Endocrine Diseases in Animals

H.S. Kooistra  S. Galac  J.J.C.W.M. Buijtels  B.P. Meij

Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

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Abstract
Background: Several endocrine disorders that affect humans also occur as endocrinopathies in companion animals. Spontaneous endocrine disorders in animals may provide valuable information for their counterparts in human endocrinology. For example, the discovery of progesterone-induced growth hormone production in the mammary gland of dogs may have important consequences for understanding the pathogenesis of breast cancer in women. In addition, the majority of diabetic cats have a type of diabetes mellitus that closely resembles type 2 diabetes mellitus in humans and therefore may serve as an animal model for this disease in humans. This review describes several endocrine diseases in companion animals that are quite similar to those in humans and emphasizes their usefulness as spontaneous animal models for human endocrine disorders.

Introduction

Companion animals, in particular dogs and cats, share the same living environment as humans and thus are exposed to similar noxae. In addition, dogs and cats are kept until old age, which allows accurate observation of the development of diseases and the process of aging. As in humans, the canine (2004) and feline (2007) genomes have been sequenced and are available for study, making these animals of great interest in comparative medicine. Further underscoring the importance of companion animals in comparative medicine is the observation that, in general, canine genes have a higher degree of homology with their human counterparts than do those of the frequently studied mouse and rat [1, 2].

Several human endocrine disorders are also known to occur as similar, spontaneous endocrinopathies in companion animals, and these animals may serve as models for the diseases in humans. This review summarizes several endocrine diseases in companion animals that are similar to those in humans.

Growth Hormone (GH) Disorders

GH Deficiency
Pituitary dwarfism due to combined pituitary hormone deficiency (CPHD) is well known as an autosomal, recessively inherited disorder in German shepherd dogs. CPHD in these dogs is characterized by underdevelopment of the pituitary gland and a combined deficiency of GH, thyrotropin, prolactin and gonadotropins, though adrenocorticotropin secretion is preserved [3]. This canine disorder is due to a mutation in the gene encoding for the pituitary transcription factor Lhx3. Therefore,
this form of pituitary dwarfism in dogs may serve as a model for CPHD caused by homozygous Lhx3 defects in humans [4].

**GH Excess**

The pathogenesis of GH excess is completely different in dogs and cats. In cats, as in humans, excessive GH secretion is most often due to a somatotroph pituitary adenoma. In dogs, GH excess due to a pituitary tumor is a rare event [5]. More often, canine acromegaly is due to progesterone-induced GH production in the mammary gland [6].

The estrous cycle of the domestic bitch is characterized by a follicular phase and spontaneous ovulations followed by a luteal phase (i.e., metestrus has an average duration of about 2 months, irrespective of pregnancy). A non-seasonal anestrus, with a duration that may last from 2 to 10 months, follows each estrous cycle. During metestrus, under the influence of progesterone, the mammary gland becomes a highly proliferative environment. Progesterone-induced production of GH in the mammary gland is associated with local production of insulin-like growth factors and their binding proteins. This local system plays an important physiological role in the regulation of mammogenesis and in preparation of the mammary gland for lactation [7]. The progesterone-induced local biosynthesis of GH and the resulting highly proliferative environment in the mammary gland also play an important role in the development and/or progression of mammary tumors in dogs [8]. Studies show that in the dog mammary-derived GH and insulin-like growth factors also reach the systemic circulation [6, 9]. Mammary GH is systemically released to the extent that acromegaly and insulin resistance may develop.

The production of GH by the mammary gland is not unique to the dog. It has also been demonstrated in cats as well as humans. The highest levels of expression have been found in cats with progestin-induced fibroadenomatous hyperplasia of the mammary gland [10]. So far, there is no evidence that GH produced in the mammary gland reaches the systemic circulation in cats. While GH is expressed in the human mammary gland [11], it is not known if mammary GH reaches the systemic circulation in women, though 40% of women with breast cancer have been reported to have elevated plasma GH concentrations [12]. Future research is needed to disclose the importance of progesterone-induced mammary GH production in the pathogenesis of breast cancer in women.

**Diabetes Mellitus**

With an estimated incidence of 2.45 cases/1,000 cat-years-of-risk, diabetes mellitus is a common disease in cats. Most diabetic cats have a type of diabetes mellitus that closely resembles human type 2 diabetes mellitus. Feline and human type 2 diabetes mellitus share several clinical and pathological characteristics, such as onset in midlife or later, variable but at least residual insulin secretion at the time of diagnosis, relative resistance to ketoadidosis, significant but incomplete loss of β cells and deposition of amyloid in the pancreatic islets [13]. The main pathogenetic mechanisms of type 2 diabetes mellitus in humans are impaired insulin secretion and insulin resistance, both of which may have a genetic etiology. Genetic predisposition also seems to play a role in feline diabetes mellitus. Analogous to the situation in humans, in cats genetically predisposed to diabetes mellitus, acquired factors such as obesity and physical inactivity may precipitate the disease by inducing insulin resistance [14].

Other diseases may also induce insulin resistance and consequently lead to other specific types of diabetes mellitus. In felines, the most common cause of this type of diabetes mellitus is GH excess due to a functional somatotroph pituitary adenoma. Transphenoidal hypophysectomy not only results in remission of acromegaly but quite often also leads to resolution of the diabetes mellitus [15].

Evidence suggests that autoimmune mechanisms affect β-cell function in more than 50% of diabetic dogs. In the rest, diabetes is often precipitated by counter-regulatory hormone excess, such as progesterone-induced GH excess or hypercortisolism.

**Primary Hyperaldosteronism in Cats**

Feline primary hyperaldosteronism was first reported in 1983 and has been diagnosed with increasing frequency ever since. Currently it is considered to be the most common adrenocortical disorder in cats. As in humans, the condition may be due to adrenocortical neoplasia or idiopathic bilateral adrenocortical hyperplasia [16]. Excessive secretion of aldosterone may result in systemic arterial hypertension and potassium depletion. Signs may include hypokalemic paroxysmal flaccid paresis; acute blindness due to retinal detachment and/or intracocular haemorrhage; and other changes attributable to hypertensive damage in such target organs as the kidney,
heart or brain. The diagnosis of feline primary hyperaldosteronism is based upon the ratio between the plasma aldosterone concentration and the plasma renin activity (i.e., an elevated plasma aldosterone:renin ratio) and results of a suppression test using fludrocortisone acetate [17].

Hypercortisolism

In both dogs and cats, approximately 80–85% of cases of chronic endogenous glucocorticoid excess (Cushing’s syndrome) are due to a functional corticotroph adenoma originating from either the anterior lobe or the pars intermedia of the pituitary gland (Cushing’s disease). In the remaining 15–20% of cases, spontaneous hypercortisolism is due to a functional adrenocortical adenoma or carcinoma. In dogs, Cushing’s syndrome may also occur due to ectopic adrenocorticotropic secretion or food-dependent hypercortisolism [18, 19].

Cushing’s disease is a very frequent endocrinologic disorder in dogs, in contrast to the situation in humans and cats where it is more rare. Nonetheless, the clinical presentation of Cushing’s disease is highly similar between dogs and humans, with characteristic signs including abdominal obesity, weight gain, fatigue, muscle atrophy and skin changes. Canine Cushing’s disease may therefore serve as an animal model for the human disease, especially since therapeutic canine hypophysectomy can generate substantial amounts of primary corticotroph pituitary adenoma tissue for in vitro research purposes.

Hypercalcemia

Disorders of calcium metabolism are also well known in companion animal endocrinology. Hypercalcemia may be due to primary hyperparathyroidism in dogs and cats, but more often the disorder is due to pseudohyperparathyroidism. Pseudohyperparathyroidism or hypercalcemia of malignancy was first described in canine and feline malignant lymphoma in the 1970s. In addition, the condition is associated with other malignant tumors. Malignancy-associated hypercalcemia in companion animals may arise through (1) local osteolysis, (2) secretion of parathyroid hormone-related peptide and (3) production of vitamin D.

Hyperthyroidism and Thyroid Tumors

No disease entity comparable to Graves’ disease in humans has been observed in dogs and cats. Nevertheless, hyperthyroidism is very common in old cats. Feline hyperthyroidism resembles hyperthyroidism caused by toxic adenomas in humans (Plummer’s disease). Studies in cats indicate that in some cases the disease is due to mutations in the genes encoding for the thyrotropin receptor or Gs.

More than 85% of canine thyroid tumors are rather large malignant solid masses. Among domestic animals, thyroid cancer in the dog – particularly the follicular type – most closely resembles human follicular carcinoma in terms of clinical behavior, the pattern of circulating thyroglobulin levels and conservation of thyrotropin receptors in primary tumors [20].

Immune-Mediated Endocrine Deficiency Syndromes

Primary hypothyroidism is common in dogs but extremely rare in cats. Other acquired endocrine deficiency syndromes such as hypoadrenocorticism and hypoparathyroidism are not uncommon in dogs but infrequent in cats. Pathogenetically, these conditions are considered to be the end stage of progressive autoimmune destruction and are associated with a high incidence of circulating antibodies. Cats seem to be much less prone to autoimmune-mediated hormone deficiency than dogs.

Conclusions

Endocrine disorders in companion animals have many similarities to those in their human counterparts. Consequently, companion animals with spontaneous endocrinopathies may serve as animal models for the corresponding diseases in humans.

Disclosure Statement

H.S.K. declares no conflict of interest. S.G. declares no conflict of interest. J.J.C.W.M.B. declares no conflict of interest. B.P.M. declares no conflict of interest.
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