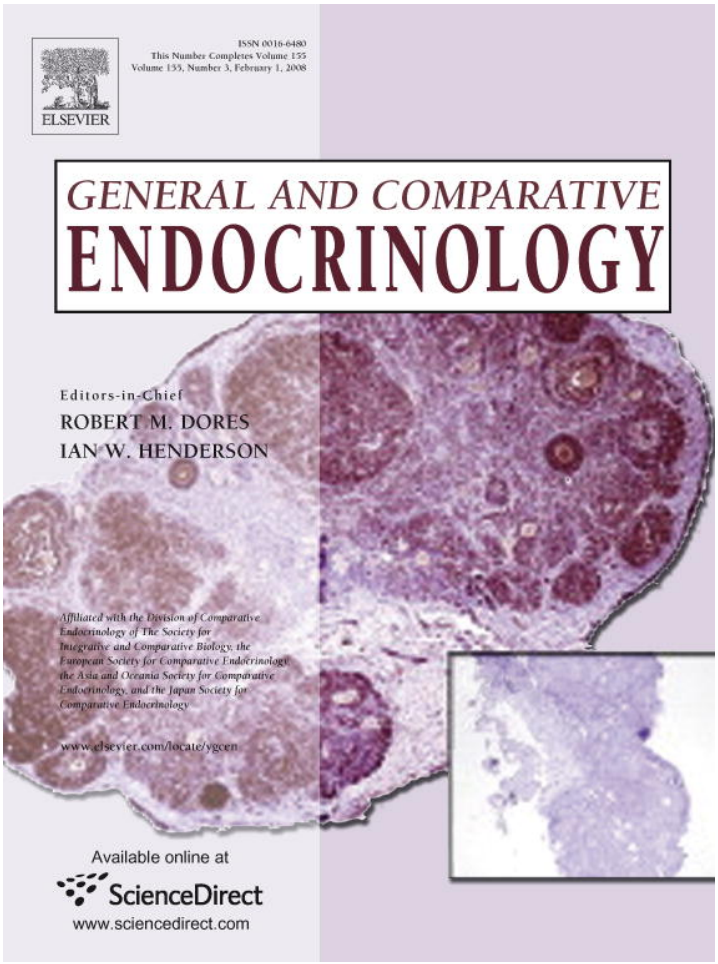

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Thyroid function testing in elephant seals in health and disease

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Abstract

Northern Elephant Seal Skin Disease (NESSD) is a severe, ulcerative, skin condition of unknown cause affecting primarily yearling northern elephant seals (*Mirounga angustirostris*); it has been associated with decreased levels of circulating thyroxine (T_4) and triiodothyronine (T_3). Abnormalities of the thyroid gland that result in decreased hormone levels (hypothyroidism) can result in hair loss, scaling and secondary skin infections. However, concurrent illness (including skin ailments) can suppress basal levels of thyroid hormones and mimic hypothyroidism; when this occurs in animals with normal thyroid glands it is called ''sick euthyroid syndrome''. The two conditions (true hypothyroidism vs. ''sick euthyroid'') can be distinguished in dogs by testing the response of the thyroid gland to exogenous thyrotropin (Thyroid Stimulating Hormone, TSH). To determine whether hypothyroidism is involved in the etiology of NESSD, we tested thyroid function of stranded yearling elephant seals in the following categories: healthy seals (rehabilitated and ready for release; $N = 9$), seals suffering from NESSD ($N = 16$) and seals with other illnesses (e.g., lungworm pneumonia; $N = 10$). Levels of T_4 increased significantly for all three categories of elephant seals following TSH stimulation, suggesting that seals with NESSD are ''sick euthyroid'' and that the disease is not associated with abnormal thyroid gland function.

Keywords: Thyroxine; Triiodothyronine; Thyroid hormones; Thyrotropin; TSH-stimulation test; Hypothyroidism; Sick euthyroid; Elephant seal

1. Introduction

Changes in circulating thyroid hormone levels are associated with normal molt or shedding and with dermatologic disease in mammals (Rust et al., 1965; Riviere et al., 1977; Feldman and Nelson, 1987; Maurel et al., 1987). Whether these changes are a cause or a consequence of changes in the skin has been long debated (Rust et al., 1965; Ling, 1970; Ashwell-Erickson et al., 1986; John et al., 1987; Ferguson, 1988; Renouf and Brotea, 1991).

Northern elephant seals (*Mirounga angustirostris*) undergo a poorly defined phenomenon known as a ''catastrophic'' molt, in which sheets of superficial epidermis are shed along with the hairs over a period of a few weeks (Ling, 1965, 1984; King, 1986). Catastrophic molt is a normal physiologic event occurring annually in a few species of phocid seals (e.g., northern elephant seals; southern elephant seals, *Mirounga leonina*; Hawaiian monk seals, *Monachus schauinslandi*).

Northern elephant seals also are afflicted with an ulcerative dermatopathy of unknown etiology affecting primarily yearling seals, termed Northern Elephant Seal Skin Disease (NESSD; described by Beckmen et al., 1997). This disease is fatal in its severest form, and without an understanding of the underlying cause of the disease, only symptomatic therapy is available. Northern Elephant Seal Skin Disease is associated with a number of biochemical abnormalities (Beckmen et al., 1997), including decreased levels of circulating thyroid hormones (thyroxine [T_4] and triiodothyronine [T_3]).

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Abnormal thyroid gland function is involved in the etiology of some mammalian skin diseases (Feldman and Nelson, 1987; Scott et al., 2000). However, non-thyroidal disease, drugs and contaminants may lower thyroid hormone (TH) levels in euthyroid animals (a condition known as "sick euthyroid syndrome"; Kantrowitz et al., 2001; Rolland, 2000). The pathophysiology of sick euthyroid syndrome is not well understood, in part because the condition appears to involve multiple pathways (i.e., production, secretion, transport and metabolism of thyroid hormones; McIver and Gorman, 1997). In humans, decreased peripheral conversion of T_4 to T_3 (resulting in decreased circulating T_3 concentrations) is associated with a variety of non-thyroidal illnesses (e.g., malnutrition, diabetes; Ferguson, 1988). A TH degradation pathway prominent in phagocytic cells (cleavage of ether linkage between phenyl rings; Ferguson, 1988) has been proposed as a possible mechanism for decreased TH levels in inflammatory or infectious diseases. Alterations in TH binding and transport systems (denBrinker et al., 2005; Henneman and Krenning, 2007) and effects of inflammatory cytokines (McIver and Gorman, 1997) have also been proposed as mechanisms in sick euthyroid syndrome.

Elephant seals with NESSD often are malnourished and dehydrated and suffer from bacterial and fungal infections (Beckmen et al., 1997); these conditions have been associated with sick euthyroid syndrome in dogs and humans. It is therefore possible that the decreased TH levels associated with NESSD are a result of non-thyroidal illness rather than true hypothyroidism. The distinction could be important in the management of animals afflicted with NESSD; if animals are truly hypothyroid, directed therapy (i.e., thyroid hormone supplementation) would be possible in addition to supportive care and treatment of secondary conditions (e.g., skin infections).

The thyroid stimulating hormone (TSH) stimulation test can be used to distinguish true hypothyroidism from sick euthyroid syndrome in dogs (Feldman and Nelson, 1987). This test evaluates thyroid gland function and is unaffected by many of the factors that can alter basal thyroid hormone levels (Feldman and Nelson, 1987). Very few hormone function tests have been performed on marine mammals. Kirby and Ortiz (1994) administered glucose and insulin tolerance tests to northern elephant seal pups just prior to weaning and again at the end of the 2-month post-weaning fast. Gulland et al. (1999) and St. Aubin and Geraci (1988) evaluated adrenal function in Pacific harbor seals and in ringed and harp seals, respectively, using adrenocorticotrophic hormone (ACTH) stimulation tests. Thyroid function tests have been conducted on one cetacean species, beluga whales (St. Aubin, 1987; St. Aubin and Geraci, 1992), but have not been described for any pinniped.

We tested thyroid gland function in northern elephant seal yearlings to examine its potential role in the pathophysiology of NESSD and perhaps improve the care of affected animals. Additionally, if true hypothyroidism could be identified as a proximal cause of NESSD it would suggest further avenues of research to determine the ultimate cause of the disease, such as contaminant-associated endocrinopathy (e.g., Beckmen et al., 1997; Chiba et al., 2001; Rolland, 2000; Brouwer et al., 1989; St. Aubin, 2001).

2. Methods

Normal elephant seal juveniles (Fig. 1a) haul out on land for 2–4 months per year during the spring to molt (Stewart and Huber, 1993). The northern elephant seal juveniles (yearlings) tested during this study stranded along the northern California coastline and were brought to The Marine Mammal Center (Marin Headlands, CA) for treatment and rehabilitation between 1997 and 2000. A subset of these ($N = 16$) were admitted with NESSD and were categorized clinically (Beckmen et al., 1997) as mild (Fig. 1b; small superficial lesions covering less than half the body surface; patchy alopecia, $N = 8$), moderate (larger ulcers or lesions covering more than half the body surface; extensive alopecia with some hyperpigmentation or thickening of the epidermis, $N = 4$) or severe (Fig. 1c; large coalescing ulcers with serosanguinous or purulent exudate, ±necrosis of the hypodermis, $N = 4$).

Comparison groups included healthy yearlings ($N = 9$; rehabilitated and ready for release) and yearling seals with non-NESSD illnesses ($N = 10$), including verminous (lungworm) pneumonia, gastrointestinal parasitism (nematodes, cestodes, acanthocephalans) and traumatic ocular lesions (secondary to bite wounds to the face). The nine healthy yearlings (4 females, 5 males) were combined with an additional ten clinically-normal free-ranging yearlings (5 females, 5 males) to test for sex differences in baseline total T_4 and total T_3.

Seals were injected intramuscularly with 5 IU bovine thyrotropin (thyroid stimulating hormone, TSH; Sigma). The TSH stimulation test evaluates thyroid function by testing responsiveness of the thyroid gland to exogenous TSH. Blood samples were collected pre-injection and at 1.5 h and 3.0 h post-injection (preliminary tests with more frequent sampling intervals, out to 24 h post-injection, indicated that T_4 tended to peak at 3 h and T_3 at 1.5 h post-injection). Thyroid hormone assays (total T_3 and total T_4) were conducted by Idexx Laboratories, Inc. (veterinary reference laboratory; Sacramento, CA, USA) using solid-phase radioimmunoassay. Circulating thyrotropin (TSH) levels were not measured. Blocking agents were used to free bound thyroid hormone from carrier proteins. Assay evaluation experiments ensure consistent performance at widely varying serum protein concentrations (4.7–14.0 g/dL); even at very high protein concentrations (14.0 g/dL), observed values were within 11–12% of expected for T_4 and 14–17% of expected for T_3. Performance data for the total T_3 assay are as follows: analytical sensitivity is 7 ng/dL; intraassay (within-run) CV ranges from 3.1% (mean 398 ng/dL, SD 12.4 ng/dL) to 8.9% (mean 56 ng/dL, SD 5.0 ng/dL); interassay (run-to-run) CV ranges from 5.7% (mean 406 ng/dL, SD 23.0 ng/dL) to 10.0% (mean 59 ng/dL, SD 5.9 ng/dL). Performance data for the total T_4 assay are as follows: analytical sensitivity is 0.25 μg/dL; intraassay (within-run) CV ranges from 2.7% (mean 7.4 μg/dL, SD 0.20 μg/dL) to 3.8% (mean 2.4 μg/dL, SD 0.09 μg/dL); interassay (run-to-run) CV ranges from 4.2% (mean 11.4 μg/dL, SD 4.8 μg/dL) to 14.5% (mean 2.3 μg/dL, SD 0.33 μg/dL). The Wilcoxon Signed-Rank Test was used to compare baseline thyroid hormone levels between normal male and female yearlings (10 free-ranging seals and 9 clinically healthy seals that had been rescued and rehabilitated at TMMC). Baseline (pre-treatment) thyroid hormone levels were compared among treatment groups using Kruskal–Wallis ANOVA. Wilcoxon Signed-Rank Test was used to evaluate pre- and post-TSH stimulation values for all groups.

3. Results

Baseline thyroid hormone levels (Table 1) for normal seals were significantly higher than levels for seals with either NESSD or non-NESSD illness ($p < 0.0001$ for both

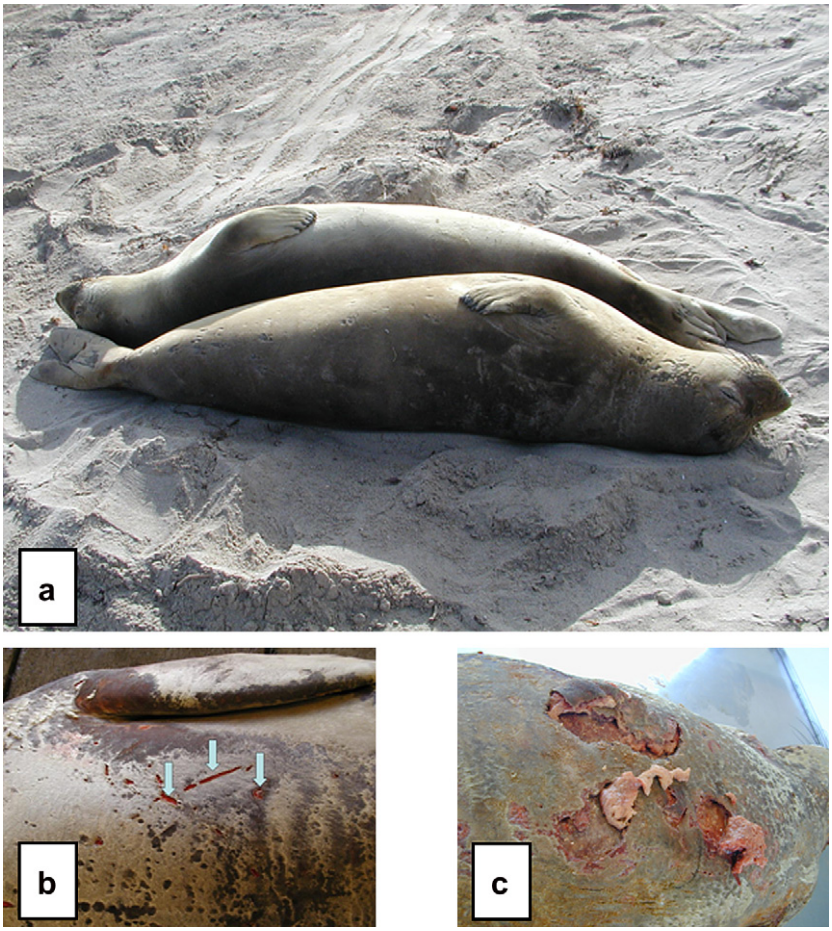

Fig. 1. Northern elephant seal yearlings with normal skin and with Northern Elephant Seal Skin Disease (NESSD). (a) Healthy northern elephant seal yearlings. The seal in the foreground is in early molt, with small patches of alopecia visible on the left side of the neck and on the flippers. Normal skin is visible underneath. (b) Northern elephant seal yearling with mild NESSD. The animal's head is to the left. The skin on the left thorax and axilla is erythematous and several small ulcers are visible (arrows). (c) Northern elephant seal yearling with severe NESSD. The animal's head is to the right. Multiple, coalescing, necrotic ulcers are present on the dorsal surface.

Table 1
Baseline thyroid hormone levels (T_4 and T_3) for normal seals, seals with northern elephant seal skin disease (NESSD) and seals with non-NESSD illness such as verminous pneumonia

Seal condition (*N*)	Baseline (pre-TSH stimulation) thyroid hormone levels (mean ± SD)	
	T_4 (μg/dL)	T_3 (ng/dL)
Normal (9)	2.5 ± 0.8 (A)	69.5 ± 23.6 (A)
NESSD (16)	1.1 ± 0.6 (B)	43.2 ± 14.6 (B)
Sick, non-NESSD (10)	0.9 ± 0.6 (B)	48.8 ± 19.1 (B)

Baseline levels of T_4 and T_3 in normal seals differed significantly from seals with NESSD or non-NESSD illnesses (values with different letters within a column are significantly different).

Table 2
Increases in thyroid hormone levels (T_4 and T_3) following thyroid-stimulating hormone (TSH) treatment in normal seals, seals with northern elephant seal skin disease (NESSD) and seals with non-NESSD illness such as verminous pneumonia

Seal condition (*N*)	Increases in thyroid hormone levels post-TSH stimulation (NS, not significant) (mean ± SD)	
	Increase in T_4 (μg/dL)	Increase in T_3 (ng/dL)
Normal (9)	1.4 ± 1.1 ($p \leqslant 0.04$)	1.4 ± 4.6 (NS)
NESSD (16)	0.6 ± 0.3 ($p \leqslant 0.01$)	15.2 ± 4.2 ($p \leqslant 0.003$)
Sick, non-NESSD (10)	0.6 ± 0.4 ($p \leqslant 0.01$)	3.6 ± 3.3 (NS)

Post-stimulation increases in T_4 levels were significant for all seals. Post-stimulation increases in T_3 were significant for NESSD seals only.

T_4 and T_3). There were no differences between normal yearling males and females in baseline levels of T_4 ($p \leqslant 0.19$) or T_3 ($p \leqslant 0.35$).

Levels of T_4 increased significantly following TSH-stimulation (Table 2) for normal seals ($p \leqslant 0.04$), seals with NESSD ($p \leqslant 0.01$) and seals with non-NESSD illness ($p \leqslant 0.01$), although the magnitude of the increase in sick seals was less than half that seen in normal seals. Levels of T_3 also increased following TSH-stimulation for all groups, but the increase was significant only for NESSD seals ($p \leqslant 0.003$; Table 2).

4. Discussion

Conditions not associated with the thyroid gland can cause decreases in circulating TH levels and mimic true

hypothyroidism. In humans and domestic animals, this phenomenon (sick euthyroid syndrome) has been associated with non-thyroid endocrine disease (e.g., diabetes, hyperadrenocorticism), renal disease, hepatic disease, respiratory disease, starvation, malnutrition, drugs (e.g., glucocorticoids, phenylbutazone), surgery and anesthesia, neoplasia, and immune-mediated disease (Ferguson, 1988; Kantrowitz et al., 2001). Mechanisms that have been proposed or demonstrated to cause alterations in basal TH concentrations in humans and domestic animals with normal thyroid glands include variation in TH production or secretion, alteration in serum binding and transport of TH, and alteration in metabolic clearance of TH (Ferguson, 1988; McIver and Gorman, 1997; Kantrowitz et al., 2001). Low circulating TH levels associated with non-thyroid disease have been hypothesized to be an adaptive mechanism to limit loss of protein and save energy in the presence of illness or other stressors (Ferguson, 1988; Henneman and Krenning, 2007).

Basal thyroid hormone (TH) levels in clinically healthy pinnipeds vary with age (Woldstad and Jenssen, 1999; Engelhardt and Ferguson, 1980; Hall et al., 1998; Haulena et al., 1998; Litz et al., 2001; Ortiz et al., 2001, 2003; Stokken et al., 1995; Leatherland and Ronald, 1979; Harrison et al., 1962; Myers et al., 2006), physiologic state (i.e., lactation; Haulena et al., 1998; Harrison et al., 1962; Engelhardt and Ferguson, 1980) and season (e.g., molt season; Boily, 1996; Engelhardt and Ferguson, 1980; John et al., 1987; Ashwell-Erickson et al., 1986; Riviere et al., 1977; Little, 1991; Bryden, 1994). Baseline thyroid hormone levels have been reported in northern and southern elephant seal pups (Kirby, 1990; Little, 1991; Ortiz et al., 2001; Bryden, 1994) and in yearling northern elephant seals with and without NESSD (Beckmen et al., 1997; see below). Thyroid gland morphology in neonate southern elephant seals has also been described (Griffiths and Bryden, 1986; Little, 1991).

Beckmen et al. (1997) suggested that PCBs might be involved in the etiology of NESSD, although skin lesions are not consistent with PCB toxicosis in other species. Variation in TH associated with exposure to pollutants (PCBs, PBDEs, CHCs) has been reported in pinnipeds, although the nature of the change (increase, decrease) is not consistent: lower TH, Brouwer et al. (1989), Debier et al. (2005), Chiba et al. (2001); higher TH, Hall et al. (2003); no significant relationship, Hall et al. (1998), Chiba et al. (2001).

In this study, we did not evaluate effects of age or physiologic (i.e., reproductive) state on TH levels or thyroid gland function because all animals tested were yearling seals. Although some seals in our study were sampled during the spring, when juveniles molt, none appeared to be in active molt at the time of our tests. We did not test for differences in TH levels with time of day, but no diurnal variation in TH has been reported in any phocid species tested (Stokken et al., 1995; Oki and Atkinson, 2004; Engelhardt and Ferguson, 1980).

We found no significant differences in basal thyroid hormone levels between male and female yearling seals. This is consistent with what others have reported for phocid seals, where no differences in TH or thyroid gland morphology were observed between male and female harbor seals (Little, 1991; Riviere et al., 1977; Harrison et al., 1962) or grey seals (Hall et al., 1998).

The baseline values we measured for T_4 and T_3 in normal seals ($T_4 = 2.5 \pm 0.8$ μg/dL, $T_3 = 69.5 \pm 23.6$ ng/dL) and seals with NESSD ($T_4 = 1.1 \pm 0.6$ μg/dL, $T_3 = 43.2 \pm 14.6$ ng/dL) were similar to those reported by Beckmen et al. (1997): normal $T_4 = 3.2 \pm 0.3$, normal $T_3 = 86.9 \pm 5.4$; NESSD $T_4 = 1.1 \pm 0.1$, NESSD $T_3 = 42.5 \pm 2.9$. In our study, yearling elephant seals with NESSD and with non-NESSD illnesses such as parasitism and bite wounds had significantly lower levels of circulating T_4 and T_3 than normal yearlings. However, T_4 increased significantly for all categories of elephant seals following TSH stimulation. Post-stimulation levels of T_3 were higher for all groups, but these changes were significant only in NESSD seals. This is consistent with reports that post-TSH stimulation changes in T_3 are less predictable than post-TSH changes in T_4 in dogs (Feldman and Nelson, 1987). The results of our TSH stimulation tests indicate that seals with NESSD are not truly hypothyroid but are 'sick euthyroid' (i.e., they have normal thyroid gland function).

Decreased TH levels associated with non-thyroidal inflammatory or infectious diseases in other species have been attributed to the influence of cytokines and other inflammatory mediators on endocrine glands, hormone degradation pathways or transport protein binding (McIver and Gorman, 1997; Ferguson, 1988). Yu et al. (1998) reported that treatment with endotoxin decreased not only basal T_3 but also post-TSH or post-TRH (thyroid releasing hormone) stimulation levels of T_4 in dogs. Most investigators, however, report that the TSH stimulation test is not affected by extra-thyroidal factors that can alter basal TH levels; for this reason, it is used routinely in domestic animals to distinguish thyroid from non-thyroid sources of decreased circulating TH (Feldman and Nelson, 1987).

Our results indicate that TSH-stimulation testing is a useful technique for evaluating thyroid function in seals. This technique may be of particular value to investigators interested in the effects of contaminants on pinniped endocrinology, where measurements of circulating hormone levels alone may produce contradictory or confusing results.

The etiology of NESSD remains unknown but other possible causes, such as a breakdown of the protective skin barrier secondary to a disruption of the catastrophic molt process, are under investigation.

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