16. ADRENAL GLAND

FUNCTIONAL ANATOMY OF THE ADRENAL GLAND

To understand the function of the adrenal gland, it is useful to understand the anatomical and histological differences of each section. The gland can be divided in three large sections. Moving from the outside in is the capsule, which basically is connective tissue and provides protection without participating in the endocrine function of the organ; then, the adrenal cortex which is divided into three distinct zones: glomerulosa, fasciculata and reticularis; and finally, the central part of the adrenal cortex, the medulla (Fig. 16-1).

<table>
<thead>
<tr>
<th>Adrenal gland</th>
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<tbody>
<tr>
<td><strong>Divided into capsule, cortex and medulla</strong></td>
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<tr>
<td><strong>Capsule</strong></td>
</tr>
<tr>
<td>o Non-secretory, protective</td>
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<tr>
<td><strong>Cortex</strong></td>
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<tr>
<td>o Zona glomerulosa (mineralocorticoids)</td>
</tr>
<tr>
<td>o Zona fasciculata (glucocorticoids and sex steroids)</td>
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<tr>
<td>o Zona reticularis (glucocorticoids and sex steroids)</td>
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<tr>
<td><strong>Medulla</strong></td>
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<tr>
<td>o Catecholamines (epinephrine and norepinephrine)</td>
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The hormones of the adrenal gland can be divided based on the area in which they are produced. The denomination of corticosteroids refers to all hormones produced in the adrenal cortex. The corticosteroids in turn can be divided, based on their function, into mineralocorticoids, glucocorticoids and androgens.

Adrenal cortex

As it can be seen in figure 16.2 the adrenal cortex contains the three already named distinct layers. The outermost, zona glomerulosa, is a thin layer of cells, which makes up about 15% of the total cortical mass. The cells in this zone are the only population of cells capable of producing the steroid aldosterone. This characteristic is given by the presence of the enzyme aldosterone synthase, an enzyme essential for the synthesis of this hormone. Aldosterone is mainly responsible for regulation of electrolyte balance and its production is stimulated by the circulatory concentration of angiotensin II and potassium.

The central and largest zone of the adrenal cortex is the zona fasciculata, making up about 75% of the cortex mass. Its main role is the secretion of glucocorticoids, in particular cortisol and corticosterone. It also has the capability of secreting small amounts of androgens and estrogens.

Production of corticosteroid

The details of the regulatory process are as follows: upon sensing a stressful situation, neurons in the hypothalamus secrete CRH into the portal system, carrying these molecules into the pars distalis where they attach to receptors in the corticotrophs. The result is the secretion of ACTH, which travels through circulation into the adrenal cortex where it stimulates the production of glucocorticoids by the mechanism shown in figure 16-3.
Transport of corticosteroids

Once the corticosteroids are secreted, they are transported in circulation by carrier proteins. This increases their water solubility, serves as a temporary storage, and increases the half-life of the steroid. Glucocorticoids are carried mainly by a corticosteroid binding globulin (CBG) that is produced in the liver and secreted into circulation (Fig. 16-4). A smaller proportion is carried by albumin and about 10% is circulating freely. On the other hand, 40% of mineralocorticoids are circulating freely, 50% are bound to albumin and only 10% use CBG.

The concentration of carrier proteins is modified depending on the physiological status of the animal. During pregnancy, for example, the elevated concentration of estrogen tends to increase production of CBG while in liver disease there is usually a marked decrease in CBG (Fig. 16-5).

Corticosteroid function

The majority of the corticosteroids have both mineralo and glucocorticoid capabilities (Fig. 16-6).

The potency with which corticosteroids exert their effects varies significantly. This dual action provides some advantages but it can present a serious problem if there is a situation of overproduction with some of these compounds.
Mineralocorticoids

As indicated previously, aldosterone (Fig. 16-7) provides about 90% of the mineralocorticoid activity.

Other corticosteroids, such as desoxycorticosterone, exert some mineralocorticoid activity but with only 1/30 of the potency of aldosterone. Furthermore, under normal conditions, there are very small quantities in circulation. Corticosterone has more mineralocorticoid activity than cortisol (1/400 of the potency of aldosterone) but their quantities vary with the species. Cortisol dependent species have significant concentrations of cortisol, 1000 times more than aldosterone, making them capable of exerting some mineralocorticoid action.

The role of mineralocorticoids is to regulate retention and the secretion of minerals, which otherwise would be discarded in the urine or retained in circulation. Specifically, aldosterone promotes absorption of sodium and, at the same time enhances secretion of potassium by epithelial cells of the renal tubules. The majority of the effect is exerted in the principal cells of the collecting tubules, although the distal convoluted tubules also play a minor role.

Mineralocorticoid action. Aldosterone, the main mineralocorticoid is secreted by the adrenal cortex, in response to stimulation by angiotensin II. Angiotensin II in turn is derived from angiotensin I, by the effect of Angiotensin converting enzyme, which is produced in the lungs (Figs. 16-8 and 16-9).

Angiotensin I is derived from angiotensinogen produced by the liver and it is converted by the enzyme rennin secreted by the kidneys (Fig. 16-9).

Mineralocorticoids

- Main representative is aldosterone (21C)
- Regulation of electrolyte balance
  - Absorption of Na\(^+\)
  - Secretion of K\(^+\)
- Regulation of blood pressure
Glucocorticoids

The most common glucocorticoids in domestic animals are cortisol and corticosterone (Figs. 16-11, 16-12).

It also leads to a reduction in muscle formation, which provides the substrate required (amino acids) in the liver for the formation of glucose. As a result of the increase in the production of glucose in the liver, there is a complementary process of the storage of glucose in the form of glycogen in the liver. Furthermore, in order to ensure that more glucose is available in the system, glucocorticoids reduce the rate of glucose utilization by peripheral tissue. The effect of glucocorticoids in protein synthesis in the liver is the opposite to what takes place in the rest of the organism. In the liver there is a marked increase in protein synthesis, which translates in an elevation of plasma proteins (possibly to facilitate aa transport to the liver). As stress coping hormones, glucocorticoids increase in response to any threatening environmental or physiological change. Its mechanism of action is not understood but it has been demonstrated that animals unable to produce glucocorticoids cannot adapt to any significant environmental change and could easily die.

Glucocorticoids have a tremendous influence in the regulation of metabolic activities (Fig. 16-13).

As an essential component of metabolic activity, glucocorticoids promote gluconeogenesis and to a certain extent glycogenesis by the liver through two mechanisms (Fig. 16-13). The first is by enhancing transcription, leading to the synthesis of the enzymes required to transform amino acids into glucose in the liver. The second is an increase in catabolism of proteins, which results in the mobilization of amino acids, principally from muscle tissue.
Glucocorticoids prevent inflammation by stabilizing the structure of lysosomes. This in turn prevents or significantly reduces the release of proteolytic enzymes from lysosomes. Concurrently glucocorticoids decrease capillary permeability, thus preventing plasma leakage into extravascular tissue, which is another characteristic of inflammation. They also impair phagocytosis and slow migration of white blood cells into inflamed areas (Fig. 16-14).

**Anti-inflamatory effects**

- **Stabilizing lysosomes**  
  - Lower proteolitic enzyme release
- **Reduces capillary permeability**  
  - Prevents edema
- **Impairs phagocytic activity and migration of white blood cells**  
  - Reducing production of PG and leukotrienes
- **Immunosuppressant**  
  - Slowing proliferation of lymphocytes
- **Anti-pyretic**  
  - Reduce interleukin-1 from white blood cells

Figure 16-14. Anti-inflammatoty role of glucocorticoids

This appears to be achieved through synthesis impairment of local prostaglandins and leukotrienes, which are promoters of the mobility of white cells, as well as, vascular permeability and vasodilatation. Glucocorticoids are immunosuppressant, thus reducing proliferation of lymphocytes. Finally, they can lower a fever by impairing the release of interleukin-1 which otherwise would influence the temperature control centre at the level of the hypothalamus.

### Synthesis of glucocorticoids (Cortisol)

Although adrenal cells can synthesize cholesterol in situ, it is far more common for them to utilize circulating cholesterol. The mechanism used (Fig. 16-15) is as follows: upon stimulation with ACTH, the membrane bound receptor activates a g-protein that activates adenyl cyclase. This in turn converts ATP into cAMP, which, as a second messenger promotes many simultaneous effects. It starts by enhancing the internalization of receptor bound LDL, which are incorporated into lysosomes where cholesterol is released.

The cholesterol, supported by cAMP, can be taken from lipid droplets, where it is stored as cholesterol ester. The cholesterol is then moved to the mitochondria, where again, supported by cAMP, is converted to pregnenolone and exported to the cytoplasm where it is finally converted to cortisol by hydroxylation of C-21.

Catabolism of glucocorticoids

The half-life of glucocorticoids is about one hour. To eliminate these compounds, the liver carries out conjugation of the molecule with either glucoronide or sulfates. This makes the molecule biologically inactive and highly soluble in water; therefore, it can be excreted through the urine (Fig. 16-16).
ABNORMALITIES

A persistent elevation in circulatory glucocorticoid results in Cushing’s syndrome. The causes of this syndrome can be an abnormally high secretion of ACTH from the adenhypophysis (ACTH-dependent Cushing’s), or an abnormal secretion of CRH, which in turn over-stimulates the production of ACTH (Fig. 16-17).

PATHOLOGIES

- Hyperadrenocorticism (Cushing’s syndrome)
- Caused by:
  - Pituitary abnormality
  - Adrenal abnormality

An animal with a problem in the adrenal resulting in overproduction of glucocorticoids has ACTH-independent Cushing’s and usually is accompanied by very low levels of ACTH. The symptoms of the disease are very elevated glucose in circulation and a significant deterioration of the muscle mass triggering serious weakness. Another symptom of Cushing’s is a very inefficient immune system, which may lead to serious infection and death. The protein collagen fiber of the subcutaneous tissue also weakens and tears easily, creating purplish striae. Finally, a deficient deposition of the protein matrix in the bone triggers osteoporosis with the resulting bone fragility.

CLINICAL SIGNS

- Polydipsia
- Polyurea
- Polyphagia
- Abdominal enlargement
- Heat intolerance
- Lethargy
- Obesity
- Muscle weakness

Other visible signs are polydipsia, polyurea, polyphagia, enlargement of the abdominal cavity, heat intolerance, lethargy, and obesity (Fig. 16-18).

Abnormalities

- Hypoadrenalism (Addison’s Disease)
  - Deficiency in production of corticosteroids
- Mineralocorticoid deficiency
  - Decreased tubular sodium reabsorption
  - Loss of water
  - Plasma volume drops, cardiac output decreases

The clinical signs are often very generic but they involve depression, weakness, gastrointestinal upset, and a slow heart rate.

Hypoadrenalism leads to Addison’s disease, which is characterized by low glucocorticoid (Fig. 16-19, 16-20).
According to Arnold Plotnick (2001, DOG WORLD Magazine, Vol. 86, No. 6), the following are historical and clinical findings in dogs with Addison’s disease.

<table>
<thead>
<tr>
<th>Sign</th>
<th>Percentage of affected dogs</th>
</tr>
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<tbody>
<tr>
<td>Lethargy and depression</td>
<td>95</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>90</td>
</tr>
<tr>
<td>Vomiting</td>
<td>75</td>
</tr>
<tr>
<td>Weakness</td>
<td>75</td>
</tr>
<tr>
<td>Weight loss</td>
<td>50</td>
</tr>
<tr>
<td>Dehydration</td>
<td>45</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>40</td>
</tr>
<tr>
<td>Collapse</td>
<td>35</td>
</tr>
<tr>
<td>Slow capillary refill time</td>
<td>30</td>
</tr>
<tr>
<td>Weak pulse</td>
<td>20</td>
</tr>
<tr>
<td>Slow heart rate</td>
<td>18</td>
</tr>
</tbody>
</table>

### Adrenal medulla

The adrenal medulla is an important source of catecholamines. These compounds are produced as neurotransmitters throughout the organism but they are also secreted in massive amounts by cells of the adrenal medulla (Fig. 16-21).

### Catecholamines

Catecholamines may bind at least 4 types of receptors. Alpha receptors are more potently stimulated by norepinephrine ($\alpha_1$ and $\alpha_2$), although norepinephrine can weakly stimulate beta ($\beta_1$ and $\beta_2$) receptors. Epinephrine can bind equally well to alpha and beta receptors (Fig. 16-23).

### Receptors for catecholamines

- **Use four types of receptors**
  - $\alpha$ control release from sympathetic nerve endings
    - $\alpha_1$ postsynaptic terminals
    - $\alpha_2$ presynaptic terminals
  - $\beta_1$ mainly in heart
  - $\beta_2$ smooth muscle
Metabolic effects of epinephrine

- Epinephrine more potent than norepinephrine on $\beta_2$ receptors
- Similar effects than glucagon
  - Increases blood glucose
  - Increases liver glucogenolysis and gluconeogenesis
  - Increases muscle glycogenolysis
  - Inhibits insulin secretion
  - Stimulates glucagon secretion
- Increases lipolysis rate on adipose tissue
  - Potentiated by glucocorticoids

Figure 16-23. Metabolic role of epinephrine

Metabolic effects of epinephrine. When epinephrine acts on $\beta_2$ receptors, it exerts a more potent effect than that of norepinephrine (Fig. 16-24). In other metabolic activities, epinephrine has similar effects to glucagons, as it tends to increase circulatory levels of glucose by enhancing glycogenolysis and gluconeogenesis. It also inhibits insulin secretion and stimulates glucagons production. Finally, it enhances lipolysis in adipose tissue. The action of epinephrine depends on the type of the receptor to which it binds. In figure 16-24 it can be seen that if epinephrine binds to a $\beta_2$ receptor, it translates in the activation of adenyl cyclase, while if the binding is to $\alpha_2$ receptors, there is inhibition of the activation of adenyl cyclase. Adenyl cyclase follows the pattern of a second messenger because it converts ATP into cAMP, which in turn activates a protein kinase.

Acting in the pancreas, epinephrine stimulates insulin production if it binds to $\beta_2$ receptors and decreases insulin production if the receptor used is an $\alpha_2$ (Fig. 16-25).

The role of the activated protein kinase is to phosphorylate a protein to make it active. These proteins can be other mediators or another enzyme. Another mechanism used by epinephrine to phosphorylate proteins is to increase the amount of intracellular calcium. Two routes achieve this. Epinephrine binds an $\alpha_1$ receptor which in turn activates phospholipase C. Phospholipase C activates inositol 3 phosphate which travels to the endoplasmic reticulum triggering a release of calcium stored there. Another consequence of the binding of epinephrine to the $\alpha_1$ receptor is the formation of diacyl glycerol, which facilitates the entrance of extra cellular calcium into the cytoplasm. The accumulation of intracellular calcium contributes to the phosphorylation of certain proteins. All of these translate into a desired effect.

The following are specific examples of the effects of catecholamines in different tissues. In the liver they activate glycogenolysis, lipolysis and gluconeogenesis when they bind to $\beta_2$ receptors (Fig 16-26).
Similarly, in adipose tissue and in muscle fibers they stimulate lipolysis and glycogenolysis respectively (Figs. 16-27, 16-28).

Figure 16-26. Effects of catecholamines in liver

Figure 16-27. Effects of catecholamines in adipocytes

Figure 16-28. Effects of catecholamines in muscles