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 into 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).

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 production of glucocorticoids is directly stimulated by adrenocorticotropic hormone (ACTH), a 39 amino acid hormone derived from the protein proopiomelanocortin and secreted by the corticotropes of the hypophysis. The production of ACTH is stimulated by corticotropic releasing hormone (CRH) from the hypothalamus. The entire regulatory process also involves negative feedback by the glucocorticoid in the hypothalamus.
the hypophysis and the zona fasciculata and from ACTH in the hypothalamus and the corticotropes (Fig. 16-3).

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 corticotropes. 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.

The elevation in glucocorticoids exerts a negative feedback in the corticotropes, thus reducing further production of ACTH in the hypothalamus, reducing the production of CRH and in the zona fasciculata, where it reduces glucocorticoid production. ACTH, on its own, exerts a negative feedback on the corticotropes to further control ACTH production and in the hypothalamus, where it reduces secretion of CRH.

The innermost of the three cortical zones is the zona reticularis which has the capability of secreting adrenal androgens, estrogens and some glucocorticoids. In particular, it produces dehydroepiandrosterone (DHEA) and androstenedione. These cells are under a similar control than those of the zona fasciculata through ACTH but, they also appear to be controlled by a relatively newly identified cortical androgen-stimulating hormone (CASH), an 18 amino acid peptide, also derived from proopiomelanocortin. The entire regulatory process is not yet well understood.

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) which is produced in the liver and secreted into circulation (Fig. 16-4). A smaller proportion is carried by albumin and about 10% is circulating free.

Mineralocorticoids, on the other hand, 40% are circulating free, 50% bound to albumin and only 10% uses 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 in situations of overproduction of 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 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 and collecting ducts 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).

The effect of mineralocorticoids, specifically aldosterone, is to reduce the loss of water into urine. This is carried out by stimulating re-absorption of sodium, which in turn retains water as can be seen in figure 16-10.
Glucocorticoids

The most common glucocorticoids in domestic animals are cortisol and corticosterone (Figs. 16-11, 16-12). 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 and a reduction in muscle formation, to provide the substrate required (amino acids) in the liver for the formation of glucose. As a result of the increase in production of glucose in the liver, there is a complementary process of 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 in plasma proteins (possible to facilitate aa transport to 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 can not adapt to any significant environmental change and could easily die.
They 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 intracellular tissue, which is another characteristic of inflammation. They also impair phagocytosis and slow migration of white blood cells into inflamed areas. This appears to be achieved through impairment of synthesis of local prostaglandins and leukotrienes who are promoters of mobility of white cells, as well as, vascular permeability and vasodilatation. Glucocorticoids are immunosuppressant, thus reducing proliferation of lymphocytes. Finally, they lower fever by impairing release of interleukin-1 which otherwise would influence the temperature control centre at the level of the hypothalamus.

**METABOLIC EFFECTS OF GLUCOCORTICOIDS**

- Increase gluconeogenesis/glycogenesis (liver)
- Increase muscle catabolism
- Increase liver protein synthesis
- Reduces amino acid uptake and protein synthesis (extrahepatic tissue)
- Promotes mobilization of fatty acids from adipose tissue
- Enhances fatty acid oxidation in cells

**Synthesis of glucocorticoids (Cortisol)**

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

**ANTI-INFLAMMATORY EFFECTS**

- **Stabilizing lysosomes**
  - Lower proteolitic enzyme release
- **Reduce capillary permeability**
  - Prevent edema
- **Impair 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 16-13. Metabolic effects of glucocorticoids**

**Figure 16-14. Anti-inflammatory role of glucocorticoids**

**Figure 16-15. Mechanism to synthesize glucocorticoids**
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 glucuronide 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 for this syndrome can be abnormally high secretions of ACTH from the adenohypophysis (ACTH-dependent Cushing’s), or abnormal secretion of CRH which in turn over-stimulates production of ACTH (Fig. 16-17).

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. Other symptoms 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 protein matrix in the bone triggers osteoporosis with the resulting bone fragility.

Other visible signs are polydipsia, polyurea, polyphagia, enlargement of the abdominal cavity, heat intolerance,

CLINICAL SIGNS

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

Figure 16-18. Clinical signs of adrenal insufficiency

PATHOLOGIES

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

Figure 16-17. Causes and result of hyperadrenocorticism

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>
</thead>
<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

- Synthesised as neurotransmitters throughout the body
- Produced as a hormone by the adrenal medulla
- Most important are:
  - Epinephrine (adrenalin)
  - Norepinephrine (noradrenalin)

Figure 16-21. Generalities about catecholamines
Catecholamines

Catecholamines are neurotransmitters, as well as hormones. In their role as neurotransmitters they are synthesized all through the organism. In their role as hormones they are produced by the adrenal medulla in response to sympathetic stimulation. The most common are epinephrine and norepinephrine (Fig. 16-22).

Catecholamines may bind at least 4 types of receptors. Alpha receptors, are more potently stimulated by norepinephrine (α₁ and α₂), although norepinephrine can weakly stimulate beta (β₁ and β₂) receptors. Epinephrine can bind equally well to alpha and beta receptors (Fig. 16-23).

The final response of a tissue depends on the types of its available receptors. For example, heart tissue has mainly β₁ while smooth muscle has mainly β₂ receptors. Therefore, these tissues respond more to epinephrine.

Metabolic effects of epinephrine

When epinephrine acts on β₂ 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.

The action of epinephrine depends on the type of the receptor to which it binds. In figure 16-23 it can be seen that if epinephrine binds to a β receptor, it translates in the activation of adenyl cyclase, while if the binding is to α₂ 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. This is achieved by two routes. 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 extracellular calcium into the cytoplasm. The accumulation of intracellular calcium contributes to the phosphorylation of certain proteins. All of these translate in a desired effect.

In 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).

The following are specific examples of the effects of catecholamines in different tissues.