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Pathophysiology and Drugs for Hyperadrenocorticism

Kensuke Orito*

Laboratory of Physiology II, School of Veterinary Medicine, Azabu University, 1-17-71 Fuchinobe, Chuo-ku, Sagamihara-shi, Kanagawa 252-5201, Japan

*Corresponding author: Kensuke Orito, oritok@azabu-u.ac.jp

Abstract

Cushing's syndrome (CS) is one of the most common endocrine disorders in dogs, with systemic signs caused by excessive corticosteroid (mainly cortisol) secretion from the adrenal glands. Drugs commonly used in veterinary medicine, drugs whose usefulness has been reported in case reports, and drugs used in human medicine are also introduced.

1. Introduction

1.1. Causes of hyperadrenocorticism [1]

Corticotropin-releasing hormone (CRH) released from the hypothalamus by stress or sympathetic stimulation reaches the anterior pituitary gland in the blood circulation, where it secretes adrenocorticotropic hormone (ACTH); when ACTH reaches the adrenal cortex, its bundle-like layers secrete cortisol. Cortisol forms negative feedback by acting in an inhibitory manner on the hypothalamus and anterior pituitary, regulating excessive production and release of cortisol (Figure 1).

Between 80 and 85% of canine Cushing's syndrome (CS) is due to pituitary tumors, where overproduction and secretion of cortisol are enhanced by overstimulation of the adrenocortical bundle-like zone by overproduction of ACTH (pituitary CS). The remaining 15%–20% is due to adrenal tumors (adrenal CS). Ectopic ACTH secretion, which has been reported in humans, has also been reported in dogs, but only in case reports. Tumour resection is the curative therapy for CS, but especially in pituitary CS, neurosurgery and radiotherapy are not common in veterinary medicine, so medical treatment (drug treatment) aimed at eliminating signs and improving quality of life is often chosen. Therapy is often chosen to eliminate the signs and improve the quality of life.

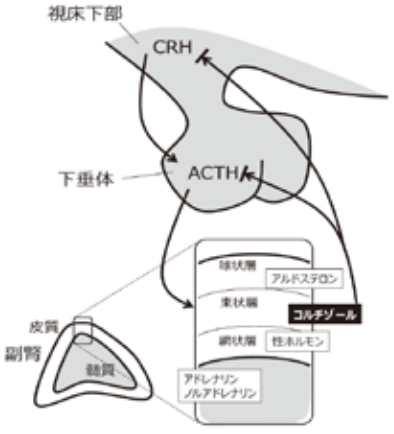

Figure 1. Hypothalamus-pituitary control of adrenocortical hormone production

2. Pathophysiology of hyperadrenocorticism

Glucocorticoid receptors, to which cortisol binds and exerts physiological effects, are distributed throughout the body and are involved in the maintenance of various physiological functions. Excessive cortisol secretion, therefore, causes the following clinical signs [2,3].

yuria and polydipsia

The causes of polydipsia and polyuria in canine CS are unclear. In both pituitary and adrenocortical CS, disruption of vasopressin osmotic regulation is thought to be one cause. In human medicine, increased serum central natriuretic peptide (ANP) is considered to contribute to polyuria. However, it has been reported that serum ANP levels in canine CS do not differ from those in normal dogs.

2.2. Polyphagia

Polyphagia resulting from CS is frequently observed in dogs. Cortisol is thought to act directly, but the site of action is unclear. Rarely, the appetite may be decreased, possibly due to increased cerebrospinal fluid pressure as a result of concomitant disease or pituitary tumor compression of the brain parenchyma.

2.3. Enlarged liver

The liver of canine CS is large, pale, and fragile. This is due to the deposition of glycogen whose synthesis is accelerated by glucocorticoids. If vacuole formation is present, it is associated with elevated liver enzymes including alkaline phosphatase (ALP), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and aspartate transaminase (AST).

2.4. Abdominal fat gain

Abdominal fat gain has been observed in 53%–73% of canine CS. Although not entirely clear, the localization in the fat of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) (Figure 2), which converts the inactive substance cortisone to the active form cortisol, is thought to be one factor. Enlargement of adipocytes, activation of lipoprotein lipase (a lipolytic enzyme that degrades triglycerides), reduced lipolysis and activated lipogenesis have also been reported in human patients with Cushing's syndrome. These may also be involved in abdominal fat gain.

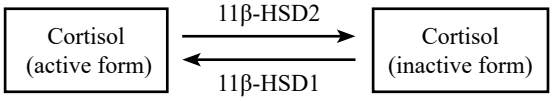

Figure 2. Activation and inactivation of cortisol Inactive cortisone is converted to active cortisol by 11β-HSD1. Cortisol is also converted to cortisone by 11β-HSD2. The proportion of cortisol and cortisone varies according to the degree of activation of these enzymes.

2.5. Muscle weakness

Cortisol causes atrophy of type 2 muscle fibers (fast-twitch muscle) through anabolic and catabolic effects. It also inhibits protein synthesis by suppressing amino acid uptake, suppresses myogenin (a transcriptional activator involved in skeletal muscle formation, growth, and repair) and stimulates proteasomal degradation.

2.6. Abdominal enlargement (drumming belly)

Drumming belly is caused by enlargement of the liver, increased abdominal fat, and decreased abdominal muscle tone. Bladder enlargement associated with polyuria may also be a factor. An enlarged abdomen is more pronounced in the presence of thinning of the abdominal muscles. Owners may note an increase in body weight, but this may be due to redistribution of fat to the trunk and the presence of a drum belly, when in fact the weight is often maintained or the increase is less pronounced.

2.7. Skin lesions

(1) Alopecia/acne: Atrophy of the hair follicle results in hair loss, as the maintenance of the hair shaft is impaired. Increased keratin accumulation in follicular sebaceous glands and clogging of the hair follicles results in comedones.

(2) Skin thinning and delayed wound healing: Cortisol disrupts keratinocytes, inhibiting skin fibrosis and the synthesis and metabolic turnover of collagen and mucopolysaccharides, resulting in skin atrophy and vascular fragility. These effects cause thinning of the dermis and epithelium, delayed wound healing, and bruising-like changes even after venipuncture or minor contusions. In humans, they cause skin atrophy, striae, petechiae, and hemorrhagic plaques.

(3) Hyperpigmentation: Histological examination of sporadic or localized hyperpigmentation shows an increased number of melanocytes in the stratum corneum, basal layer, and other skin tissues. Pituitary-secreted α-MSH may cause hyperpigmentation by binding to melanocortin receptors on melanocytes. However, other mechanisms may also be involved, as hyperpigmentation has also been observed in adrenal CS.

(4) Cutaneous calcinosis: Cortisol affects the collagen fiber synthesis system and ions accumulate in the collagen fibers that form. These changes, including secondary hyperparathormonemia, may contribute to calcinosis.

2.8. Increased blood coagulability

In CS, there is an increase in platelet factor (platelet count, von Willebrand Factor), the activity of the coagulation cascade (factor VIII, fibrinogen), antithrombin and plasminogen activator inhibitor 1 (PAI1). Indeed, in 19 canine cases of ACTH-dependent CS, increased coagulability of the blood has been confirmed by close examination with thromboelastometry. Pulmonary thromboembolism can occur chronically or acutely and can cause dyspnoea [4].

2.9. Hypertension

In canine CS, this has been reported in 31%–86% of patients. The following factors are thought to contribute to this [5].

(1) Activation of the renin-angiotensin system: vasoconstriction by angiotensin II.

(2) Mineralocorticoid activation: fluid retention due to antidiuresis.

(3) Sympathetic activation: increased cardiac output due to increased beta receptor sensitivity.

(4) Vasoactive substance changes: increased endothelin-1 (ET-1), decreased atrial natriuretic peptide (ANP), decreased nitrate-nitrite-nitric oxide (NO) pathway, decreased prostacyclin (PGI2)

2.10. Cardiac hypertrophy

Cardiac overload due to hypertension is one cause. However, human studies have shown that, for the same degree of hypertension, cardiac hypertrophy is more severe in patients with CS than in regular hypertensive patients. This is due to increased angiotensin II and mineralocorticoid (aldosterone) activation, which are also factors in hypertension. These bioactive substances are involved in cardiac hypertrophy and the worsening of heart failure through receptor-mediated cell hypertrophic and fibrotic effects.

2.11. Panting

Panting occurs due to some or all of the following causes: pressure on the diaphragm by weakened respiratory muscles and enlarged abdominal organs (liver, abdominal fat, etc.), reduced extensibility due to mineral deposits in the lung interstitium and trachea, and, although rare, microthrombi in the lungs. Effects on respiratory motility of diseases not related to CS, such as tracheal collapse, may also be included.

2.12. Central nervous system

Psychiatric disorders such as depression, anxiety,

and bipolar illness (manic-depressive illness) have been recognized in human CS. Excessive effects on glucocorticoid receptors, which are abundantly distributed in brain regions important for emotion and cognition, such as the hippocampus, amygdala, and frontal lobe, are thought to be one possible cause. In a veterinary clinical study in which dogs were repeatedly treated with synthetic corticosteroids for dermatological and orthopedic diseases and their mental status before and after repeated administration was scrutinized, it was reported that scores for nervousness, fear, food obsession, startle response, irritable aggression, barking and escape were worse after repeated administration than before synthetic corticosteroids were given [6]. The possibility that hyperadrenocorticism may also have psychological effects on dogs cannot be ruled out.

As the pituitary gland is surrounded by bone in the pituitary fossa, an enlarged tumor mass in the pituitary gland compresses the hypothalamus and other parts of the back, affecting the pituitary stalk, funnel depression, and cranial nerves. These changes can lead to slowed movements, fatigue, and anorexia, which in severe cases can lead to anorexia, restlessness, reduced responsiveness, and paraesthesia. Signs of ataxia, aggression, blindness, and nondrinking may also be present.

3. Useful drugs for hyperadrenocorticism

The cause of hyperadrenocorticism may be central (hypothalamus, pituitary gland) or adrenocortical. Drug treatment is effective by inhibiting the production of oversecreted hormones or by receptor antagonism (Figure 3).

In veterinary medicine, trilostane is often used, but mitotane and ketoconazole are drugs that have been used for many years. This section introduces drugs with proven usefulness, including these drugs also used in human medicine [7]. The dosage of any of these drugs should be adjusted according to the condition of the case, using tests such as the ACTH stimulation test to ascertain the drug's efficacy.

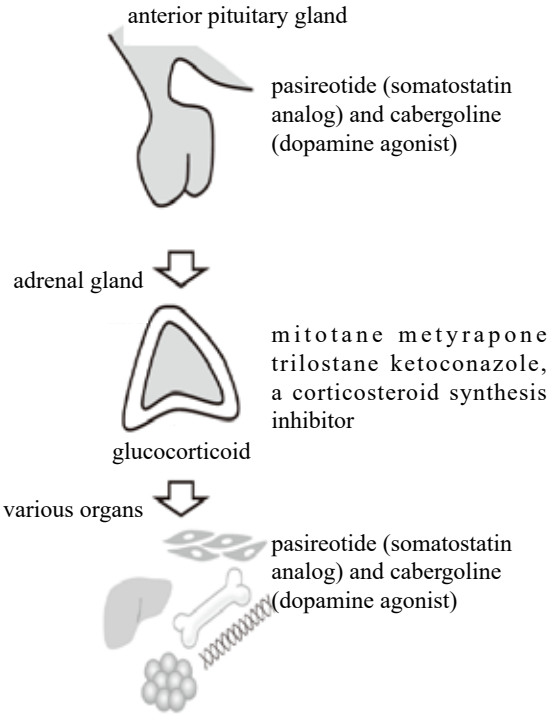

Figure 3. Sites of action of various Cushing's syndrome drugs. Some drugs inhibit the secretion of anterior pituitary hormones, others inhibit adrenocortical hormone synthesis, and others inhibit glucocorticoid receptors in various organs in the periphery.

3.1. Trilostane

The most common steroid hormones produced in the adrenal cortex are cortisol, as well as aldosterone and sex hormones. These are made from cholesterol as a raw material. By replacing part of the cholesterol skeleton with a hydroxyl group (-OH) or another group, they can be converted into hormones and their intermediates with different activities. Among these, 3β-hydroxysteroid dehydrogenase (3β-HSD) is a hormone that plays an important role in steroid hormone production (Figure 4). Trilostane inhibits cortisol production by selectively and reversibly suppressing 3β-HSD.

Trilostane needs to be administered with food, as its absorption is altered by food. It is also more useful at lower doses per body weight in large dogs than in small

dogs. As the efficacy of trilostane is less than 12 hours, some reports suggest that lower doses given twice daily may be more effective and reduce side effects. Activity, polydipsia, polyuria, and overeating improve within 1 week of starting repeated doses, but improvement in skin and hair takes several months. Due to hair loss and skin desquamation during the resting phase, the skin condition may appear worse when medication is started.

Although usually well tolerated, the main side-effect is transient adrenocortical hypofunction. As a reversible enzyme inhibitor, discontinuation of the drug often alleviates adverse effects. On the other hand, in rare cases, it can cause permanent adrenocortical hypofunction, possibly due to adrenal necrosis. In this case, the possibility of fatality cannot be ruled out.

Trilostane effectively suppresses increased adrenocortical function but does not affect the cause of the disease - pituitary or adrenal tumors. Hence, it should be noted as a symptomatic treatment.

Trilostane is a chemically stable drug, but it has been reported that when capsules were opened and the fractions adjusted to include other drugs, only 41% of the fractions contained sufficient amounts of trilostane for treatment [8]. Although the cause is unknown, such drug adjustments may have resulted in lower-than-expected doses being administered.

3.2. Mitotane (o, p'-DDD)

Mitotane selectively inhibits mitochondria in adrenocortical cells, causing necrosis and atrophy of cells in the zona fasciculata and zona reticularis, as well as inhibiting several adrenocorticotrophic hormone-producing enzymes (Figure 4). It is used for pituitary CS but may also be useful against adrenal tumors. However, caution should be exercised as the action is irreversible.

It is a fat-soluble drug and is not well absorbed in the fasting state. Absorption is better when administered with food. The onset of action often takes 1–3 months. Side effects reported include decreased appetite, fatigue, collapse, and diarrhea.

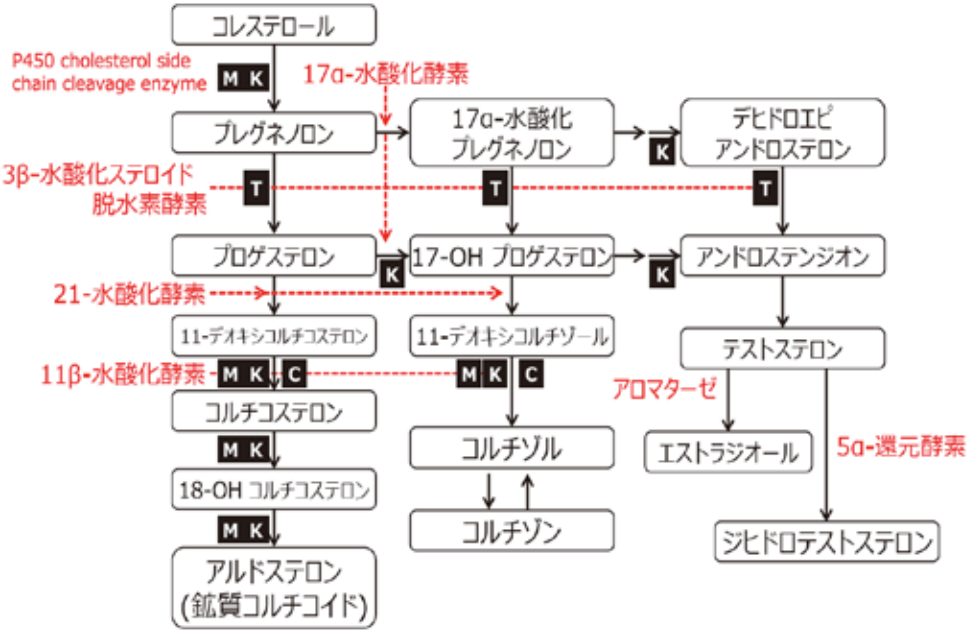

Figure 4. Hormone-producing systems in the adrenal cortex and sites of action of inhibitors Adrenocorticosteroids are produced from cholesterol via several enzymatic reactions. Drugs for Cushing's syndrome inhibit hormone production by suppressing this pathway; T: trilostane, M: mitotane, K: ketoconazole, C: metyrapone inhibitory sites.

3.3. Ketoconazole

Ketoconazole is a drug marketed as an antifungal agent, typically characterized by its inhibition of the enzyme cytochrome P450. Itraconazole inhibits corticosteroid production by suppressing multiple steps in the adrenocorticosteroid production pathway (Figure 4). Itraconazole as an antifungal drug for humans was withdrawn from the market in Europe in 2013 from a risk-benefit standpoint but was approved in 2014 for the treatment of endogenous Cushing's syndrome in adults [9].

In a retrospective clinical study investigating the benefit of repeated ketoconazole administration to dogs with pituitary CS by clinical signs and blood tests, 48 matched dogs were investigated, and cortisol secretion was reduced in all cases, with 69% reaching the therapeutic range. Clinical signs included polydipsia, polyuria, and overeating in more than 90% of cases, exercise intolerance and panting in 71%, and improvement in skin lesions and abdominal distention in 47% and 24% of cases, respectively. Adverse effects included eating disorders (67%), vomiting (29%), and diarrhea (10%). These side effects were more common in the high-dose group, but were transient and resolved with a dose reduction of 25% for 1–2 days [10].

3.4. Metyrapone

Metyrapone is a drug that inhibits the synthesis of adrenal corticosteroids by specifically suppressing β-hydroxylase (Figure 4). It has been used in human medicine in Japan to measure pituitary ACTH secretory reserve but was approved for the treatment of Cushing's syndrome in 2011 due to the high medical necessity. Adverse effects in humans are headache, dizziness, sedation, allergic rashes, nausea, and vomiting. Use in veterinary medicine is scarce. It has been used to temporarily suppress adrenocortical function before adrenal tumorectomy in cats [11].

3.5. Cabergoline, selegiline (L-deprenyl)

In the pituitary gland of dogs, ACTH-secreting cells are regulated by the inhibitory system via dopamine D2 receptors (D2Rs). Stimulation of this receptor may inhibit ACTH secretion, and Castillo et al. used the D2R agonist cabergoline in pituitary CS and followed the patients for four years, and found that 17 cases (42.5%) responded to cabergoline treatment, reducing ACTH levels and urinary cortisol excretion [12]. The D2R is involved in the regulation of other dopaminergic systems in the brain. This feature has been exploited in human medicine, where cabergoline is used as a therapeutic agent for Parkinson's disease and hyperprolactinemia.

Selegiline (L-deprenyl), which increases dopamine levels in the brain by inhibiting the dopamine-degrading enzyme monoamine oxidase (MAO) type B, has also been reported to be useful for pituitary CS [13], although some clinical studies have failed to verify its efficacy [14,15].

3.6. Mifepristone

Mifepristone is a glucocorticoid receptor antagonist. In humans, repeated administration in cases of adrenal carcinoma, adrenal hyperplasia, and ectopic ACTH secretion has resulted in symptomatic improvement in 75% of patients. Side effects include hypokalaemia (more than half) and increased blood pressure (15%). It is considered a particularly suitable treatment for patients with severe CS who cannot undergo operation [16].

Mifepristone is also a progesterone receptor antagonist. It is on the WHO Model List of Essential Medicines for Abortion due to its high efficacy, safety, and simplicity of this pharmacological action.

3.7. Pasireotide

As a somatostatin receptor (SSTR) agonist, it inhibits ACTH and growth hormone secretion in the pituitary gland. It has a particularly high affinity for SSTR5, which plays an important role in ACTH hypersecretion. It has been reported to be well tolerated in dogs

with pituitary CS in combination with trilostane or mitotane [17], but future clinical studies are needed to determine its usefulness. In human medicine, an extended-release formulation (Signifor®) is indicated for growth hormone excess and Cushing's syndrome when surgical treatment is ineffective or difficult. Four weekly intramuscular formulation may be useful in veterinary medicine, but may not be practical as it is very expensive.

4. Conclusion

Adrenocorticosteroid synthesis inhibitors and receptor antagonists only inhibit corticosteroid production, secretion, or cellular response and are not the causative agents of hormone production or secretion excess. Some signs cannot be corrected by suppressing hormone production and secretion alone, such as hypertension. These chronic effects need to be taken into account in treatment.

Disclosure statement

The author declares no conflict of interest.

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