WHAT THYROIDS?
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Thyroid dysfunction, and in particular, hypothyroidism, has been discussed as a possible contributing factor in many equine diseases. However, it has been difficult to establish the true role of thyroid dysfunction in these diseases due to the lack of highly reliable diagnostic tests. Recent studies in this area should help to clarify the actual incidence of thyroid disease.

ANATOMY AND PHYSIOLOGY

The equine thyroid gland consists of 2 lobes (located at the caudal aspect of the larynx) and the thyroid gland body or isthmus. In the adult horse, the average size of each lobe is approximately 5 cm x 2.5 cm x 2 cm, and it is not uncommon for the lobes to be slightly asymmetric in size. The isthmus is generally present only as a fibrous remnant connecting the caudal poles of the lobes, although it may be more prominent in foals, donkeys, mules. The thyroid gland is highly vascular.

The thyroid gland consists of large numbers of closed follicles interspersed with C cells. The follicles contain colloid, a secretory substance composed primarily of thyroglobulin, a large glycoprotein containing the thyroid hormones. The C cells produce calcitonin, which plays a role in calcium homeostasis.

Thyroid hormone production: Iodide is pumped from the basal membrane to the interior of the thyroid cell in a process called iodide trapping. Once within the cell, the iodide is oxidized and then bound to tyrosyl residues within the thyroglobulin to form mono- and diiodotyrosine, which undergo coupling to form the thyroid hormones, thyroxine (T₄) and triiodotyrosine (T₃). The thyroid hormones remain part of thyroglobulin for storage within the follicles.

The synthesis and release of thyroid hormones is controlled by thyroid stimulating hormone (TSH, thyrotropin) released from the anterior pituitary which is in turn controlled by thyroid releasing hormone (TRH) from the hypothalamus. Circulating thyroid hormones feedback on both the anterior pituitary and hypothalamus. In addition, iodine availability influences thyroid hormone production.

When thyroid hormones are needed, T₄ and T₃ are cleaved from thyroglobulin and enter the circulation. Once in the circulation, most thyroid hormones are bound to proteins, primarily thyroid-binding globulin, but also T₄ binding prealbumin and albumin. The thyroid hormones are slowly released from the protein, and cross the capillary endothelium primarily in the unbound or free state. The thyroid hormones found in the circulation include:

1. T₄ (thyroxine): Approximately 90% of the thyroid hormone released from the thyroid gland is in the form of T₄. T₄ is less biologically active than T₃, and ultimately most is converted to T₃ by peripheral deiodination.
2. T₃ (triiodothyronine): Accounting for about 10% of the hormone secreted by the thyroid gland, most T₃ is formed by peripheral deiodination. It is about 3-5 times as active as T₄.
3. rT₃ (reverse T3): The major product of peripheral deiodination is T₃, however, some rT₃ is formed by deiodination of the carboxyl end. The precise function of rT₃ is unclear. In people, concentrations are high in the fetus and patients with systemic illness. Currently, it is thought to have little activity in adult horses.
4. fT₃ and fT₄ (free T₃ and free T₄): Only about 1% of the total concentration of thyroid hormone in the circulation is unbound to carrier proteins. It is this unbound hormone that is biologically active and acts in the feedback loop to regulate the synthesis and release of thyroid hormones.

The thyroid hormones are essential throughout the body. In general terms, they function to increase nuclear transcription of multiple genes, which leads to an increase in protein synthesis and an increase in the metabolic activity of most tissues. Some specific functions of the thyroid hormones include maintenance of the basal metabolic rate, neural transmission, and thermogenesis, as well as stimulation of the heart rate, cardiac output and blood flow. In the fetus and neonate, the thyroid hormones promote differentiation and play an important role in overall growth and development, especially of skeletal and neuronal tissues.

DIAGNOSIS OF THYROID DYSFUNCTION

Making an accurate diagnosis of thyroid dysfunction has been difficult due to several factors including limited availability of validated tests, wide variation in normals, and the influence of extrathyroidal factors.

1. Hormone concentrations: Serum concentrations of T₃, T₄, fT₃, and rT₃ can be measured, although some laboratories only report a TT₄. Normal values will vary with the laboratory. Thyroid hormone transport and metabolism can be affected by a wide variety of factors, and single measurements of resting thyroid hormones are difficult to interpret and are often not accurate in diagnosing thyroid dysfunction.
2. TSH concentrations: Measurement of serum TSH concentration has proven to be a reliable means of diagnosing hypothyroidism in people, but has not been as consistent in dogs, where up to 20-40% of hypothyroid dogs do not have elevated TSH concentrations and up to 14% of euthyroid dogs can have elevations. Recently, measurement of TSH has been validated in euthyroid horses and horses made hypothyroid by propylthiouracil. The hypothyroid horses had significantly increased TSH concentrations, and their TSH response to TRH was exaggerated. The value of the TSH concentration in the diagnosis of naturally occurring thyroid disease still needs to be established. Also, the TSH assay has not been available commercially.
3. Trophic response tests: Both TSH and TRH stimulation tests have been performed and advocated for the diagnosis of thyroid disease. Recently, the TRH stimulation test, with subsequent measurement of TSH and thyroid hormone concentrations has been used in many studies. Unfortunately, approved TRH and TSH products for use in these assays are often either unavailable or too costly to be practical.
4. Aspirate or biopsy: Sampling to the thyroid gland can help to establish a pathologic process within the gland, but does not evaluate thyroid function. The high vascularity of thyroid should be considered.
5. Other: Ultrasound of the thyroid can help define structural abnormalities, but does not assess function.
Basal metabolic rate can be determined as a direct measure of metabolic activity, but this is not practical as a routine clinical test. Scintigraphic imaging has been used, primarily as an aid in the assessment of carcinomas.

EXTRATHYROIDAL FACTORS WHICH MAY AFFECT THYROID FUNCTION
1. **age**: The concentrations of circulating thyroid hormones are normally about 10-20 times higher in neonatal foals than in adult horses. The concentrations decrease rapidly within the first few weeks of life and then decline slowly.

2. **drugs**: Several commonly used drugs may influence circulating thyroid hormone concentrations. Phenylbutazone decreases serum concentrations of T4 and T3, primarily by competition for binding to carrier proteins, although decreased production of T4 may also play a role. Corticosteroids have been shown to affect thyroid hormone concentrations in humans and dogs, but administration of dexamethasone for 5 days in normal horses did not change serum concentrations. Recently, the effects of trimethoprim-sulfa on thyroid function have been investigated. In one study in which thyroid function was assessed by the measurement of TSH and thyroid hormones in response to TRH, there was no detectable difference in thyroid function between treatment and control groups when trimethoprim-sulfadiazine was administered for eight weeks.

3. **diet**: Anorexia or food deprivation causes a decrease in circulation thyroid hormones, especially T3. This may be due to inhibition of the 5' deiodinase, resulting in decreased conversion of T4 to T3. Concentrations of rT3 may increase. Additional iodine may potentially cause transiently elevated serum concentrations of thyroid hormones, but continued feeding of diets with either deficient and or excess dietary iodine can suppress thyroid hormone concentrations. Selenium plays a role in conversion of T4 to T3, and deficiencies of selenium may contribute to thyroid dysfunction. Diets high in carbohydrates are thought to tend to decrease concentrations.

4. **climate**: Thyroid activity tends to increase in cool climates.

5. **activity**: Studies evaluating the effects of training or single exercise bouts on baseline concentrations of thyroid hormones have had conflicting results.

EUTHYROID SICK SYNDROME (NON-THYROIDAL ILLNESS SYNDROME)
Systemic illness has been shown in people and small animals to cause decreases in thyroid hormones, particularly T3. TSH may be low or normal. The degree of suppression appears to correlate with the severity of illness and mortality. While it has been assumed that this occurs in horses, it has not been well-documented. Preliminary data from North Carolina State University (Breuhaus) in horses with systemic illness, suggests that serum concentrations of thyroid hormones decrease, sometimes profoundly. The contribution of anorexia and drugs administered in these cases is difficult to assess.

HYPOTHYROIDISM
A syndrome of hypothyroidism, known as congenital hypothyroidism and dysmaturity, has been defined in foals. Hypothyroidism has been discussed in association with a variety of clinical problems in adult horses including poor performance, infertility, rhabdomyolysis, anhidrosis, laminitis and obesity. However, primary hypothyroidism in adult horses is probably rare. Hypothyroidism has been experimentally induced in adult horses by surgical removal of the thyroids and administration of propylthiouracil. Changes seen in these horses included decreases in basal heart rate, respiratory rate, cardiac output, and rectal temperature and also increases in blood volume, plasma volume, and serum concentrations of triglycerides, cholesterol and very low density lipoproteins. In an early study in young horses, animals had dull haircoats as well as decreased feed consumption and weight gain.

**Congenital Hypothyroidism and Dysmaturity (CHD)**: CHD, also known as thyroid hyperplasia and musculoskeletal deformities, is a syndrome in which hypothyroidism causes a number of abnormalities in newborn foals, primarily in the musculoskeletal system. The syndrome is primarily identified in foals born at full-term, and has only recently been identified as a cause of abortion. The predominant clinical characteristics include: prolonged gestation (average 360 days), mandibular prognathism, hypo-ossification and contracted tendons, often with accompanying rupture of the common digital extensor tendon. The severity of the musculoskeletal deformities varies widely between cases. Other signs may include signs of immaturity such as a soft, silky hair coat and pliable ears. Also, incomplete closure of the abdominal wall and poor muscle development, particularly evident over the sternum, have been described. While some foals are weak and nonresponsive at birth, many are bright and alert with a strong suckle reflex. Importantly, there is generally no palpable enlargement of the thyroid glands, although there is histologic evidence of thyroid hyperplasia.

Initially reported in the early 1980's in foals from the western provinces of Canada, it was originally thought that the syndrome might be limited to this region. However, while it may be more common in certain geographic locations, cases have been reported from several areas in the US and in Finland. Due to the often guarded prognosis and the fact that multiple foals may be affected in a given year, the syndrome can be devastating.

Complete blood counts, serum chemistries and electrolytes are within normal limits if the complications of failure of passive transfer and septicemia are avoided. Baseline concentrations of T3 and T4 may be either low or within normal ranges for neonatal foals, but there is a diminished response to TSH. Dams have been found to have normal thyroid function at the time of parturition. Biopsy of the thyroid gland can be used to confirm the diagnosis.

Treatment of CHD has been largely supportive: prevention of failure of passive transfer, splints, physical therapy, nutritional supplementation, restricted exercise. It is unclear if administration of a thyroid supplement is of benefit in these cases. Limited data suggest that surviving affected foals become responsive to TSH over time even without thyroid supplementation, and the thyroid tissue becomes histologically normal.
The prognosis tends to vary with the severity of the condition and whether concurrent septicemia develops. However, a variety of orthopedic diseases have been identified in surviving foals, including tarsal collapse, angular limb deformities, physisitis, and lesions associated with osteochondrosis. Often the prognosis for soundness is poor, unless the musculoskeletal deformities are mild.

The underlying defect in CHD appears to be hypothyroidism, which is supported by the observation that thyroidectomy in foals and in other species results in a similar clinical syndrome. However, in most cases, relatively little is known about the specific cause of impaired thyroid function. As there is no sex or breed predisposition, a genetic cause is considered unlikely. In general, the occurrence appears sporadic. In the Pacific Northwest, foals that are at risk tend to be born in the latter half of the foaling season. Since many factors potentially influence thyroid function, the insult to the fetal thyroid might not be the same in all cases.

Some previously identified causes of congenital hypothyroidism in foals include a dietary deficiency or excess of iodine and possibly exposure to feed contaminated with fungi (Acremonium coenophialum, Claviceps purpurea). However, the thyroid lesions seen in these foals appear to vary slightly from those seen in foals affected with CHD in Canada and the Pacific Northwest. Currently, an exposure related cause is suspected for CHD. Current theories include exposure to high nitrate levels or exposure to mustard plants which contain glucosinolates, a known thyrotoxic compound. Lack of mineral supplementation may also be a risk factor for the syndrome. Deficiencies of minerals such as iodine and selenium may adversely affect thyroid function. A multitude of factors may be involved in the development of CHD, and investigation into this devastating syndrome is ongoing.

Obese/laminitic horses: Obesity, often associated with laminitis, is a widely recognized problem of horses. Some affected horses may have pars intermedia dysfunction (Cushing’s disease), and others may have the more recently described metabolic syndrome (peripheral Cushing’s syndrome), while others may not have an underlying endocrine disorder. Hypothyroidism has been implicated as some affected horses may have low baseline thyroid hormone concentrations and anecdotally some horses appear to respond to treatment.

Recently, efforts have been made to more critically assess the role of thyroid dysfunction in these horses. In a study by Graves et al, increases in serum thyroid hormone concentrations in response to the administration of TRH were either not different or greater in horses with peripheral Cushing’s (n = 9) as compared with normal control horses (n = 7). It was concluded that the function of the pituitary-thyroid gland axis was normal in horses with peripheral Cushing’s syndrome.

Laminitis was not seen in 3 studies in which hypothyroidism was induced by surgery or propylthiouracil. In studies by Breuhaus, horses that have suffered an episode of laminitis or have recurrent bouts demonstrated normal TSH and thyroid hormone responses to TRH once stabilized and off medications.

Reproduction: The role of thyroid hormones in fertility is unclear. Many mares are treated with thyroid supplements based on clinical impression and/or a presumptive diagnosis from a serum T4. Gutierrez et al documented T4 levels and pregnancy rates at 15-16 days post-ovulation in 329 clinically normal broodmares and found no relationship. Similarly, Meredith et al looked at thyroid function using a TRH stimulation test in 79 broodmares ranging in age from 2-22 years old. Baseline and stimulated serum T3 and T4 concentrations were not significantly different between mares that became pregnant and those that did not. The results suggest that decreased thyroid function is uncommon in mares and is not a common cause of infertility.

Anhidrosis: Anhidrosis is a condition in which adult horses have a diminished ability to sweat in response to appropriate stimuli. Preliminary data from Breuhaus indicate that baseline concentrations and hormone responses to TRH stimulation are normal in anhidrotic horses, but that the TSH response to TRH is increased. There are anecdotal reports that some anhidrotic horses improve with thyroid supplementation. This may be a pharmacologic effect as thyroid hormones modulate adrenergic receptor function and sweat glands are stimulated by activation of beta-2-adrenergic receptors.

Endophyte infected fescue: Alkaloids produced by the endophytic fungus, Neotyphodium coenophialum, that lives on fescue, act as a dopamine agonist. Since the release of TSH from the anterior pituitary is inhibited by dopamine, it has been suggested that ingestion of endophyte infected fescue could lead to hypothyroidism. However, in a study by Breuhaus, ingestion of endophyte-infected fescue by mature, non-pregnant horses had little effect on thyroid function.

Thyroid supplementation: Several different protocols have been used for oral thyroid hormone replacement therapy. These include desiccated thyroid extract (2 mg/kg/day), iodinated casein (5-10 gm/day), T4 supplementation (20 mg/kg/day) and T3 supplementation (1 mg/kg/day). It has been recommended to monitor thyroid hormone concentrations and clinical response. While anecdotally many horses respond to thyroid hormone supplementation, this should not be used as the basis of a diagnosis of hypothyroidism, as even euthyroid animals may experience an increase in basal metabolic rate and general activity level with additional thyroid hormone.

The effects of unnecessary thyroid supplementation are not clear. Currently data related to long-term thyroid supplementation are lacking. In other species, supplementation may result in a decrease in endogenous TSH and varying degrees of thyroid gland atrophy, and it is reasonable that similar changes occur in horses. It has been recommended that thyroid supplementation not be discontinued abruptly, but by gradually decreasing the dose.

HYPERTHYROIDISM

Hypothyroidism also appears to be uncommon in horses. In many cases, isolated high thyroid hormone concentrations have been identified, which return to normal on repeated sampling. A poorly defined syndrome of hyperthyroidism characterized by tremors, excitability, tachycardia, sweating and weight loss despite good appetite has been described in racehorses. Recently, hyperthyroidism was reported in a 23-year-old Quarter Horse gelding with a primary complaint of cachexia and hyperactive behavior. High plasma thyroid hormone concentrations and a triiodothyronine suppression test confirmed hyperthyroidism. The enlarged right lobe of the thyroid was identified as an adenoma on histologic exam. The horse was successfully treated with hemithyroidectomy.

THYROID TUMORS

Enlargement of the thyroid gland is fairly common, especially in older horses. In one study, 32% of horses > 10 years of age had some type of tumor mass, and 75% of
horses greater than 20 had masses. Three types of tumors have been described: adenomas, adenocarcinomas and medullary or C-cell tumors. It can sometimes be difficult to determine the exact tumor type by fine needle aspirate or biopsy, and especially to differentiate adenomas and adenocarcinomas. Adenomas are generally thought to be the most common tumor type. They are usually benign, unilateral masses and are typically not associated with thyroid dysfunction. Adenocarcinomas are less common. Thyroid hormone concentrations are variable, but are typically normal. Systemic metastasis has been reported in one horse with a concurrent pituitary adenoma. Medullary tumors (C-cell or parafollicular tumors) are generally non-functional. In one study from Japan, they were the most common tumor type.

Surgical excision may be indicated in those cases where there is confirmed thyroid dysfunction or the size of the mass causes clinical signs such as tracheal compression. In one study, ipsilateral laryngeal hemiplegia was seen in several cases following surgical excision.

SELECTED REFERENCES

7. Gutierrez CV, Riddle WT, Bramlage LR. Equine thyroid hormone levels and pregnancy rates at 15 to 16 days post-ovulation. AAEP Proc 2000;46:319-320.