothalamo-hypophyseal portal system.

Five cell types are functionally defined by the hormones they release. Types 1 and 2 below appear histologically as acidophils whereas types 3-5 are basophils. All hormones released by the adenohypophysis are proteins or glycoproteins which effect changes via transcriptional regulation.

1. Somatotrophs (GH cells) secrete somatotropin (growth hormone; GH), a protein that alters transcriptional regulation to stimulate growth of muscle, cartilage and bone, and lactation.
2. Lactotrophs (PRL cells, mammotropes) secrete prolactin (PRL), a protein which alters transcriptional activity and stimulates development of the mammary gland during pregnancy and lactogenesis during nursing.
3. Corticotrophs (ACTH cells) secrete corticotropin (adrenocorticotropic hormone, ACTH), a small peptide that alters transcriptional regulation to stimulate secretion of glucocorticoids and gonadocorticoids from the suprarenal cortex.
4. Gonadotrophs (FSH and LH cells) usually secrete FSH or LH rather than both. Follicle stimulating hormone (FSH) is a glycoprotein that alters transcriptional regulation to stimulate ovarian follicle development and spermatogenesis. Leutinizing hormone (LH) is a glycoprotein that alters transcription (1) to stimulate steroid secretion from ovarian follicles and corpora leutia (females) and (2) to stimulate steroid secretion from the Leydig cells of the testes (males).
5. Thyrotophs (TSH cells) secrete thyrotrophic hormone, a glycoprotein that alters transcriptional regulation to stimulate growth of the thyroid follicular cells and their release of thyroid hormone.

VI. Pineal body (gland) [epiphysis cerebri]

The pineal body (descriptive name) or epiphysis cerebri (toponymic name) lies opposite the hypophysis in the roof of the brain. This neurosecretory organ is part of the epithalamic region of the diencephalon. The gland consists of pinealocytes, interstitial cells and capillaries. The interstitial cells are glial cells, mostly astrocytes. The pinealocytes are neurosecretory cells that are arranged into clumps or cords. They secrete melatonin into both the systemic circulation and ventricular system (CSF). Also present are corpora arenacea, calcified concretions that are a by-product of hormone exocytosis. These bodies accumulate with age and, being radio-dense, serve as an excellent radiographic landmark in the brain.

Synthesis and release of melatonin is inhibited by light and it functions in circadian entrainment, that is, the synchronization of intrinsic biological rhythms with diurnal cycles. Disorders involving disruption of melatonin cycles include jet lag and seasonal affective disorder (SAD). Melatonin is also produced by cells in the retina but its function here is strictly paracrine and is part of the dark-adaptive response (night vision).

VII. Thyroid gland

Arguably the phylogenetically oldest of the endocrine organs, the thyroid gland is a bi-lobed gland lying ventral to the (gasp!) thyroid cartilage of the larynx. It is a compound gland containing 2 sets of endocrine producing cells: (1) Follicular cells that produce thyroid hormones and (2) parafollicular cells that secrete calcitonin.

The thyroid gland is invested by a connective capsule; trabeculae (setpa) extending from the capsule divide the gland into irregular lobules. The functional units of the glands are the follicles with each follicle consisting of a simple cuboidal or low columnar epithelium (follicular cells) surrounding a colloidal-filled lumen; the colloid of the lumen is thyroglobulin, an inactive form of thyroid hormone stored extracellularly. Capillaries run in the spaces between adjacent follicular walls. Parafollicular cells are found occurring in isolation or in small clusters at the junctions of the follicles.
Thyroid gland hormones

Calcitonin is produced by the parafollicular cells. This protein hormone acts via membrane receptors to lower blood calcium levels by (1) suppressing osteoclast activity (bone resorption and release of calcium) and (2) promoting osteoid mineralization. Calcitonin secretion is regulated by serum levels of calcium.

Triiodothyronine (T3) and tetraiodothyronine (T4) are produced by the follicular cells. These iodinated amino acid analogues bind to DNA and alter transcription to regulate basal metabolic rate and influence body and tissue growth. T3 and T4 secretion is regulated directly by the TRH-TSH system of the hypophysis.

Follicular cells have histological characteristics of both secretory and absorptive cells; these features relate to the complex synthesis of thyroid hormone that is summarized as follows:
1. Thyroglobulin is synthesized and secreted into the follicular lumen.
2. Iodide is absorbed from the blood stream by iodide transporters and oxidized intra-cellularly to form iodine that is then secreted into the follicular lumen.
3. In the follicular lumen the iodine iodinates the thyroglobulin.
4. Iodinated thyroglobulins are oxidized in the lumen to form T3 and T4.
5. Colloid containing T3 and T4 is re-sorbed by the follicular cells via receptor-mediated endocytosis; the absorbed products are degraded intracellularly by lysosomes to free the T3 and T4
6. T3 and T4 are secreted into the extracellular space.

VIII. Parathyroid glands

The parathyroid glands are paired (superior and inferior), bilateral glands lying along the dorsal margins of the (drum roll) thyroid gland. Each member is surrounded by a thin connective tissue capsule with setpa extending internally to form poorly defined lobes. Two types of parenchymal cells are present: (1) principal (chief) and (2) oxyphil cells. Principal cells are the most numerous and are responsible for the secretion of parathyroid hormone (PTH). Oxyphil cells are much less numerous and occur singly or in clusters; their function is unknown.

Parathyroid hormone (PTH or parathormone) is a protein hormone that acts via cell membrane receptors. It is essential for life and is regulated by serum calcium levels. Its secretion causes serum calcium levels to rise and phosphate levels to fall. It acts on several organs: (1) In bone, it stimulates bone resorption by osteoclasts resulting in elevated calcium and phosphate levels; (2) in the kidney, it decreases excretion of calcium and increases excretion of phosphate; (3) also in the kidney it increases vitamin D synthesis which leads to increased calcium absorption by the small intestine.

IX. Endocrine pancreas

The pancreas is a compound gland with exocrine and endocrine components. The exocrine component consists of serous acini whose digestive secretions drain to the duodenum via the pancreatic duct. The endocrine component is contained within the pancreatic islets (islets of Langerhans). The islets appear as variably sized clusters of pale-staining cells. The cells are arranged in irregular cords that invest a capillary network draining to a large efferent capillary. Three principal cell types (A, B, and D) can be distinguished by immunocytochemistry; each produces its own unique hormone.

The B cells account for approximately 70% of the islet cells and produce insulin. Insulin is a dipeptide that acts through cell membrane receptors. Release of insulin (1) promotes the uptake of glucose from the systemic circulation by membrane glucose transporters, (2) stimulates storage of glucose by glycogenesis in muscle and liver, and (3) promotes lipogenesis. The absence or insufficient levels of insulin results in diabetes mellitus.
The A cells account for approximately 20% of the islet cells and produce glucagon. Glucagon is a peptide that acts through cell membrane receptors. The effects of glucagon secretion are largely reciprocal to that of insulin, specifically it (1) stimulates the formation (by gluconeogenesis and glycogenolysis) and release of glucose by the liver, and (2) stimulates fat catabolism in the adipocytes.

The D cells account for approximately 10% of the islet cells and produce somatostatin. This cyclic polypeptide is identical to that released by the hypothalamus. Thus, it inhibits somatotropin (GH) and TSH synthesis and secretion.

The endocrine cells of the pancreas are under neural and environmental control. Approximately 10 percent of the islet cells are directly innervated by neurons of the autonomic nervous system (ANS) with the rest receiving neural stimulation electrotonically via gap junctions. Parasympathetic stimulation increases secretion of both insulin and glucagons whereas sympathetic stimulation increases glucagons secretion but inhibits insulin release. In addition to neural control, the islet cells respond to changes in the blood serum levels of glucose, amino acids and fatty acids.

X. Suprarenal (adrenal) glands

The suprarenal glands are bilateral, triangular shaped glands positioned over the superior pole of the kidneys. A thick connective tissue capsule invests each gland and the parenchyma is divided into two regions, cortex and medulla. The cortex is the steroid-secreting portion and accounts for approximately 90% of the gland volume; it is divided into 3 zones, from external to internal, the zonulae glomerulosa, fasciculate, and reticulata. The teeny-tiny medulla is the catacholamine-secreting portion and it surrounds portions of the central (medullary) vein. A rich vascular network invests the entire organ.

The two portions of the suprarenal glands have distinct embryonic origins. The cortex is derived from mesoderm whereas the medulla arises from neural crest (ectomesenchyme) and can be viewed as a modified sympathetic ganglion. The hormonal cells of the medulla are basically post-ganglionic sympathetic neurons which have abandoned their neural functions and become secretory cells.

Suprarenal cortex

The suprarenal cortex is divided into 3 zones based on the arrangement of their cells. The zona glomerulosa is the most superficial and its cells are arranged in ovoid clusters surrounded by sinusoidal capillaries. These cells secrete the mineralocorticoid steroid aldosterone. After secretion aldosterone is transported through the blood stream by a special carrier protein and binds to the DNA of its target cells to alter transcriptional activity. It acts on cells in the kidney, stomach and salivary glands to take up sodium (Na+2) and excrete potassium (K+) ions. It is part of the renin-angiotensin-aldosterone system that helps regulate blood pressure (see text for excruciating details).

The zona fasciculata is the middle cortical layer and its cells are arranged in long straight cords surrounded by sinusoidal capillaries. These cells have a vacuolated appearance and are often binucleate; they secrete glucocorticoid and androgen steroids. Cortisol (hydrocortisone) is a glucocorticoid that binds directly to DNA to alter transcription. It acts on a wide variety of cell, often in an antagonistic manner; among its effects are (1) stimulation of gluconeogenesis and glycogenesis in the liver; (2) lipid catabolism in adipocytes and protein catabolism in muscle; and (3) depression of immune and inflammatory responses. Secretion of cortisol is under control of the CRH-ACTH system. The cells of the zona fasciculate are also a minor, secondary source of androgens whose effects include masculinization and anabolic activity.

The zona reticularis is the deepest layer of the cortex and its cells are arranged in interwoven cords separated by capillaries. Many of its cells contain lipofuscin pigment granules, a by-product of lysosomal digestion. These cells secrete the same hormones as the zona fasciculata.
**Suprarenal medulla**

The parenchyma of the medulla is formed by chromaffin cells (medullary cells) arranged into short cords. Also present in the medulla are the axons of sympathetic neurons, capillaries, and post-ganglionic sympathetic neurons. The latter project their axons to innervate the suprarenal cortex and surrounding viscera.

The chromaffin cells secrete epinephrine and norepinephrine; both are amino acid analogues (catecholamines) that act via membrane receptors. Along with the glucocorticoids secreted by the cortical cells, these hormones are the messengers of the “fight-or-flight” response which is activated by the sympathetic nervous system in times requiring maximum physical effort. These hormones have multiple target cells through the body and their effects include (1) increasing respiration rate and bronchiole dilation, (2) increasing heart rate and blood pressure, (3) stimulation of glycogenolysis in muscle and liver, (4) stimulation of sweat gland secretion (cooling), and (5) decreasing digestive activities.

**Blood supply and regulation of chromaffin cell secretion**

Arterial blood is supplied by the suprarenal arteries whose branches target (supply) specific regions of the gland (see below); all capillaries within the gland drain to the medullary vein and the blood returns to the caval (systemic) venous system.

All chromaffin cells are directly innervated by pre-ganglionic sympathetic neurons; release of acetylcholine by the pre-synaptic neurons triggers release of hormone by the chromaffin cells. The type of hormone, epinephrine or norepinephrine, released is determined by the source of the blood perfusing the chromaffin cells. Chromaffin cells perfused by the cortical sinusoids (capillaries carrying glucocorticoids) synthesize and release epinephrine; chromaffin cells perfused by medullary arterioles synthesize and release norepinephrine.