Pathology of the Endocrine System

Lecture 2
Adrenal & Thyroid Glands
(Web review)
Adrenal Gland
Adrenal Cortex

STRUCTURE AND FUNCTION

- cortex ~75% of adrenal → produces over 50 different steroids

Figure 20–14 (Mesher) Adrenal gland. Inside the capsule of each adrenal gland is an adrenal cortex, formed from embryonic mesodermal cells, which completely surrounds an innermost adrenal medulla derived embryologically from neural crest cells. Both regions are very well vascularized with fenestrated sinusoidal capillaries. Cortical cells are arranged as three layers: the zona glomerulosa near the capsule, the zona fasciculata (the thickest layer), and the zona reticularis.
Adrenal Cortex

- Capsule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Adrenal medulla

Image: Microscopic view of adrenal cortex layers.
**Zona glomerulosa** - 15% (SALT)

Aldosterone secreted by the zona glomerulosa of the adrenal cortex acts on the distal portions of the nephron to increase tubular excretion of potassium and increase resorption of sodium (and secondarily of chloride). The resulting osmotic gradient facilitates movement of water from the glomerular filtrate into the extracellular fluid (ECF).
Zona fasciculata - 70% (SUGAR)

- Glucocorticoids → CHO (↓ use of glucose in muscle/fat & ↑ gluconeogenesis, esp liver)
  → protein catabolic
  → lipolytic

- cause hyperglycemia → increase glucose production // antagonistic to action of insulin

- suppress inflammation, healing and immune response
Zona reticularis - 15% (SEX)
Developmental Anomalies & Miscellaneous Lesions

1) Agenesis, unilateral or total
2) Hypoplasia 2° to maldevelopment of pituitary gland
3) Accessory adrenal cortical tissue
4) Mineralization
5) Amyloid deposition
6) Capsular sclerosis
7) Telangiectasis
8) Hemorrhages - sepsis / toxemia; severe stress or trauma in newborn

Diffuse hemorrhage of the inner region of the adrenal cortical; gross (left) and histo (right)
**Inflammation (Adrenalitis)**

1) **Viruses** → herpesvirus
2) **Bacteria** → gram negatives & mycobacteria
3) **Fungi** → dimorphic fungi
4) **Parasites** → Toxoplasma

Multifocal necrosuppurative adrenalitis in a foal with sepsis due to *A. equuli*
Hypoadrenocorticism (Addison’s disease)

1) Primary Hypoadrenocorticicism
   a) Bilateral idiopathic adrenal cortical atrophy:
      • esp young to middle-aged female dogs; autoimmune / hereditary
      • destruction of all 3 layers → deficient production of all cortical hormones

Figure 12-59 (Zachary). Adrenal cortical atrophy, brain stem and pituitary gland, adrenal glands, dog. Bilateral atrophy of all three cortical layers (arrows) is characteristic of hypoadrenocorticism. The pituitary gland (arrowhead) was grossly normal with microscopic evidence of corticotroph hyperplasia.
Hypoadrenocorticism (Addison’s disease)

a) Bilateral idiopathic adrenal cortical atrophy (cont’d)

Normal

Bilateral adrenal cortical atrophy
Normal (above)
Adrenal cortical atrophy – low power (top right) and high power (bottom right)

note: collapsed, thickened capsule (*) (top right) and macrophages filled with yellow ceroid / lipofuscin pigment (below right)
Hypoadrenocorticism (Addison’s disease)

1) Primary Hypoadrenocorticism
   b) Bilateral destruction of adrenal glands
      • due to inflammation, infarction, hemorrhage, tumor

2) Secondary Hypoadrenocorticism
   • ACTH deficiency $\rightarrow$ trophic atrophy of inner 2 zones (not mineralocorticoids)

   a) Destructive pituitary lesions
      • damage to the cells making ACTH

   b) Iatrogenic
      • following sudden withdrawal of glucocorticoid after prolonged usage
Hypoadrenocorticism (Addison’s disease)

Clinical Signs / Lesions

- primarily dogs

- lethargy, stress intolerance, bradycardia, anorexia, vomiting & diarrhea → dehydration / emaciation

- possible acute circulatory failure, ie cardiogenic / hypovolemic shock

- electrolyte imbalance (hyponatremia & hyperkalemia) → hallmark of Addison’s

- hypoglycemia, hemoconcentration & low plasma cortisol (no response to ACTH when 1°)
1) Diffuse hyperplasia:

- ↑ ACTH (pit. adenoma or idiopathic) → cortex uniformly enlarged (inner 2 zones)
- excess glucocorticoids → Cushings

Fig. 12-17 (Zachary) Secondary hyperfunction of adrenal glands, brain, pituitary gland and left and right adrenal glands, dog. Corticotroph (adrenocorticotropic hormone [ACTH]-secreting) chromophobe adenoma (A) in the pituitary gland and bilateral (symmetrical) enlargement of the adrenal glands. The chronic secretion of ACTH has resulted in bilateral (symmetrical) hypertrophy and hyperplasia of secretory cells of the zona fasciculata and zona reticularis in the adrenal cortex (arrows) and excessive secretion of cortisol.
Adrenal Cortical Hyperplasia / Neoplasia

2) Nodular hyperplasia:

- seen in old horses, dogs & cats (+/- functional)
- often multiple, bilateral and yellow

Multiple hyperplastic nodules of cortical scattered throughout adrenal; note: minimal compression.
3) Cortical adenomas:
• especially old dogs (often functional)
• nodular hyperplasia vs adenoma (generally larger, encapsulated and compressive)

Cortical adenoma note: single, larger mass with some evidence of compressive atrophy of adjacent adrenal tissue
Figure 12-28 (Zachary). Adrenocortical carcinoma and contralateral cortical atrophy, adrenal glands, dog. The adrenal gland (right) has a large adrenocortical carcinoma that is almost half the size of an adult kidney (left). Multifocal to coalescing areas of hemorrhage and necrosis are apparent (arrowheads) in this tumor. The cortex of the contralateral adrenal gland (lower) is notably thinned (arrow) because of severe trophic atrophy of the zona fasciculata and zona reticularis.

4) Cortical carcinoma:
- old dogs (may be functional)
- often bilateral and may invade vena cava
Hypercortisolism (Cushing’s Disease)

a) Primary hyperadrenocorticism (10-15%): functional cortical neoplasm, esp adenoma
b) Secondary hyperadrenocorticism (80%): PDH or idiopathic (altered -ve set-point?)
c) Iatrogenic (pharmacological) hyperadrenocorticism (5-10%): overmedication

Meuten: Tumors of Domestic Animals
Hypercortisolism (Cushing’s Disease)

Clinical Signs / Lesions

- due to combined gluconeogenic, lipolytic, protein catabolic & anti-inflammatory / immunosuppressive effects.

- polyuria / polydipsia → ↑ GFR &/or interfer with ADH

- polyphagia → direct affect on satiety center

- hepatomegaly → “steroid (glycogen) hepatopathy”

- pendulous abdomen → muscle atrophy/weakness from protein catabolism & hepatomegaly

- skin lesions → dermal atrophy, bilateral symmetric alopecia, delayed wound healing

- dystrophic mineralization → esp skin; +/- lung, etc (catabolism alters collagen / elastin)

- ↑ susceptibility to bacterial infections → due to immunosuppressive effects

- others: hypercoagulability

  - eosinopenia

  - lymphopenia / lymphoid involution
Dehiscence of surgical wound, skin, dog.

Wounds heal slowly in dogs with cortisol excess because of an inhibition of fibroblastic proliferation.

Glucocorticoid-induced hepatopathy, liver, dog.

In dogs with glucocorticoid excess (Cushing's disease) from endogenous or exogenous sources, an extensive accumulation of glycogen in hepatocytes results in an enlarged, pale-brown to beige liver.

Figure 12-07 (Zachary). Dehiscence of surgical wound, skin, dog. Wounds heal slowly in dogs with cortisol excess because of an inhibition of fibroblastic proliferation.
Adrenal Medulla

STRUCTURE AND FUNCTION

- derived from neuroectoderm / neural crest → 25% of adrenal gland
- composed of pheochromocytes and a few ganglion cells
- catecholamines derived from tyrosine → norepinephrine to epinephrine

Figure 20–16. (Mescher) Adrenal medulla. The hormone—secreting cells of the adrenal medulla are chromaffin cells, which resemble sympathetic neurons. (a): The micrograph shows they are large pale-staining cells, arranged in cords interspersed with wide capillaries. Faintly stained cytoplasmic granules can be seen in most chromaffin cells. X200. H&E. (b): TEM reveals that the granules of norepinephrine—secreting cells (NE) are more electron—dense than those of cells secreting epinephrine (E), which is a function of the chromogranins to which the catecholamines are bound in the granules. Most of the hormone produced is epinephrine, which is only made in the adrenal medulla. X33,000.
**Adrenal Medullary Hyperplasia / Neoplasia**

**Pheochromocytoma:**
- mainly in dogs & cattle
- tumor is often large and encapsulated → may invade the vena cava and metastasize
- rarely functional → tachycardia, edema and cardiac hypertrophy
- $K_2Cr_2O_7$ or KI on cut surface → dark-brown coloration in 5-20 min

**Figure 12-36 (McGavin).** Pheochromocytoma, adrenal gland, horse. A pheochromocytoma compressing the adjacent unaffected adrenal cortex.
Figure 12-31 (Zachary). Pheochromocytoma, kidney, adrenal gland, caudal vena cava, dog. A large pheochromocytoma (P) has obliterated the adrenal gland medial to the kidney (K) and has extensively invaded into the lumen of the caudal vena cava (arrow).
Pheochromocytoma, kidney, adrenal gland, caudal vena cava, dog. Opened caudal vena cava showing invasion of a pheochromocytoma into the lumen (arrow).
THYROID FOLLICULAR CELLS

THYROID C (PARAFOLLICULAR) CELLS

[Anatomy of the Dog, Miller et al]
Normal thyroids and parathyroids
Thyroid Follicular Cells

**STRUCTURE AND FUNCTION**

- largest endocrine organ and secretion controlled by TSH & TRH
- $T_4$ and $T_3$ act like steroid hormones, but act on virtually all cells
- regulate growth / differentiation / rate of metabolism → increase BMR
- evaluate via serum cholesterol, $T_4$ & $T_3$, TSH Stimulation Test, biopsy

thyroid follicles containing colloid
Figure 20–21 (Mescher) Thyroid follicular cell functions. The diagram shows the multistep process by which thyroid hormones are produced via the stored thyroglobulin intermediate. In an exocrine phase of the process, the glycoprotein thyroglobulin is made and secreted into the follicular lumen and iodide is pumped across the cells into the lumen. In the lumen tyrosine residues of thyroglobulin are iodinated and then covalently coupled to form T3 and T4 still within the glycoprotein. The iodinated thyroglobulin is then endocytosed by the follicular cells and degraded by lysosomes, releasing free active T3 and T4 to the adjacent capillaries in an endocrine manner. Both phases are promoted by TSH and may occur simultaneously in the same cell.
Developmental Anomalies

1) Aplasia and Hypoplasia
2) Accessory Thyroid Tissue
3) Thyroglossal duct cysts
Degenerative and Inflammatory Changes

1) Lymphocytic (Immune-mediated) Thyroiditis:
- esp dogs, develop clinical hypothyroidism
- due to autoantibodies to thyroglobulin and other colloid Ag’s
- multifocal to diffuse infiltrate of lymphocytes, plasma cells and macrophages → later fibrosis
- vacuolated colloid which may contain inflammatory cells / cellular debris

note: severe lymphoid infiltration with destruction / effacement of normal thyroid architecture
Degenerative and Inflammatory Changes

2) Idiopathic Follicular Atrophy ("Collapse"):

- cause of hypothyroidism in dogs
- progressive loss of follicular epithelium & replacement by adipose tissue

Thyroid atrophy, note **apparent** (not real) enlargement parathyroids because of reduced size of thyroid gland.

FIG 51-2 (Small Animal Internal Medicine, 4th Edition) .Histologic section of a thyroid gland from a dog with idiopathic atrophy of the thyroid gland and hypothyroidism. Note the small size of the gland, decrease in follicular size and colloid content, and lack of a cellular infiltration.
### Hypothyroidism

- mostly dogs
- esp due to: idiopathic follicular collapse or lymphocytic thyroiditis [rarely bilateral nonfunctional tumors, chronic pituitary lesions or severe I\textsubscript{2} deficiency]

### Clinical Signs / Lesions

- **reduced BMR** → lethargy, weight gain, muscular weakness & slow reflexes
- **skin** → bilaterally symmetric alopecia, hyperpigmentation, myxedema
- **reproductive abnormalities** → lack of libido, infertility, etc
- **joint pain & effusion** → ? pathogenesis?

### Clin Path

- low T4 & T3, normocytic normochromic anemia & high serum cholesterol
- hypercholesterolemia → atherosclerosis & hepatic / glomerular / corneal lipidosis
note: symmetric alopecia (above) and obesity and myxedema (right)
Web Figure 12-5 (Zachary). Atherosclerosis, hypothyroidism with marked hyperlipidemia, heart, coronary arteries, dog. Note the atherosclerosis (arrows) of the coronary arteries which are thickened, firm, yellow-white, and often beaded.
Thyroid Hyperplasia (Goiter)

• nonneoplastic, noninflammatory enlargement due to increased TSH secretion
• results from inadequate thyroxine synthesis and decreased T₄ & T₃ blood levels
• the four major pathogenetic mechanisms include:
  a) iodine deficient diet
  b) excess dietary iodine
  c) goitrogenic compounds interfering with thyroxinogenesis
  d) genetic enzyme defects in hormone synthesis
1) Diffuse Hyperplastic Goiter:

- in young of dams on I\(_2\) deficient / excess I\(_2\) diets or fed goitrogenic substances
- marked enlargement → irregular hyperplastic follicles with pale & vacuolated colloid

Figure 12-38 (Zachary). Hyperplastic goiter, thyroid gland, dog. Hyperplastic follicular epithelium forms a papillary projection (arrow), which extends into the follicular lumen devoid of colloid. Note that the majority of follicular lumens are small and collapsed. Periodic acid–Schiff reaction.
2) Colloid goiter:

- represents involutionary phase of hyperplastic goiter
- see large follicles with densely eosinophilic colloid & less vascularization
3) Congenital dyshormonogenetic goiter (inherited goiter):

- AR in some breeds of sheep, goats and cattle
- genetic impairment of thyroglobulin synthesis
- $T_4$ & $T_3$ levels are low even though $I_2$ uptake / turnover are increased
- see subnormal growth rate, sparse haircoat, myxedema, weakness & sluggish behaviour
- thyroid lobes are symmetrically enlarged at birth

Neonatal goat kid with congenital dyshormongenetic goiter
Nodular hyperplasia, thyroid glands, cat. Note the multiple hyperplastic nodules in thyroid glands.
2) Follicular Cell Adenoma

- may be functional; cats > dogs & horses
- adenomas usually single, encapsulated nodular or cystic masses

Follicular cell adenoma, thyroid gland, horse. Note compression of adjacent thyroid tissue on histology (right).
Thyroid carcinoma (arrows), dog. Note, this poorly circumscribed and well-vascularized thyroid carcinoma (arrows) is locally invasive and has extended into the wall of the esophagus.

**Thyroid Hyperplasia / Neoplasia**

3) Follicular Cell Carcinoma:

- carcinomas are more common in dogs (+/- functional)
- typically multinodular, invade local tissues & often metastasize early to the lungs
- may arise from accessory thyroids (ie mediastinum or heart base regions)
Hyperthyroidism

- esp aged cats with nodular hyperplasia or functional adenomas / carcinomas

Clinical Signs / Lesions

- PU / PD, restlessness, increased activity and weight loss in spite of polyphagia
- may be cervical swelling, coughing and dyspnea, left ventricular hypertrophy

Note the obvious weight loss in this cat with hyperthyroidism.