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Comparison of thyroid analytes in dogs aggressive to familiar people and in non-aggressive dogs [☆]

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ABSTRACT

A cross-sectional study was performed in order to examine the association between canine aggression to familiar people and serum concentrations of total thyroxine (TT4), free thyroxine (fT4), thyroxine autoantibodies (T4AA), total triiodothyronine (TT3), free triiodothyronine (fT3), triiodothyronine autoantibodies (T3AA), thyroid stimulating hormone (TSH), and thyroglobulin autoantibodies (TgAA). The subjects were 31 dogs historically aggressive to familiar people and 31 dogs with no history of aggression. Behavioral evaluation and physical examination were completed for each dog in addition to a complete blood count, serum chemistry panel, TT4, fT4 by equilibrium dialysis, TT3, fT3, TgAA, T3AA, and T4AA.

Significant differences were found between the two groups with respect to only T4AA, which was increased in the aggressive group, but the concentrations for both groups were within the normal reference range. There were no differences between the two groups in the thyroid analytes most commonly measured by veterinary practitioners evaluating thyroid function in dogs. The results of this study revealed no significant difference between aggressive and non-aggressive dogs in the thyroid concentrations most commonly used to diagnose canine hypothyroidism.

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Introduction

Canine aggression is the most common problem referred to behavior specialists in the United States (Beaver, 1994; Reisner, 2003; Denenberg et al., 2005). Aggression directed to familiar people can be especially distressing to owners and damaging to the human–animal relationship, frequently leading to the relinquishment of dogs to humane shelters and resulting in euthanasia (Salman et al., 2000). The trauma of dog bites to humans is significant and costly, in many cases requiring emergency room care, surgical intervention and hospitalization (Sacks et al., 1996). Emotional sequelae might also require mental health counseling (Peters et al., 2004).

Although most dogs presenting for aggressive behavior are apparently healthy, irritability or aggression can occur secondary to medical disease (Landsberg et al., 2003). Hypothyroid disease-related aggression has been anecdotally reported in dogs (Reinhard, 1978; Beaver, 1999; Juarbe-Diaz, 2002; Beaver and Haug, 2003; Fatjo, 2003; Mertens and Dodman, 2003) and it has

been suggested that hypothyroidism accounts for 1.7% of aggressive behaviors, which may occur even in the absence of lethargy, weight gain and other characteristic clinical signs of hypothyroidism (Beaver, 1983, 1999; Juarbe-Diaz, 2002).

In dogs, aggression has been associated with increased thyroglobulin autoantibody (TgAA) concentrations, along with normal thyroxine (T4) and thyroid stimulating hormone (TSH) concentrations (Graham et al., 2004). Associations have also been reported between serum thyroglobulin autoantibodies (TgAA), total T4 (TT4), free T4 (fT4), and TSH outside of normal reference ranges and the incidence of separation-related behavior problems, training problems, and coprophagia (Barlow et al., 2003; Graham et al., 2004). Proposed mechanisms for hypothyroid-related aggression include lowered threshold for aggression due to lethargy and irritability (Feldman and Nelson, 1996; Beaver, 1999), impaired transmission of serotonin at the postsynaptic 5-HT_{2A} receptors in the cerebral cortex (Henley and Valdic, 1997) and increased metabolism of serotonin in the cerebrospinal fluid (CSF) (Henley et al., 1991). Decreased CSF 5-HIAA concentrations have been linked to aggression in several species, including dogs (Mehlman et al., 1994; Reisner et al., 1996).

However, there are gaps in the evidence linking canine hypothyroidism with aggression. Some published reports relied on few animals or on studies providing little information about diagnosis of aggression or follow-up after supplementation with

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thyroid hormone (Beaver, 1983; Aronson, 1998; Aronson and Dodds, 2005). In contrast to anecdotal reports and suggestions of an association with abnormal thyroid function, aggression is a common presentation in dogs with normal thyroid concentrations. Because an association is unclear, there is uncertainty in veterinary medicine regarding the relationships between canine aggression, hypothyroidism, and subclinical thyroiditis. Misinformation or lack of information for veterinarians regarding the relationship between aggression and hypothyroidism may result in empirical treatment with thyroid hormone supplementation, regardless of whether clinical signs of hypothyroidism (other than aggression) are present. Inappropriate or unnecessary supplementation of thyroid hormone may lead to problems including tachycardia, aggressive behavior, nervousness and weight loss in dogs (Feldman and Nelson, 1996; Ferguson, 2007).

It has been proposed that dogs with behavior disorders such as aggression, fearfulness and hyperactivity may have an increased incidence of hypothyroidism without its typical clinical signs (Dodds, 1999). Furthermore, thyroid hormone supplementation of 95 hypothyroid dogs was reported to significantly improve the behavior of 61% (Dodds, 2003). However, these reports did not undergo peer review. Dogs with several behavioral disorders and neurologic disorders were grouped together; dogs were not examined by a board-certified veterinary behaviorist or behavioral medicine resident, but instead were assessed only by means of a written questionnaire; and they were not grouped by objective criteria (for example, confirmation of historical biting). In addition, because thyroid hormone is functionally linked to brain dopamine and serotonergic systems (Henley et al., 1991; Henley and Valdic, 1997; Strawn et al., 2004), L-thyroxine supplementation, even in euthyroid patients, may affect the same systems involved in canine aggression disorders, indicating that an individual's response to thyroid supplementation cannot be used to assess whether or not the etiology of the aggression is thyroid related.

This study was performed to examine the association between canine aggression to familiar people, a relatively common and easily recognized behavior problem, and serum concentrations of TT4, fT4 by equilibrium dialysis (fT4 (ED)), thyroxine autoantibodies (T4AA), total triiodothyronine (TT3), free triiodothyronine (fT3), triiodothyronine autoantibodies (T3AA), TSH, and TgAA.

Materials and methods

Recruitment

Male and female dogs, 2–8 years of age, were recruited by an email-posted solicitation to staff and veterinary students of the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) and through scheduled appointments of the MJR-VHUP Behavior Service.

Screening of subjects

All dogs underwent physical examination performed by a licensed veterinarian and in-house complete blood count (CBC) and serum chemistry panel to screen for underlying illnesses. Serum from each participant was submitted to the Michigan State University Endocrinology Laboratory for a canine thyroid panel, which included TT4, fT4 (ED), T4AA, TT3, fT3, T3AA, TSH, and TgAA. For five dogs in the aggressive group, the fT4 (ED) was not performed at the same time as the rest of the thyroid panel. For these dogs, the serum was frozen after the TT4, T4AA, TT3, fT3, T3AA, TSH and TgAA were completed. Between 69 and 147 days (mean=114 days) after blood collection, the serum was thawed and the fT4 (ED) assay was completed.

Group assignment

Dogs were evaluated behaviorally by use of written and oral owner interviews and an owner-report aggression screening tool similar to that used by the MJR-VHUP Behavior Service. Interviews were conducted by either a diplomate of the American College of Veterinary Behaviorists or a clinical behavioral medicine

resident at MJR-VHUP. Owners of dogs with behavioral diagnoses received standard-of-care treatment recommendations. The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee.

Dogs were assigned to one of two groups based on the behavioral history questionnaire and the behavioral interview: the aggressive group consisted of dogs aggressive to familiar people and the control group were dogs with no history of aggression – including growling, snarling, lunging, or biting – to either familiar or unfamiliar people. To be assigned to the aggressive group, the dog must have bitten a familiar person at least once in the preceding 6 months or more than once in the preceding 12 months. A familiar person was defined as someone with whom the dog interacted at least once per week on average and with whom they had interacted for at least 1 month. Interaction included, but was not limited to, petting, feeding, walking, playing and grooming, with the exclusion of professional groomers or veterinarians in their respective offices.

Exclusion criteria

To eliminate the risk of drug interaction effects on thyroid function, dogs were excluded if they were currently receiving or had received the following drugs within 60 days of the start of the study: sulfonamides (Gookin et al., 1999), tricyclic antidepressants, phenobarbital, potassium bromide, carprofen, thyroxine, amiodarone, iodide, furosemide, heparin, propranolol and glucocorticoids (Gullikers and Panciera, 2002; Daminet and Ferguson, 2003). In addition, dogs were excluded if they had been vaccinated with a rabies vaccine subcutaneously or intramuscularly within the previous 4 weeks (Scott-Moncrieff et al., 2002). Dogs were also excluded if they had been historically aggressive in the following circumstances: (1) biting a person only during play, and/or if precipitated or followed by a play-bow body posture; (2) biting a person while fighting with another dog.

Statistical analysis

Student's *t* test was used to determine differences in thyroid function test concentrations between the two groups. Sample size required to detect a 20% difference or larger in thyroid function tests between aggression groups with α set at 0.05 and $\beta = 0.2$ was 30 per group. To adjust for multiple comparisons, a Bonferroni correction was used and the *P* level set at 0.006. All analyses were performed using SAS statistical software v. 9.1 (SAS Institute).

Results

Behavioral diagnoses for dogs in the aggressive group included fear-related aggression ($n = 23$; 85%), resource guarding ($n = 21$; 78%), conflict-related aggression ($n = 12$; 44%), territorial aggression ($n = 5$; 19%), status-related aggression ($n = 3$; 11%), pain-related aggression ($n = 3$; 11%), predatory behavior ($n = 3$; 11%) and irritable aggression ($n = 2$; 7%) (see Mertens (2002) for diagnostic criteria). Each dog could be assigned more than one diagnosis. All dogs in the aggressive group received a diagnosis of aggression directed to people (i.e. resource-guarding, conflict, irritable, pain- or fear-related). Aggressive dogs were treated with standard-of-care recommendations including safety counseling, recommendations for behavior modification and, when indicated, anxiolytic or other medications.

Table 1

Breed distribution in a group of 31 dogs aggressive to familiar people and 31 non-aggressive dogs.

Aggressive dogs ($n = 31$)		Control dogs ($n = 31$)	
Breed	<i>n</i> (%)	Breed	<i>n</i> (%)
Mixed	7 (26)	Mixed	11 (41)
Cairn Terrier	2 (7)	Golden Retriever	3 (11)
Dachshund	2 (7)	Labrador Retriever	3 (11)
Shih Tzu	2 (7)	Border Collie	2 (7)
Soft-coated Wheaten Terrier	2 (7)	American Bulldog	1 (3)
Bearded Collie	1 (3)	American Pit-bull Terrier	1 (3)
Boxer	1 (3)	Australian Shepherd	1 (3)
Cocker Spaniel (American)	1 (3)	Bernese Mountain Dog	1 (3)
English Setter	1 (3)	Dachshund	1 (3)
Labrador Retriever	1 (3)	Norwich Terrier	1 (3)
Portuguese Water Dog	1 (3)	Pug	1 (3)
Shiba Inu	1 (3)	Welsh Springer Spaniel	1 (3)
Tibetan Terrier	1 (3)		
Welsh Corgi (Pembroke)	1 (3)		

Table 2
Comparison of serum thyroid analytes between dogs aggressive to familiar people and non-aggressive dogs.

	Aggressive dogs Mean \pm SD (range)	Control (non-aggressive) dogs Mean \pm SD (range)	<i>P</i>	Reference range
TT4 (nmol/L)	30.3 \pm 11.4 (9–51)	24.1 \pm 8.1(13–39)	0.0159	16–57
fT4 (ED) (pmol/L)	23.6 \pm 7.8 (10–44)	24.1 \pm 10.0 (5–42)	0.8318	6–42
TT3 (nmol/L)	1.2 \pm 0.27 (0.8–1.7)	1.1 \pm 0.19 (0.7–1.5)	0.0895	1.0–2.5
fT3 (pmol/L)	4.9 \pm 1.4 (2.6–8.4)	4.6 \pm 1.2 (2.5–8.5)	0.3529	4.5–12
T4AA (%)	7.0 \pm 3.2 (2–15)	4.6 \pm 1.9 (1–8)	0.0006 ^a	0–20
T3AA (%)	1.8 \pm 2.3 (0–9)	1.1 \pm 1.3 (0–4)	0.1667	0–10
TSH (μ m/L)	13.3 \pm 5.5 (0–25)	11.6 \pm 8.1 (0–32)	0.3438	0–27
TgAA (%)	11.8 \pm 6.5 (5–32)	11.4 \pm 5.4 (4–26)	0.7999	0–35

^a Concentrations for both groups were within the reference range for T4AA.

Mixed breeds were the most frequently represented breed in each group (32% of aggressive dogs; 42% of control dogs; Table 1). The ages of dogs in the aggressive group ranged from 3 to 8 years (mean, 5.1 years) and in the non-aggressive group ranged from 2.5 to 8 years (mean, 5.5 years). The weights of the dogs in the aggressive group ranged from 4.1 to 50 kg (mean, 21.8 kg) and in the control group from 3.8 to 42.8 kg (mean, 23.4 kg). In the aggressive group, there were 20 male, castrated dogs and 11 female, ovariohysterectomized dogs compared with the control group, which consisted of 18 castrated male dogs, 10 ovariohysterectomized female dogs, one sexually intact male and one sexually intact female.

The mean T4AA concentrations for the aggressive group were significantly higher than for the control group (7% vs. 4.6%; $P=0.0006$); however, concentrations in both groups were within the normal reference range. Although two other analytes (TT3 and TT4) had $P<0.1$, neither reached statistical significance as defined in this study (Table 2).

None of the dogs in either group had thyroid analyte profiles consistent with hypothyroidism. All thyroid concentrations of 48% ($n=15$) of the dogs in the aggressive group and 39% ($n=12$) of the dogs in the control group were within their respective normal reference ranges. The analyte concentration most frequently outside the reference range (in all cases lower than the lowest reference concentration) for both groups was fT3 (12 dogs [39%] in the aggressive group and 15 dogs [48%] in the control group). The second most frequent analyte outside the reference range was TT3, again, in all cases below the lowest reference concentration. Altogether, 19% ($n=6$) of dogs in the aggressive group and 23% ($n=7$) of dogs in the control group had TT3 concentrations outside (below) the reference range. In the aggressive group, the fT4(ED) of one dog (4%) was higher than the reference range (44 pmol/L; reference range, 6–42 pmol/L). There were no other concentrations outside the reference range for this dog. There were no dogs in the control group with thyroid concentrations higher than the reference ranges.

Discussion

The only thyroid measure found to be different between the two groups was serum T4AA, which was significantly higher in the aggressive group than in the control group. However, no dogs in either group had a T4AA concentration outside the reference range. There were no significant differences between the groups with regard to any other thyroid analyte concentration. The finding that aggressive dogs had significantly higher T4AA concentrations than control dogs may indicate that these dogs will develop autoimmune thyroiditis in the future. However, none of the dogs in either group had thyroid profiles which were consistent with

clinical hypothyroidism (i.e., decreased TT4 and fT4, and increased TSH) (Ferguson, 2007).

An elevation of T4AA can be an indicator of underlying thyroiditis, but this alone is not sufficient for a diagnosis of hypothyroidism, and a high normal concentration is not an indication for treatment with thyroid supplementation (Ferguson, 2007). Both groups had similar numbers of dogs with TT3 and fT3 concentrations below the normal range and these were the most likely analytes to be outside the reference range for both groups. Unfortunately, the current assays for fT3 and TT3 are not highly accurate or sensitive for a diagnosis of hypothyroidism or prediction of future disease (Peterson et al., 1997; Ferguson, 2007).

Although we did not detect a difference in thyroid analytes between the aggressive and non-aggressive groups, we cannot confirm that no difference exists. Larger numbers of dogs or different measures of aggressive behavior may be needed in order to detect a difference, if there is one, due to the reported low incidence of hypothyroid-related aggression. Further studies involving larger groups of dogs, dogs with other behavior problems, comparisons of behaviorally appropriate and aggressive dogs within the same breed, behavioral assessment of dogs already diagnosed with hypothyroidism and longitudinal studies would be helpful to elucidate any association between thyroid analytes and aggression in dogs.

Conclusions

While this study showed only one significant difference (T4AA) between thyroid analytes in dogs that were aggressive to familiar people and those that were not, dogs who exhibit aggression should continue to receive an appropriate medical screening, including thyroid testing prior to institution of the behavioral treatment plan. However, caution should be exercised when assessing thyroid function and subsequently arriving at a diagnosis of hypothyroid-associated aggression.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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