Behavior Changes Associated with Metabolic Disease of Dogs and Cats

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KEYWORDS

• Hypothyroidism • Aggression • Endocrine disease • Anxiety behavior

KEY POINTS

- Endocrine diseases in dogs and cats can, directly and indirectly, affect behavior patterns.
- Through operant conditioning, behavior changes associated with physical disease can progress to long-term behavior patterns which do not resolve with treatment of the primary endocrine disease.
- Emotional and physical processes in the body are inextricably linked and both can influence clinical signs which are historically characterized as behavioral.

INTRODUCTION

A healthy animal body can cope with a certain amount of change without entering a state of chronic stress and possible behavioral or physical disease. The amount of change that an individual can handle is referred to as "allostatic load." When the change exceeds the allostatic load, clinical signs of behavioral or physical disease can result (Sterling 2014). The allostatic load can be altered by medications (eg, phenobarbital, corticosteroids, benzodiazepines, antidepressants, tramadol, levetiracetam, gabapentin)[1–6]; gastrointestinal problems (eg, inflammatory bowel disease, intestinal neoplasia)[7,8]; dermatologic diseases (eg, atopy, food allergy, flea allergy dermatitis)[9]; orthopedic disease (eg, neoplasia, osteoarthritis),[10] metabolic disease (eg, hypothyroidism, hypoadrenocorticism, diabetes mellitus), and any disease that causes pain or discomfort. See **Table 1** for a list of clinical signs caused by metabolic diseases.

When a stressor is encountered, whether physical (eg, metabolic disease, acute injury, surgery, inflammatory disease, chronic disease) or emotional (eg, fear, anxiety, stress, conflict, and/or panic [FASCP]), the body launches a physiologic stress response. This response can be acute (ie, immediate) or chronic (eg, days, weeks, months). Acute stress will trigger an adaptive change, while chronic stress may be

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Table 1
Behavioral clinical signs of endocrine disease

Disorder	Dogs	Cats
Hypothyroidism	Aggression, coprophagia, poor focus and learning, fear of sounds, distress during separation, hyperactivity, difficulty training, mental dullness, lethargy, changes in mentation, disorientation, changes in interactions with family.	Lethargy, inappetence, decreased interactions with the environment.
Hyperthyroidism	Restlessness, anxiety, dysrexia, lethargy	Anxiety, restlessness, nighttime vocalization, increased appetite, hyperactivity, changes in litter box habits
Hypoadrenocorticism	Restlessness, increased anxiety, depression, changes in mentation, erratic behavior, disorientation, circling, aggression, lethargy	Behavioral periuria, perichezia, lethargy, depression, dysrexia, polyuria, polydipsia, changes in interactions with the pet parent, pica, increases in fear.
Hyperadrenocorticism	Panting, polyuria, polyphagia, lethargy	Lethargy, behavioral periuria, perichezia, urine spraying, aggression, polyphagia, polydipsia, polyuria, licking the vulva, vocalizing, rolling on the ground, head rubbing
Sex hormone–secreting adrenal tumors	Polyphagia, polydipsia, polyuria, panting	Hyperactivity, urine marking, estrus behavior (pacing, vocalizing, lordosis)
Diabetes mellitus	Polyuria, anxiety, polyphagia, polydipsia	Anxiety, irritability, aggression, altered sleep, changes in litter box habits, mental dullness, decreased activity, restlessness, increased sleep, confusion, difficulty jumping, reduced tolerance of handling.

maladaptive as it exceeds the allostatic load. Both acute and chronic stress result in behavior changes as the patient attempts to cope.

Behavior changes, including those resulting from changes in physiology due to metabolic disease, can be reinforced or punished intrinsically (eg, hormones, neurochemicals, alleviation of discomfort) or extrinsically (eg, environment, people, other animals). Through positive and negative consequences (ie, reinforcement, punishment),

behavior changes associated with physical disease can progress to long-term behavior patterns. For example, a dog with polyuria and polydipsia due to hyperadrenocorticism may have urinary accidents in the home. Urination is intrinsically reinforced immediately when pressure on the bladder is alleviated. In this way, the dog may learn that urination in the home is reinforcing, which will in the end affect the consistency of elimination outside despite previous house-training. Despite the effective treatment of the hyperadrenocorticism, the learning cannot be undone; however, with appropriate behavior modification the urination in the house can be improved. The dog may need to be reminded of the previous house-training in order to eliminate the possibility of future accidents. In another example, a cat who vocalizes at night resulting from undiagnosed hyperthyroidism and is fed by the caregivers in order stop the meowing is reinforced for vocalizing and/or waking the caregivers up. When the hyperthyroidism is treated, the cat may feel healthy. However, he has learned that when he desires food, waking up the caregivers is the most effective way to satisfy that need.

In the past, veterinarians may have been encouraged to rule out physical problems before considering behavioral diagnoses or delay treatment for what was categorized as behavioral clinical signs while physical disease was ruled out. However, recent research supports the concept that emotional and physical processes in the body are inextricably linked and both can influence clinical signs that are historically characterized as behavioral.[10,11] In fact, "behavioral" clinical signs can be caused by diseases of any body system, with no real separation between the emotional and physical components, in spite of the fictitious distinction being often used for teaching purposes.

Therefore, clinicians must diagnose and treat all clinical signs, such as pain, fear, and distress, of the same condition immediately and simultaneously to improve the health and welfare of a patient. The early recognition of behavioral clinical signs and the associated reinforcement and punishment of resulting behaviors allow the veterinary health care team to educate the caregivers immediately and prevent negative progression of behavior patterns. Additionally, treatment with diet, supplements, medications, probiotics, pheromone analogues, environmental changes, and behavior modification can immediately alleviate stress and potentially reduce the progression of the negative behavior while diagnostics are being performed and treatment is initiated for the physical disease.

For any of the endocrine diseases discussed later, it is possible for patients to present with only behavioral changes. This emphasizes the importance of a complete diagnostic workup on all pets presenting with behavior problems, even if the caregivers feel strongly that the problem is not health-related.[12] A complete workup includes a physical examination, complete blood count, serum chemistry, thyroid analysis (free thyroxine measured by equilibrium dialysis [fT4 (ED)] in dogs and total thyroxine [TT4] in cats), urinalysis, fecal examination antigen, and fecal float.[13,14] Additional diagnostics should be at the veterinarian's discretion and may include ultrasound, radiographs, blood pressure measurement, and/or urinary culture.

If the clinical signs at presentation are consistent with FASCP, treatment with psychotropic medications, supplements, probiotics, pheromone analogues, and/or diets should be instituted. Avoid the use of medications that may alter testing (**Table 2**). Instruct clients to avoid interactions or situations which stimulate the FASCP-related behavior patterns. Recommend changes in the environment and behavior of the caregivers to reduce reinforcement and punishment of behavior patterns.

For example, if a dog shows aggression when pushed or pulled, recommend that the caregivers use food or toys to lure the dog from that spot to the desired area instead of physically handling the dog. If the dog is aggressive on walks, recommend

Table 2
Medications and ingredients which may affect testing for common endocrine disease

Effect	Medication/Ingredient
Hypoglycemia	SSRIs, L-theanine
Hyperglycemia	TCAs, benzodiazepines, glucocorticoids
Altered cortisol/ACTH	Clonidine, trazodone, dexmedetomidine
Altered thyroid	Glucocorticoids, TCA, SSRI

Abbreviations: ACTH, adrenocorticotropic hormone; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

that they refrain from walking the dog at peak times or entirely if they have a yard in which the dog can exercise. For cats who vocalize overnight, recommend that the caregivers ignore the cat at those times and utilize an automatic feeder set to open prior to when the cat wakes the caregivers up. For cats who have changes in litter box habits, recommend that the caregivers offer the ideal number of boxes for the household, ideal size boxes with the cat's preferred shape and side height, and about 3 inches of litter depth, placed in the cat's core area. While working with a positive reinforcement training professional cannot change metabolic changes in the body, it can help the caregivers to understand environmental changes and adopt alternative strategies for living with their pet and so should be recommended.

Disorders of the Thyroid Gland

Proposed mechanisms for thyroid-related behavior changes and influences on behavior disorders include a lowered threshold for aggression due to primary clinical signs (eg, changes in appetite, energy level), impaired transmission of serotonin at the postsynaptic 5-HT_{2A} receptors in the cerebral cortex,[15] regulation of noradrenergic function,[16] alterations in monoamine (ie, dopamine, epinephrine, serotonin) synthesis, turnover, and release,[17] and increased metabolism of serotonin in the cerebrospinal fluid.[18,19]

Several medications which are commonly used to treat behavior problems can affect serum thyroid levels. Clomipramine (Clomicalm) at a dose of 3 mg/kg PO q12, has been shown to reduce serum thyroxine (T4), fT4 (ED), and triiodothyronine (T3) in dogs after 28 days of use and decreases continued through 112 days (end of study). In the aforementioned study, there was no effect on thyrotropin-releasing hormone or thyroid-stimulating hormone (TSH).[20] Proposed mechanisms include the binding of iodine by clomipramine, decreasing iodine availability in the thyroid gland, and irreversible inhibition of the synthesis of thyroid peroxidase which oxidizes iodide ions used in the production of T4 and T3.[21] Selective serotonin reuptake inhibitors (SSRIs) can reduce serum T4, fT4, and T3 in humans; however, results are inconsistent.[22,23] Avoid the use of tricyclic antidepressants (eg, clomipramine, imipramine, amitriptyline) and potentially SSRIs (eg, fluoxetine, sertraline, paroxetine) until thyroid status is known.

Hypothyroidism

Hypothyroidism is a multisystemic disorder with the potential for dermatologic, cardiac, neurologic, metabolic, gastrointestinal, hematologic, and ocular clinical signs.[24] Well-recognized behavioral clinical signs in dogs include mental dullness, lethargy, changes in mentation, disorientation, and altered social interactions.[15] Anecdotally, hypothyroidism in dogs has been linked to noise and storm phobia, separation-related disorders,

hyperactivity, poor focus and learning, compulsive behaviors, training disorders, coprophagia, and aggression.[25–28] In fact, aggression may be the only presenting complaint in some cases.[29]

While hypothyroidism is the most common endocrine disease in pet dogs, its prevalence is only 0.2% in the population.[30,31] Because of the low prevalence in the general population, finding an aggressive dog who is also hypothyroid may be as difficult as finding a needle in a haystack. Additionally, aggression is a common presentation in dogs with normal thyroid concentrations. In a study measuring TT4, fT4, total triiodothyronine (TT3), free triiodothyronine (fT3), thyroglobulin autoantibodies (TgAA), TSH, triiodothyronine autoantibodies, and thyroxine autoantibodies (T4AA) in[31] aggressive and nonaggressive dogs, aggressive dogs had higher concentrations of T4AA when compared to non-aggressive dogs; however, T4AA values were still within normal range.[32] In a second study comparing TT4 and TSH in 39 aggressive and nonaggressive dogs, TT4 was higher in aggressive dogs but was not outside the normal range.[33]

In a case report, a hypothyroid (low T4, increased TSH) dog diagnosed with aggression was treated with levothyroxine for 1 month at which time, owner-directed aggression was decreased; however, territorial aggression was not.[17] In a case series of 4 dogs who were presented for aggression to familiar and unfamiliar people and also had thyroid values consistent with hypothyroidism, all dogs responded to treatment with supplementation and management recommendations, but none resolved completely.[20] In cases of hypothyroid dogs presenting with aggression, some clinicians recommend treatment for 1 month before reassessment.[34,35] Aggression has been associated with increased TgAA concentrations, along with normal TT4 and TSH concentrations in dogs.[26]

Inappropriate or unnecessary supplementation of thyroid hormone may lead to tachycardia, irritability, aggression, nervousness, and weight loss in dogs. In addition, because thyroid hormone is functionally linked to brain dopamine and serotonergic systems, L-thyroxine supplementation, even in euthyroid patients, may affect the same systems involved in canine aggression disorders; therefore, improvement with thyroid supplementation does not confirm that the cause is thyroid-related. However, in a study examining the effect of T4 supplementation on behavior change and serum levels of prolactin and serotonin in hypothyroid[36] dogs, the only behavior change seen was increased activity and there were no changes in serum serotonin or prolactin levels.[37] In a double-blinded, placebo-controlled study examining the effect of thyroid supplementation on dogs who directed aggression at family members and had fT4 in or below the lower 20th percentile of the normal range; TT4, TT3, or fT3 in or below the lower 30th percentile of the normal range; or the presence of TgAA, no difference was found between the supplemented and placebo groups in the level of aggression.[38] At this time, evidence supporting the safety and efficacy of supplementation with levothyroxine in euthyroid dogs is lacking. For that reason, supplementation without testing supportive of hypothyroidism is not recommended.[5]

Hypothyroidism in cats is rare. In fact, it is the least common endocrine disorder in cats. Most commonly, it occurs in kittens and in cats following radioiodine treatment; however, adult-onset hypothyroidism has been reported.[39] Behavioral clinical signs include lethargy, inappetence, and lack of interest in the environment.[30,40–42]

Hyperthyroidism

Hyperthyroidism is rare in dogs; however behavior changes such as restlessness, anxiety, dysrexia, and lethargy have been noted in dogs with thyroid cancers (eg, thyroid carcinoma) leading to clinical hyperthyroidism and resolution after thyroidectomy.[43,44]

Hyperthyroidism is the most common endocrine disease in cats.[45] Behavioral clinical signs are common and include anxiety, restlessness, nighttime vocalization, increased appetite, hyperactivity, and changes in litter box habits.[46] Because hyperthyroidism is more common in cats over 10 years of age, complicating factors, including cognitive dysfunction, may be present. Cats over 11 years of age may display increased aggression, marking, behavioral periuria, vocalization, restlessness, changes in interactions and sociability, and aggression as a normal part of aging or due to cognitive dysfunction complicating the clinician's ability to distinguish the etiology of behavioral clinical signs.[47]

Disorders of the Adrenal Gland

Changes in the secretion of sex hormones, mineralocorticoids, or glucocorticoids due to impaired adrenal gland function can result from excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland most likely due to a pituitary tumor; excessive secretion of cortisol by the adrenal gland (adrenal tumor), iatrogenic medication administration (eg, glucocorticoids, ketoconazole), and excessive sex hormone (androgens, estrogen) secretion (adrenal tumor).[48,49]

Administration of exogenous glucocorticoids in dogs has been associated with increases in startle response, fear, vigilance, avoidance of people, barking, and aggression and decreases in recovery from stressful events, exploratory behavior, and play.[1–3] Glucocorticoids have been shown to alter post-TSH values (endogenous), lower serum TT4 (endogenous and exogenous), and lower fT4 (exogenous) measurements potentially through inhibition of TSH secretion in the pituitary gland, changes in thyroid binding, and/or metabolism.[4–6]

Along the hypothalamic-pituitary-adrenal axis, there are alpha-1 and alpha-2 adrenergic receptors and as such its production of hormones can be affected by medications that modulate binding at those receptors. For example, in humans, trazodone can decrease plasma cortisol levels when compared to placebo.[50,51] The literature is conflicting regarding clonidine's effect on ACTH and cortisol levels. In 1 study in humans, clonidine decreased cortisol and ACTH concentrations in adults and in a subsequent study, it had no effect.[52,53] In a study in children, clonidine reduced plasma ACTH and cortisol.[54] Dexmedetomidine is commonly used for sedation in dogs prior to procedures. The transmucosal preparation (Sileo) has been used off-label as a pre-visit pharmaceutical to reduce stress during procedures and veterinary visits.[55] Studies in dogs appear to demonstrate that at higher doses or with prolonged use of injectable dexmedetomidine given intravenously, basal cortisol levels can decrease and the response to ACTH stimulation can be blunted.[56,57] Because of the potential for alterations in cortisol and ACTH secretion, clinicians should consider avoiding trazodone,[58] dexmedetomidine,[56,57,59] and clonidine[52] in patients for whom impaired adrenal function is suspected until testing is complete. Evidence is lacking at this time as to the effect, if any, of a transmucosal preparation of dexmedetomidine on cortisol and ACTH.

Hypoadrenocorticism

Hypoadrenocorticism (Addison's disease) can result from the destruction of the adrenal cortices (primary) or a decrease in ACTH secretion from the pituitary gland (secondary). Patients can be deficient in mineralocorticoids and glucocorticoids (typical) or only glucocorticoids (atypical). It is more common in dogs than cats. Aside from the clinical signs directly resulting from changes in adrenal hormone levels, the presence of a tumor may exert its own behavioral clinical signs such as restlessness, increased anxiety, depression, changes in mentation, erratic behavior, disorientation, circling, and aggression.[60,61]

The most common behavioral clinical sign of hypoadrenocorticism in dogs is lethargy although some dogs with atypical hypoadrenocorticism exhibit polydipsia. The behavioral clinical signs associated with hypoadrenocorticism in cats include behavioral periuria, perichezia, lethargy, depression, dysrexia, polyuria, polydipsia, changes in interactions, pica, and increases in fear.[62,63,64]

Hyperadrenocorticism (Cushing's disease)

Typically, clinical signs result from excessive secretion of cortisol from the adrenal cortex; however, clinical signs can result from oversecretion of aldosterone, testosterone, androstenodione, progresterone, and estrodiol.[3,65–67]

Behavioral clinical signs in dogs include panting, polyuria, polyphagia, and lethargy.[68] Hyperadrenocorticism is rare in cats; however, it has been reported.[3] Behavioral clinical signs in cats include lethargy, behavioral periuria, perichezia, urine spraying, aggression, polyphagia, polydipsia, polyuria, licking the vulva, vocalizing, rolling on the ground, and head rubbing.[3,37,69,70] About 80% of cases in cats have concurrent diabetes mellitus.[71]

Sex hormone–secreting adrenal tumors

Behavior changes such as aggression (eg, people, other cats), hyperactivity, urine marking, and estrus behavior (pacing, vocalizing, lordosis) have been reported in cats with sex hormone–secreting tumors such as an adrenocortical carcinoma.[40] In dogs, behavioral clinical signs may be similar to typical hyperadrenocorticism and include polyuria, polydipsia, panting, and polyphagia.[52]

Disorders of the Pancreas

Diabetes mellitus

Behavioral clinical signs in dogs include polyuria, anxiety, polyphagia, and polydipsia.[72,73] Clinical signs of diabetes mellitus in cats include anxiety, irritability, aggression, altered sleep, changes in litter box habits, mental dullness, decreased activity, restlessness, increased sleep, and confusion.[37] Diabetic neuropathy is more common in cats than dogs. Cats with diabetes may have difficulty jumping and an aversion to being petted or handled due to discomfort resulting from diabetic neuropathy.

L-theanine, a common ingredient in antianxiety supplements, has several effects on the endocrine system. In rats, L-theanine has been shown to have insulin-like actions, increasing glucose tolerance, and lowering blood glucose.[74] In humans, SSRIs such as fluoxetine and sertraline can have a hypoglycemic effect, normalize glucose homeostasis, and increase insulin sensitivity.[75] Tricyclic antidepressants (imipramine, clomipramine) can cause a hyperglycemic effect.[67] Benzodiazepines such as diazepam may induce hyperglycemia in diabetic rats; however, it may reduce hyperglycemia related to stress in nondiabetic mice.[76,77] More research is needed to determine if this effect is reliably present in dogs.

SUMMARY

Like many physical disorders, clinical signs associated with metabolic diseases affecting thyroid, adrenal, and pancreatic function are reflective of nonspecific changes in behavior. Additionally, patients who have underlying disorders of FASCP may be under treatment with medications that alter basal thyroid, glucose, and cortisol levels. Through reinforcement and punishment of behaviors associated with clinical signs caused by organic or iatrogenic endocrine disease, behaviors can be perpetuated and become persistent behavior patterns. Screening all patients presenting with

a primary behavior complaint or those with behavioral clinical signs for endocrine diseases is essential. Alleviating stress immediately while completing a physical and diagnostic workup or treating metabolic disease alleviates suffering and may stave off the adoption of behavior patterns in a more permanent way.

CLINICS CARE POINTS

- Screening all patients presenting with a primary behavior complaint or those with behavioral clinical signs for endocrine diseases is essential.
- Treat behavioral clinical signs immediately with medications, supplements, pheromone analogues, probiotics, and/or diet, with consideration given to the medications and ingredients which may alter testing.
- Make recommendations for environmental and behavioral changes immediately.

DISCLOSURE

Dr L. Radosta currently serves on advisory boards for Purina, Zoundz, and Ellevet.

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