Steroidogenic response of adrenal tissues after administration of ACTH to dogs with hypercortisolemia

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Objective—To evaluate adrenal sex hormone concentrations in neutered dogs with hypercortisolemia.

Design—Case series.

Animals—11 neutered dogs with hypercortisolemia.

Procedure—Serum samples obtained before and 1 hour after administration of ACTH were evaluated for concentrations of cortisol, progesterone, testosterone, dehydroepiandrosterone sulfate or androstenedione or both, and 17-hydroxyprogesterone.

Results—For all dogs, concentrations of 1 or more adrenal sex hormones were substantially greater than reference range values before or after administration of ACTH. Testosterone concentration was not greater than reference range values in any of the dogs.

Conclusions and Clinical Relevance—Results emphasize the importance of ruling out hypercortisolemia before measuring adrenal sex hormone concentrations as a means of diagnosing adrenal hyperplasia syndrome (alopecia X) in dogs. (*J Am Vet Med Assoc* 2001;218:214–216)

Endocrine alopecia associated with sex hormone imbalance of adrenal origin is a recognized problem in the "plush-coated" breeds such as Pomeranian, Chow Chow, Keeshond, and Samoyed.[1] This condition, formerly called growth hormone-responsive dermatosis, now is simply referred to by many veterinary dermatologists as alopecia X (also known as adrenal hyperplasia syndrome) because of the mystery that surrounds the pathogenesis of the hair loss.[2] Schmeitzel and Lothrop[3] reported the association between abnormal adrenal steroidogenesis and hair loss in Pomeranians and suggested the use of the ACTH stimulation test, whereby several adrenal sex hormones are measured as a means of diagnosing this condition. It is recommended that hypothyroidism and hypercortisolemia be ruled out prior to measuring the more inclusive panel of adrenal-derived sex hormones for diagnosis of alopecia X because of the clinical similarities of the alopecia caused by these diseases.[1,a]

Hypercortisolemia is a common endocrine disease in dogs and is often associated with truncal alopecia that cannot be differentiated clinically from other endocrine-related alopecias.[4] In addition to coat changes, hypercortisolemia is often accompanied by polyuria, polydipsia, polyphagia, pendulous abdomen, enlarged liver, and muscle wasting. However, coat changes may be the only initial clinical sign in dogs with hypercortisolemia.[4]

When a dog has truncal alopecia without other clinical signs, adrenal hormone analyses are sometimes requested without first ruling out hypercortisolemia.[a] Although the adrenal analyses measure cortisol concentration, emphasis is often placed on adrenal sex hormones. The purpose of the study reported here was to evaluate adrenal sex hormone concentrations in neutered dogs with hypercortisolemia.

Materials and Methods

Eleven dogs with hypercortisolemia for which an ACTH stimulation test had been performed were identified by review of medical records. Dogs with hypercortisolemia were selected on the basis of clinical signs, clinicopathologic abnormalities, and abnormally increased serum cortisol concentration in response to administration of ACTH. Pituitary-dependent hypercortisolemia was confirmed in 5 dogs (2 via **low-dose dexamethasone suppression test** [**LDDS**], 1 via ultrasonography, and 2 via LDDS and ultrasonography). Diagnostic tests to further characterize the disease were not done for the remaining 6 dogs. In 9 treated dogs, clinical signs and serum cortisol concentrations improved with administration of mitotane (formerly o,p'-DDD). The owners of 2 dogs with pituitary-dependent hypercortisolemia elected not to treat their dogs.

For the study reported here, archived serum samples from all dogs were evaluated for serum concentrations of cortisol, progesterone, testosterone, **dehydroepiandrosterone sulfate** (**DHEAS**) or androstenedione or both, and 17-hydroxyprogesterone before and 1 hour after ACTH administration; results were compared with reference ranges established by the laboratory. Analyses of serum adrenal sex hormone and cortisol concentrations were performed in our Clinical Endocrinology Service[a] by use of radioimmunoassay procedures validated for use in dogs.[1]

Results

Four male and 7 female dogs were studied; all had been neutered. Age ranged between 4 and 13 years (mean, 9.5 years). Breeds included Australian Shepherd (n = 1), Cocker Spaniel (1), Fox Terrier (1), Husky (1), Lhasa Apso (1), Scottish Terrier (1), Shetland Sheepdog (1), Shih Tzu (1), Springer Spaniel (1), and mixed-breed dogs (2). Results of an ACTH stimulation test were diagnostic (cortisol concentration, > 200 ng/ml) for hypercortisolemia in 10 of 11 dogs (mean cortisol concentration, 307.2 ng/ml). Cortisol concentrations did not increase to > 200 ng/ml after stimulation with ACTH in 1 dog; however,

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Table 1—Mean (SD) adrenal hormone concentrations (ng/ml) determined before (baseline) and after ACTH administration in dogs with hypercortisolemia

Hormone	No. of dogs	Baseline	After ACTH
Cortisol	11	77.2 (54.9)	307.2 (95.7)
Reference range		7–65	100–175
Androstenedione	10	5.7 (6.7)	35.3 (50.2)
Reference range		3–14	3–10
Progesterone	11	0.3 (0.3)	3.6 (2.3)
Reference range		0–0.2	0–1.2
Testosterone	11	0.2 (0.1)	0.2 (0.2)
Reference range		0.1–0.5	0.2–0.7
17-OH-Prog	11	1.3 (3.6)	4.2 (4.3)
Reference range		0–0.4	0.4–1.5
DHEAS	9	12.6 (12.0)	27.8 (31.0)
Reference range		0.1–12	0.3–14

17-OH-Prog = 17-Hydroxyprogesterone. DHEAS = Dehydroepiandrosterone sulfate.

a subsequent ACTH stimulation test revealed hypercortisolemia (217.9 ng/ml). This dog had high serum activity of alkaline phosphatase, compared with reference range values, and ultrasonography revealed bilaterally enlarged adrenal glands.

All dogs had substantially high concentrations of 1 or more adrenal sex hormones, compared with reference ranges, before, after, or before and after stimulation with ACTH (**Table 1**). Four of 9 dogs had high serum concentrations of DHEAS before and after stimulation with ACTH. Whereas only 1 dog had high concentration of androstenedione before ACTH stimulation, 7 of 10 dogs had high concentrations of androstenedione after stimulation. Four of 11 dogs had high baseline progesterone concentrations, whereas all 11 had high progesterone concentrations after administration of ACTH (3 of these were slightly greater than reference range); 3 dogs had high baseline 17-hydroxyprogesterone concentrations, whereas 6 dogs had high concentrations after stimulation with ACTH. Testosterone concentration was not above reference range in any of the 11 dogs.

Discussion

The adrenal glands are the primary source of cortisol and DHEAS.[5] In addition, in neutered dogs, they are the source of progesterone, 17-hydroxyprogesterone, and androstenedione. All 11 neutered dogs with hypercortisolemia in the study reported here had high concentrations of at least 1 adrenal sex hormone; 8 of these dogs had high concentrations of adrenal androgens (androstenedione, DHEAS, or both).

Intuitively, the results of our study are not surprising. The hormone 17-hydroxyprogesterone is a precursor of cortisol (**Fig 1**). Therefore, any disease that initiates excessive synthesis of cortisol should also cause increased synthesis of 17-hydroxyprogesterone. In addition to being a precursor of cortisol, 17-hydroxyprogesterone is an indirect substrate for synthesis of DHEAS by the adrenal glands; DHEAS is then converted to androstenedione, which serves as a substrate for conversion to the more potent androgens in the peripheral tissues. Therefore, it would seem logical that hypercortisolemia could be associated with hyperandrogenism. Interestingly, production of cortisol is not always linked to adrenal production of androgens,

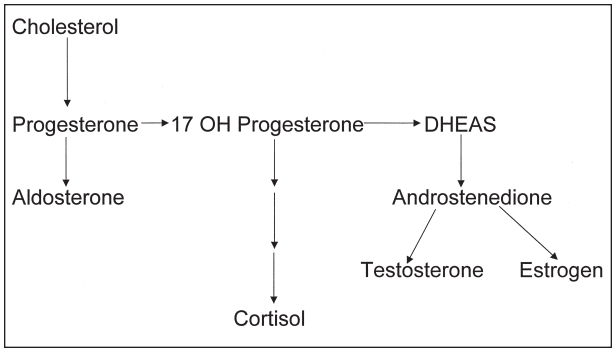

Figure 1—Schematic diagram of the adrenal steroidogenesis pathway. DHEAS = Dehydroepiandrosterone sulfate.

either under normal physiologic conditions or in states of disease. Adrenal biosynthesis of androgens occurs mainly in the zona reticularis of the adrenal cortex, whereas production of cortisol occurs in the zona fasciculata.[6,7] Thus, the mere presence of 17-hydroxyprogesterone in the zona fasciculata usually is not sufficient to lead to synthesis of androgen in that region of the adrenal cortex. In children, concentrations of adrenal sex hormones are low until 6 to 8 years of age, at which time they increase without concurrent increases in cortisol.[8] Lastly, humans with pituitary-dependent hypercortisolemia usually do not have concomitant increases in concentrations of adrenal androgens, whereas humans with ectopic ACTH syndrome (associated with nonpituitary tumors) may have either normal or extremely high concentrations of adrenal androgens.[9,10] Because of the discrepancies between ACTH-producing diseases and adrenal production of androgens, it is theorized that there is another regulatory hormone that controls synthesis of adrenal androgens.[9-11]

Testosterone is one of the more potent androgens and in women is mainly produced by peripheral conversion from androstenedione or DHEAS.[8] This mechanism also occurs in neutered animals. The fact that testosterone was not greater than reference range in any of the dogs in our study may suggest that peripheral conversion from androstenedione or DHEAS did not occur. Conversely, because testosterone is formed in target tissues, increases in testosterone precursors may not be associated with increases in plasma concentration of testosterone.[8]

Clinical signs of adrenal hyperplasia syndrome (alopecia X) in dogs are primarily limited to coat abnormalities. Systemic illness is not associated with this disease. Schmeitzel et al[1] first proposed the comparison of this disease in dogs to late-onset congenital adrenal hyperplasia in humans. Affected humans have high concentrations of 17-hydroxyprogesterone at baseline or after ACTH stimulation because of a partial deficiency of 21-hydroxylase, an enzyme needed for cortisol synthesis.[12] The high concentrations of 17-hydroxyprogesterone in this disease are associated with hyperandrogenism.[10,12] Clinical signs, therefore, are attributed to the high androgen concentrations.

Results of the study reported here indicate that in dogs with hypercortisolemia, concentration of adrenal sex hormones, including 17-hydroxyprogesterone and the adrenal androgens, commonly are greater than ref-

erence ranges, similar to what might be found in dogs with adrenal hyperplasia syndrome. These findings stress the importance of first ruling out hypercortisolemia, a disease with many systemic ramifications if left undiagnosed and untreated, before pursuing the less common diagnosis of adrenal hyperplasia syndrome. Because there was variability regarding which adrenal sex hormone concentrations were high in the dogs of our study, each of these hormones may have a role in development of the many different clinical manifestations of hypercortisolemia in dogs.

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